

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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JOINT

MEDICAL REVIEW(S)

AND

STATISTICAL REVIEW(S)

JOINT CLINICAL & STATISTICAL REVIEW

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Reviewer Name(s)	Tsvi Aranoff, M.D. Fanhui Kong, Ph.D.
Review Completion Date	11-19-2010
Established Name (Proposed)	Aliskiren, Amlodipine, Hydrochlorothiazide n\a
Trade Name	
Therapeutic Class	Antihypertensive (combination product: renin inhibitor,

	calcium channel blocker, thiazide diuretic)
Applicant	Novartis
Formulation(s)	Oral tablet
Dosing Regimen	Aliskiren/Amlodipine/Hydrochlorothiazide (mg): 150/5/12.5, 300/5/12.5, 300/5/25, 300/10/12.5, 300/10/25
Indication(s)	Hypertension (not for initial therapy)
Intended Population(s)	Adult Patients with HTN

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend that Brandname, the fixed combination of aliskiren, amlodipine, and HCTZ, be approved for the treatment of hypertension. This conclusion is supported by efficacy and safety data from a short-term, double-blind, pivotal efficacy study, a long-term, open-label major safety trial, as well as four other supportive clinical trials.

In the pivotal efficacy trial (SAH2302), the triple therapy combination demonstrated clinically and statistically significant reductions from baseline in blood pressure compared to each of the component double therapy combinations in patients with moderate to severe hypertension. Moreover, in this same pivotal study, triple therapy demonstrated superior reductions in BP from baseline over the entire 24 hour interdosing interval.

The greater BP lowering effect with triple combination over component dual combinations was generally demonstrated in a broad range of patient populations without regard to age, race, gender, BMI status and other demographic or disease status factors such as patients with diabetes.

In terms of safety, the safety profile for aliskiren/amlodipine/HCTZ was consistent with that previously known for aliskiren, amlodipine, or HCTZ when used as monotherapy or as dual combination. There were no unexpected safety findings in the clinical program. There were no deaths in any patients who took triple therapy. The incidence and severity of total and individual adverse events for aliskiren/amlodipine/HCTZ treatment were generally similar to the component dual combination treatments.

Peripheral edema, a known side effect of amlodipine, occurred more in treatment groups containing amlodipine. The aliskiren/amlodipine/HCTZ showed slightly less reported peripheral edema than aliskiren/amlodipine treatment. Peripheral edema was mostly mild to moderate in severity and rarely led to patient discontinuation.

With the exception of peripheral edema, there was no increase in AE incidence and severity when the dose of aliskiren/amlodipine/HCTZ was increased from 150/5/12.5 mg to 300/10/25 mg. AEs potentially related to low blood pressure such as hypotension, orthostatic hypotension, syncope and dizziness occurred at low incidence and rarely led to patient discontinuation in patients treated with aliskiren/amlodipine/HCTZ.

Hyperkalemia occurred uncommonly with the treatment of aliskiren/amlodipine/HCTZ triple combination with the incidence similar to the component dual combinations. No case of angioedema was reported in the entire clinical program. Changes in laboratory parameters observed with aliskiren/amlodipine/HCTZ were generally minor and

consistent with the known effect of aliskiren, amlodipine, or HCTZ. There were no meaningful differences between aliskiren/amlodipine/HCTZ triple combination and component dual combinations.

Aliskiren/amlodipine/HCTZ was generally well-tolerated regardless of gender, age or race.

1.2 Risk Benefit Assessment

The safety profile for aliskiren/amlodipine/HCTZ was consistent with that previously known for aliskiren, amlodipine, or HCTZ when used as monotherapy or as dual combination. There were no unexpected safety findings in the clinical program. There were no deaths in any patients who took triple therapy. The incidence and severity of total and individual adverse events for aliskiren/amlodipine/HCTZ treatment were generally similar to the component dual combination treatments. Peripheral edema, a known side effect of amlodipine, occurred more in treatment groups containing amlodipine. The aliskiren/amlodipine/HCTZ showed slightly less reported peripheral edema than aliskiren/amlodipine treatment. Peripheral edema was mostly mild to moderate in severity and rarely led to patient discontinuation. With the exception of peripheral edema, none of the other most common AEs demonstrated dose-dependency. Based on review of the submitted clinical studies, this combination appears to have a favorable risk-benefit profile considering the long-term outcome of anti-hypertension therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I have no recommendation for postmarket risk evaluation and mitigation beyond the standard FDA processes for monitoring drug safety.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend that sponsor conduct a food effect study measuring relationship between food (tested at various levels of fat: high, intermediate, low), exposure and, pharmacodynamics (msSBP and msDBP). Once this study is conducted and a better understanding is gained for the relationship between food and BP effect, labeling for all aliskiren products (including this triple combination product) should be updated.

2 Introduction and Regulatory Background

2.1 Product Information

Brandname is a fixed combination tablet comprised of Aliskiren, Amlodipine, and Hydrochlorothiazide for the treatment of hypertension.

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin. Aliskiren targets the renin-angiotensin-aldosterone system (RAAS) at the point of activation by binding to the enzyme renin, thereby blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of plasma renin activity (PRA), angiotensin I and angiotensin II. It has been developed for the treatment of hypertension, alone or in combination with other anti-hypertensive agents including HCTZ, valsartan, and amlodipine.

Amlodipine is a long-acting dihydropyridine calcium channel blocker and the most commonly prescribed drug in this class. It has demonstrated clinical efficacy and cardioprotective effect in a wide range of the hypertensive patient populations by reducing BP. Amlodipine acts on vascular smooth muscle cells causing a reduction in peripheral vascular resistance and thus reduces the BP. Amlodipine is effective as monotherapy as well as add-on therapy to diverse classes of antihypertensive medications (Bisognano et al 2004). The primary dose-dependent adverse event (AE) induced by amlodipine, peripheral edema, results from the increased capillary hydrostatic pressure from pre-capillary vasodilatation. Amlodipine (Norvasc®) monotherapy is approved for the treatment of hypertension, angina, and in some countries angiographically documented coronary artery disease and is available in the dose strengths of 5 and 10 mg and in some countries in a 2.5 mg dose in special populations for once-daily administration.

Hydrochlorothiazide (HCTZ) is the most commonly prescribed thiazide-type diuretic. It affects renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, HCTZ reduces plasma volume, with consequent increases in PRA, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. Aliskiren reduces elevations in PRA induced by HCTZ therapy (Azizi et al 2004). Thus the combination of HCTZ and aliskiren is expected to significantly reduce elevations in PRA caused by HCTZ monotherapy as well as the consequences of elevated renin activity. Hydrochlorothiazide (HCTZ) monotherapy has been marketed since 1959 and is approved for the treatment of hypertension and edema. It has been used alone or in combination with other antihypertensive agents in once-daily doses of 12.5 or 25 mg.

Product will be manufactured in the following five strengths and appearances:

- 150/5/12.5 mg tablets: Violet white, ovaloid convex shaped film-coated tablet with a beveled edge embossed with “YIY” on one side and “NVR” on the reverse side of the tablet
- 300/5/12.5 mg tablets: Light pink, ovaloid convex shaped film-coated tablet with a beveled edge embossed with “LIL” on one side and “NVR” on the reverse side of the tablet
- 300/5/25 mg tablets: Pale orange brown, ovaloid convex shaped film-coated tablet with a beveled edge embossed with “OIO” on one side and “NVR” on the reverse side of the tablet
- 300/10/12.5 mg tablets: Light red, ovaloid convex shaped film-coated tablet with a beveled edge embossed with “UIU” on one side and “NVR” on the reverse side of the tablet
- 300/10/25 mg tablets: Brown, ovaloid convex shaped film-coated tablet with a beveled edge embossed with “VIV” on one side and “NVR” on the reverse side of the tablet

2.2 Tables of Currently Available Treatments for Proposed Indications

A large number of drugs are currently available for reducing blood pressure. Table 1 below provides a list of the commonly used antihypertensive agents.

In terms of combination products, there are several such products available for the treatment of hypertension including ACEIs/CCBs, ACEIs/HCTZ, ARBs/HCTZ, Beta blockers/HCTZ, Central-acting drug/HCTZ, aliskiren/HCTZ, aliskiren/valsartan, ARBs/amlodipine, Amlodipine/Valsartan/HCTZ; Amlodipine/Benazepril/HCTZ etc. There is no combination product of aliskiren/CCBs/thiazide on the market.

Table 1: Commonly Used Drugs Approved For Treatment Of Hypertension (From Draft Of Antihypertensive Guidance)

Pharmacologic Class	Approved Drugs
aldosterone antagonists	eplerenone, spironolactone
alpha adrenergic blockers	doxazosin , phenoxybenzamine, phentolamine, prazosin , terazosin
angiotensin converting enzyme inhibitors	benazepril, captopril , enalapril , fosinopril, lisinopril , moexipril, perindopril, quinapril, ramipril , trandolapril
angiotensin II receptor blockers	candesartan , eprosartan, irbesartan , losartan , olmesartan, telmisartan, valsartan
arteriolar vasodilators	hydralazine , minoxidil
autonomic ganglionic vasodilators	mecamylamine
beta adrenergic blockers	acebutolol , atenolol , betaxolol, bisoprolol, carvedilol , carteolol, esmolol, labetalol, metoprolol , nadolol, penbuterol, pindolol , propranolol , timolol
catecholamine-depleting sympatholytics	deserpidine, reserpine
central alpha-2 adrenergic agonists	clonidine , guanabenz, guanfacine, methyldopa
calcium channel blockers	diltiazem , verapamil
dihydropyridine calcium channel blockers	amlodipine , felodipine , isradipine , nicardipine , nifedipine , nisoldipine
loop diuretics	bumetanide, ethacrynic acid, furosemide , torsemide
potassium-sparing diuretics	amiloride , triamterene
renin inhibitors	aliskiren
thiazide diuretics	chlorothiazide, hydrochlorothiazide , hydroflumethiazide, methyclothiazide, polythiazide
thiazide-like diuretics	chlorthalidone , indapamide, metolazone

2.3 Availability of Proposed Active Ingredient in the United States

Aliskiren is approved for use as either monotherapy or in combination with other antihypertensive agents in once daily doses of 150 and 300 mg. Fixed dose combinations of aliskiren and HCTZ (Tekturna HCT®), aliskiren and valsartan (Valturna™) have been approved for the treatment of hypertension.

Amlodipine is approved for use as either monotherapy or in combination with other antihypertensive agents in once daily doses of 5 and 10 mg. Fixed dose combinations of ACEI or ARB with amlodipine including Benazepril/amlodipine (Lotrel), Azor

(Amlodipine/Olmesartan), Twynsta (Amlodipine/Telmisartan) and Valsartan /amlodipine (Exforge®) have been approved for the treatment of hypertension.

Hydrochlorothiazide is approved in the United States as a diuretic and antihypertensive and is available as 25-mg and 50-mg tablets for oral administration. It is approved for two indications: treatment of edema and treatment of hypertension. As a treatment for edema, it is approved as an adjunct treatment associated with various conditions. As a treatment for hypertension, it is approved for the management of hypertension either as the sole therapeutic agent or to enhance the effect of other antihypertensive drugs in the more severe forms of hypertension.

Hydrochlorothiazide is also available as approved component of several combination drug products including: Aliskiren \ Hydrochlorothiazide, Valsartan \ Amlodipine \ Hydrochlorothiazide, Olmesartan \ Amlodipine \ Hydrochlorothiazide, etc.

2.4 Important Safety Issues With Consideration to Related Drugs

RAAS inhibitors share certain adverse events (AEs). Because all affect aldosterone, all can cause increases in serum potassium. 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. It is assumed that renin inhibitors should not cause these latter AEs. However, this has not been confirmed in clinical trials. Finally, ARBs have recently been implicated in rare cases of rhabdomyolysis.

Amlodipine is a long-acting dihydropyridine CCB. The primary dose-dependent adverse event (AE) induced by amlodipine, peripheral pedal edema, results from the increased capillary hydrostatic pressure from pre-capillary vasodilatation.

Hydrochlorothiazide is a thiazide diuretic that affects renal tubular mechanisms of electrolyte reabsorption. It increases excretion of sodium and chloride in approximately equivalent amounts. The natriuresis causes a secondary loss of potassium. The prime safety concern with thiazide diuretics is, therefore, related to electrolyte derangement. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On March 14, 2008, a pre-IND meeting was held with FDA and sponsor. Discussion revolved around sponsor's plans to conduct clinical trials aimed at obtaining approval for a fixed combination drug product combining Aliskiren, Amlodipine, and

Hydrochlorothiazide in patients with hypertension. The stated indication was for patients whose hypertension was not sufficiently controlled on the dual therapies of: Aliskiren and Amlodipine, or Aliskiren and Hydrochlorothiazide, or Hydrochlorothiazide and Amlodipine. In addition, the targeted population included patients whose hypertension required free combination of Aliskiren, Amlodipine, and Hydrochlorothiazide.

The meeting focused on the clinical development plan, the biopharmaceutics development plan, the preclinical safety development plan, and the technical development plan for the fixed-dose combination of aliskiren (Tekturna), amlodipine, and hydrochlorothiazide (HCTZ). It was agreed upon that systolic blood pressure would be an acceptable primary endpoint, that triple combination therapy would have to be shown to be superior to double therapy by a clinically-meaningful threshold of 2mmHg, and that 24-hour ambulatory blood pressure should be assessed so as to demonstrate blood pressure control throughout the inter-dosing interval.

On March 12, 2009, a pre-NDA meeting was held with the participation of sponsor as well as FDA reviewers. Several issues were agreed upon at this meeting including: sponsor's pooling strategy for efficacy and safety, sponsor's commitment to submit all case report forms for all deaths and discontinuations. Sponsor's bioequivalence program was discussed in detail as well.

2.6 Other Relevant Background Information

n/a.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In my analysis of the datasets from all of the submitted clinical trials, I did not encounter any problems or major discrepancies with the data which might confound efficacy and safety results of this NDA.

3.2 Compliance with Good Clinical Practices

It was decided that no GCP site inspections would be required as the clinical activity in the pivotal efficacy trial was widely distributed across a large number of sites. Only one site was shown to represent more than 5% of patient load (at 5.84%). And, upon statistical analysis, this single site had no discernible effect on primary endpoint analysis. I do not think, therefore, that any audit is indicated.

Sponsor states that all studies were conducted in full compliance with Good Clinical Practice (as stated in ICH Guideline E6 (1996)) and were closely monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it. However, at a late stage in the review process, sponsor submitted to the FDA the results of GCP inspections conducted by agents of the EMA\CHMP (Committee for Medicinal Products for Human Use) at three study sites (one in Latvia and two in Canada). GCP violations were, in fact, exposed by this inspection. I discuss these violations below in Section 6.1.4, under headings "Protocol Deviation #1" and "Protocol Deviation #2".

3.3 Financial Disclosures

The following findings were reported by Novartis:

- No clinical investigators are full or part-time employees of Novartis

(b) (6)

Furthermore, sponsor claims that any bias resulting from these arrangements is minimized by: independent data monitoring by Novartis, multiple investigators used in the studies, and double-blind placebo controlled trials.

Reviewer's comment: given how large the study is and how many sites there were, and given the mitigation provided by double-blinding I think the two fees listed above are acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review did not have any objections to approvability. In their review of this NDA, CMC had the following comments.

The drug product, Aliskiren/Amlodipine/Hydrochlorothiazide Tablets, 150/5/12.5mg, 300/5/12.5mg, 300/10/12.5mg, 300/5/25mg and 300/10/25mg, is recommended as APPROVABLE from a CMC perspective, pending DMETS's, Office of Compliance's and EA's recommendations. A final memorandum will be submitted when these pending recommendations are received.

4.2 Clinical Microbiology

This submission does not include microbiology data.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical studies using the combination product were submitted with this application.

The Pharm/tox review, conducted by Dr. G. Jagadeesh, recommends approvability for this application. His only issues were recommendations to modify certain aspects of the following sections of the prescribing information: fetal/neonatal morbidity and mortality, pregnancy, overdosage, and carcinogenesis, mutagenesis, and impairment of fertility. These comments on labeling, did not affect his overall, final position of product approvability.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Aliskiren

Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I 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. Ang II also inhibits renin release, thus providing a negative feedback to the system. This cycle, from renin through angiotensin to aldosterone and its associated negative feedback loop, is known as the renin-angiotensin-aldosterone system (RAAS). Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to Ang I. Whether aliskiren affects other RAAS components, e.g., ACE or non-ACE pathways, is not known.

All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE inhibitors and ARBs, the result is increased levels of PRA. During treatment with aliskiren, however, the effect of increased renin levels is blocked, so that PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents

Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and

vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound ($pK_a=8.6$), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Hydrochlorothiazide

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 co-administration of agents that block the production or function of angiotensin II are theorized to reverse the potassium loss associated with these diuretics.

4.4.2 Pharmacodynamics

No specific pharmacodynamic interaction studies with the aliskiren/amlodipine/HCTZ combination have been performed. The pharmacodynamic properties of aliskiren, amlodipine, and HCTZ monotherapies are well characterized and relevant information is reflected in the respective package inserts for aliskiren hemifumarate (Tekturna®), for amlodipine besylate (Norvasc®), and for HCTZ (Esidrex®).

4.4.3 Pharmacokinetics

Food Effect

Sponsor conducted a food effect study (Study SAH100A2101) to test for the effect of a high fat diet on the pharmacokinetics of oral administration of the fixed dose triple combination.

The study was an open label, two treatment, cross over, single dose study to determine the effect of food on the pharmacokinetics of a fixed dose combination of Aliskiren/Amlodipine/Hydrochlorothiazide 300/10/25 mg tablet in healthy subjects under fasted and fed conditions. The results of the study are demonstrated below in Figure 1, Figure 2, and Figure 3, which demonstrate the plasma concentration profile for the three

component drug substances. Figure 1 and Figure 2 show that there is virtually no food effect for either Amlodipine or Hydrochlorothiazide. Figure 3, however, shows that there is a marked food effect for Aliskiren. More specifically, results showed that the high fat diet led to a decrease in AUC (as compared to fasted) of 78%, a decrease in C_{max} of 89%, and an increase in median T_{max} from 1.5 to 3hrs.

Figure 1: Mean (SD) amlodipine plasma concentration time profile following single dose administration of fixed combination aliskiren\amlo\ HCTZ 300\10\25 mg tablet under fed and fasted conditions (Sponsor's Figure)

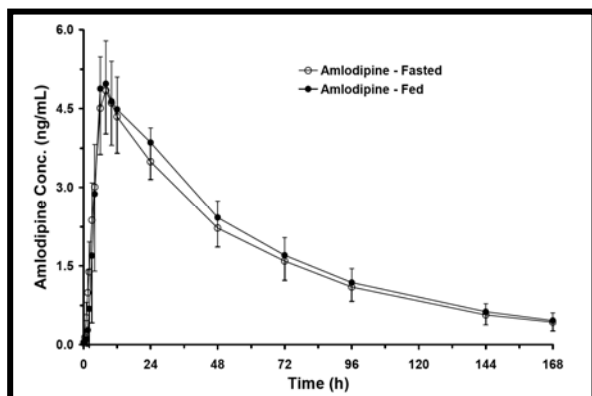


Figure 2: Mean (SD) HCTZ plasma concentration time profile following single dose administration of fixed combination aliskiren\amlo\ HCTZ 300\10\25 mg tablet under fed and fasted conditions (Sponsor's Figure)

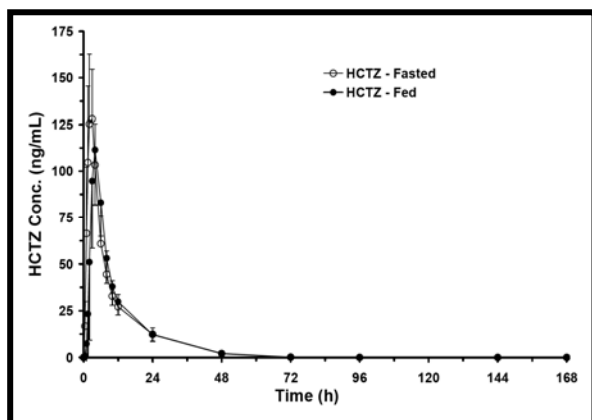
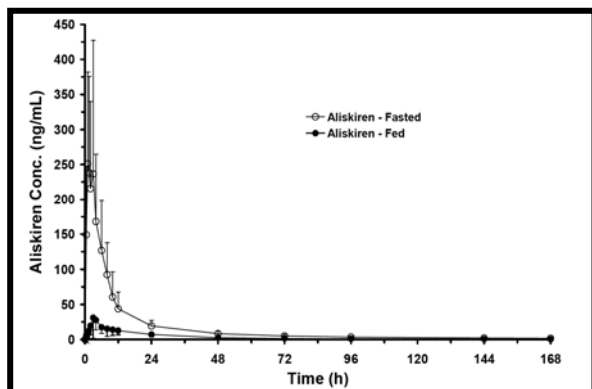


Figure 3: - Mean (SD) aliskiren plasma concentration time profile following single dose administration of fixed combination aliskiren\amlo\ HCTZ 300\10\25 mg tablet under fed and fasted conditions (Sponsor's Figure)



Reviewer's comment: My initial concern emanating from the Aliskiren food effect was one of safety. My concern was over patients who transition from a dual-therapy antihypertensive regimen, which they might be in the practice of taking fed, who then transition to Brandname and happen to take their first dose in a fasting state. The concern I had was that they may experience an unusually abrupt drop in blood pressure due to the abrupt increase in exposure brought on by the added third drug substance in addition to the elevated exposure brought on by fasting administration of the Aliskiren. However, analysis (conducted by FDA's clin-pharm staff) of data from the Aliskiren monotherapy program dose-ranging study data suggests that average ambulatory systolic blood pressure decreased only 2.5-3 mmHg in fasted as compared to fed patients, while diastolic decreased even less: only 2 mmHg. This greatly mitigated my concern of abrupt blood pressure reduction. As a result, I have taken the final position that the food effect is acceptable with the following provisos:

- 1. This correlation between food effect and change in ambulatory blood pressure should be included in the label.*
- 2. The label should instruct patients to take their medication in a fixed relationship to their meals.*
- 3. Sponsor should conduct a post marketing food effect study of Brandname utilizing several diets of varying fat concentrations, not merely the high fat diet used in the Aliskiren monotherapy program. Endpoints should include not only pharmacokinetics, but Δ msSBP and Δ msDBP as well.*

Bioavailability\Bioequivalence

All the major safety and efficacy studies included in this application utilized the free combination of the drug substances. Therefore, a bioavailability\bioequivalence program was conducted by the sponsor to bridge the findings of the safety and efficacy studies to the fixed combination product.

Two bioavailability and one bioequivalence studies were conducted. The bioavailability studies were conducted prior to conduct of the bioequivalence study. The purpose of the bioavailability studies was to select a final marketing image of the fixed combination product for use in the bioequivalence study.

The two bioavailability studies were SAH100A2104 and SAH100A2105.

- SAH100A2104 was an open-label, randomized, single dose, five period, crossover study aimed at determining the relative bioavailability of four fixed dose combinations 300+10+25 mg Aliskiren \ Amlodipine \ Hydrochlorothiazide tablet variants relative to the free combining of the market formulations of the three component drugs.
- SAH100A2105 was identical to SAH100A2104 except that it constituted four periods and only compared 3 fixed dose combinations to free combination.

Collectively, the two BA studies compared seven variants of fixed dose combination to free combination. Of the seven variants tested, only three satisfied C_{max} and AUC criteria for bioequivalence. Of those three successful variants, one was chosen as the final marketing image, to be used for testing in the definitive, pivotal BE study. This variant was selected based on its successful BE results (AUC and C_{max}) as well as its successful six-month stability data and positive dissolution characteristics.

The bioequivalence study (SAH100A2102) was an open-label, randomized, two treatment, cross over, single dose study aimed at evaluating bioequivalence between a fixed dose combination of 300\5\25 mg Aliskiren \ Amlodipine \ Hydrochlorothiazide tablet and free combination of market formulations of those same drugs, in healthy subjects.

Results of the bioequivalence study were as follows. While AUC and C_{max} were within acceptable ranges for Amlodipine and Hydrochlorothiazide, and the AUC of Aliskiren was within an acceptable range, the C_{max} for Aliskiren was not within the acceptable range. Specifically, the C_{max} for Aliskiren was 0.84, with a 90% confidence interval of 0.76-0.93. The lower end of the confidence interval fell outside of the standard range of 0.8-1.25.

Reviewer's comment: The bioequivalence argument for the Aliskiren component of the fixed combination is challenging, but, ultimately, I find it acceptable for the following reasons:

1. *Aliskiren has a high intra-subject PK variability (45% in this study), and therefore, I think it is reasonable to allow for a C_{max}:C_{max} ratio range to be slightly larger than what is normally tolerated in such situations. The EMA, for example, allows for a range of 0.75-1.33 for high PK-variable products, which is a wider range than the FDA's usual standard of 0.8-1.25. If this slightly wider range is adopted for Aliskiren, then its C_{max} does fall into an acceptable range.*

2. *While there is an issue with C_{max}, there is no issue with AUC, which falls wholly within the standard range of 0.8-1.25. Moreover, there is a good argument for saying that AUC is more important than C_{max} in the case of Aliskiren because Aliskiren demonstrates superior reduction in blood pressure (ambulatory) over the entire 24-hour range.*
3. *One of the relative bioavailability studies from which the final marketing image was selected did show the C_{max}:C_{max} ratio (fasted to fed) and its 90% confidence interval to be within the requisite 0.8 -1.25 limits. This study was not prospectively powered to serve as a bioequivalence study, but its demonstration of C_{max} relative equivalence is supportive of the bioequivalence conclusion nonetheless.*

5 Sources of Clinical Data

The sources of clinical data for this review are the 6 clinical trials listed in Table 2 below and the 5 clinical pharmacology and biopharmaceutic trials listed in Table 3 below. In this review, greatest focus will be placed on the 2 clinical trials that constituted the pivotal efficacy and safety trials of the application (SAH2302 and SAH2301).

5.1 Tables of Studies/Clinical Trials

Table 2: Summary of Efficacy and Safety Studies (Reviewer's Table)

Summary of Efficacy and Safety Studies							
#	Study	N (treated)	Design	Duration	Drugs	Control	Endpoint
1	MAJOR PIVOTAL TRIAL (SAH2302)	1188	double blind, active-controlled, four-group, parallel study, evaluating efficacy of triple therapy vs dual therapies	8wk	Aliskiren, Amlodipine, HCTZ	Active Control	Δfrom baseline msSBP
2	MAJOR SAFETY TRIAL (SAH2301)	564	open label, evaluating long term safety of triple therapy	28wk-54wk	Aliskiren, Amlodipine, HCTZ	No control	Δfrom baseline msDBP, msSBP

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Tekturna, Amlodipine, HCTZ (combination product)

3	(supportive study) SPP2344	896 (only 51 on triple therapy)	double blind, active controlled study evaluating Ali-based regimen vs Ramipril based regimen in elderly hypertensives	36wk	Aliskiren, Amlodipine, HCTZ, Ramipril	Active Control	Δ from baseline msSBP
4	(supportive study) SPP2411	450 (only 29 on triple therapy)	double blind, parallel group, active controlled dose escalation study evaluation Ali\HCTZ vs HCTZ	8wk	Aliskiren, Amlodipine, HCTZ	Active Control	Δ from baseline msSBP
5	(supportive study) SPA2301	556 (only 86 on triple therapy)	open label study evaluating long term safety and efficacy of al\amlo with optional HCTZ	54wk	Aliskiren, Amlodipine, HCTZ	Active Control	Δ from baseline msDBP, msSBP
6	(supportive study) SPP2360	256 (119 on triple therapy)	open label, non-comparative study, patients treated with Ali-based regiment, with optional add-on of HCTZ and amlo	24wk	Aliskiren, Amlodipine, HCTZ	No control	proportion of patients who reached the BP target

Table 3: Clinical Pharmacology and Biopharmaceutical Trials (Sponsor's Table)

Study No.	N	Objective	Population	Dosage form	Dose (mg)
SAH2101	36	Food effect on the PK of the fixed combination of SAH, safety & tolerability	HS M	Aliskiren/Amlodipine/HCTZ tablet (FMI)	300/10/25 mg SD
SAH 2102	109	Bioequivalence, safety & tolerability	HS M	Aliskiren/Amlodipine/HCTZ tablet (FMI) Aliskiren (RT) Amlodipine (CSF) HCTZ (CSF)	300/5/25 mg SD 300 mg SD 5 mg SD 25 mg SD
SAH2104	80	Relative bioavailability, safety & tolerability	HS M/F	Aliskiren/Amlodipine/HCTZ tablet (variant 1) Aliskiren/Amlodipine/HCTZ tablet (variant 2) Aliskiren/Amlodipine/HCTZ tablet (variant 3) Aliskiren/Amlodipine/HCTZ tablet (variant 4) Aliskiren (RT) Amlodipine (CSF) HCTZ (CSF)	300/10/25 mg SD 300/10/25 mg SD 300/10/25 mg SD 300/10/25 mg SD 300 mg SD 10 mg SD 25 mg SD
SAH2105	72	Relative bioavailability, safety & tolerability	HS M/F	Aliskiren/Amlodipine/HCTZ tablet (variant 5) Aliskiren/Amlodipine/HCTZ tablet (variant 6) Aliskiren/Amlodipine/HCTZ tablet (variant 7) Aliskiren (RT) Amlodipine (CSF) HCTZ (CSF)	300/10/25 mg SD 300/10/25 mg SD 300/10/25 mg SD 300 mg SD 10 mg SD 25 mg SD
SAH2302 (PK)	1188/ a subset of 77 used for population PK analysis	To assess the drug-drug interaction potential at steady-state between Aliskiren, HCTZ and Amlodipine in the triple combination using a population PK approach.	M/F Moderate to severe hypertensive patients	Aliskiren/HCTZ Aliskiren/Amlodipine Amlodipine/HCTZ Aliskiren/Amlodipine/HCTZ Aliskiren/Amlodipine/HCTZ Aliskiren/HCTZ Aliskiren/Amlodipine Amlodipine/HCTZ Aliskiren/Amlodipine/HCTZ Aliskiren (RT) Amlodipine (CSF) HCTZ (CSF)	150/12.5 qd Wk 1 -4 150/5 mg qd Wk 1 -4 5/12.5 mg qd Wk 1 -4 150/0/12.5 mg 3 days 150/5/12.5 mg qd day 4 – wk 4 300/25 mg qd Wk 5 -8 300/10 mg qd Wk 5 -8 10/25 mg qd Wk 5 -8 300/10/25 mg qd Wk 5 -8

5.2 Review Strategy

I reviewed all six clinical studies supporting this NDA. These six studies are listed in Table 2 above and include: the pivotal efficacy study (SAH2302), the major safety study (SAH2301), and the four supportive studies (SPP2344, SPP2411, SPA2301, and SPP2360).

I performed a comprehensive review of efficacy in the pivotal efficacy study (SAH2302), as well as a review of efficacy in the remaining five studies. I performed a comprehensive review of safety in the pivotal safety study (SAH2301) as well as in the five other studies. I conducted my safety review of the six studies in an integrated manner – according to the pooling scheme described in section 7.1.4.

In addition to reviewing the clinical studies for safety and efficacy, I reviewed the clinical pharmacology studies as well. A list of the clinical pharmacology studies can be found in Table 3.

As a 505b(2) combination product, I have also checked the most updated labeling and some previous clinical studies for aliskiren, amlodipine and HCTZ.

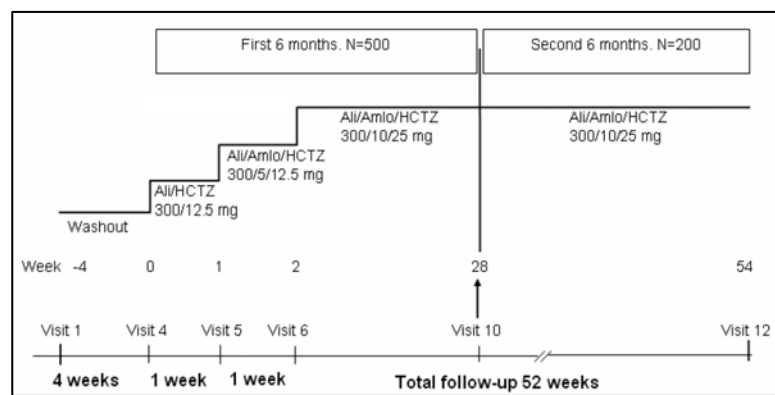
5.3 Discussion of Individual Studies/Clinical Trials

This NDA is supported by six clinical studies (see Table 2 above for list of the six studies). I will not be reviewing the pivotal efficacy study (SAH2302) in this section as I review it at length in Section 6 below. Rather, in this section, I will be discussing the five remaining studies: the major safety study (Study SAH2301) and the non-pivotal studies (SPP2344, SPP2411, SPA2301, SPP2360). These last four studies are considered supportive rather than pivotal for this NDA as they were not designed prospectively to test the safety of this NDA's study drug; moreover, they contribute only a small number of patients to this review in comparison to the number of patients contributed by the pivotal efficacy and safety studies of this NDA.

Finally, in this section I will only be discussing the efficacy analysis of these five studies rather than their safety analysis as I will be reviewing safety of all studies (pivotal as well as non-pivotal) in section 7 below.

SAH2301 – background

Figure 4: Study Design (Study SAH2301, Sponsor's Figure)



Study SAH2301 is the major safety study for the application. SAH2301 was an open-label, multicenter study conducted at 82 sites in 8 countries (Belgium, Egypt, Germany, Poland, Slovakia, Spain, Turkey, and US). Following washout, eligible patients with moderate to severe hypertension (msSBP ≥ 160 mmHg and < 200 mmHg and/or msDBP ≥ 100 mmHg and < 120 mmHg) received the treatment of aliskiren/HCTZ 300/12.5 mg for 1 week and aliskiren/amlodipine/HCTZ 300/5/12.5 mg for another 1 week. Then the doses were forced-titrated to aliskiren/amlodipine/HCTZ 300/10/25 mg for a further 52 weeks.

SAH2301 - efficacy

Efficacy was the secondary objective of the study (with safety being the first). The key efficacy variables included msSBP/msDBP reduction from baseline, BP control and BP response rate. Of the 564 treated patients, 206 patients who completed the first 6-month period entered the second 6-month period. A total of 493 patients (87.4%) completed the study (either the first or second 6-month treatment phase). Overall, clinically meaningful incremental mean reductions from baseline in msSBP (32.2 mmHg) and msDBP (18.9 mmHg) were observed at Week 4, as early as 2 weeks after the patients had received the high dose of the aliskiren/amlodipine/HCTZ triple combination therapy. A significant proportion of patients ($> 62\%$) achieved BP control ($< 140/90$ mmHg) at Week 4, after 2 weeks of treatment with the triple combination. The BP reduction effect was sustained over the long-term treatment (up to 1 year) with the aliskiren/amlodipine/HCTZ triple combination therapy.

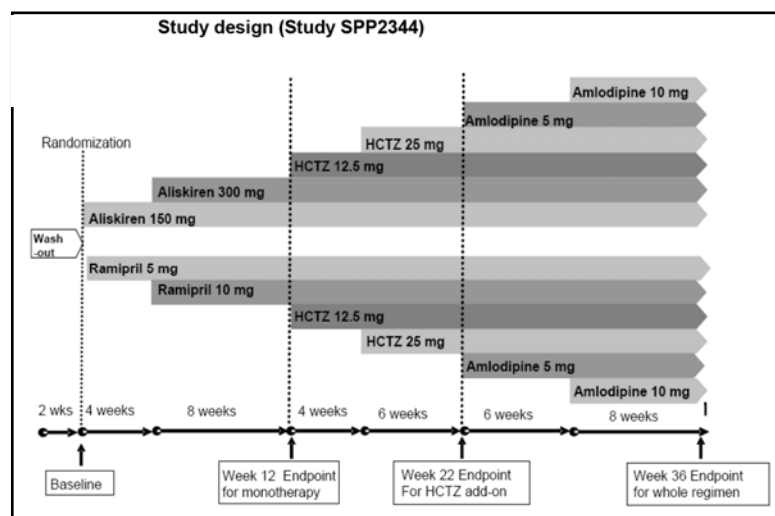
Reviewer's comment: Though BP reduction has been shown over the 52 weeks of the study, (b) (4)

For Plasma Renin Activity (PRA), a decrease was observed from baseline to Week 28 Endpoint (41.8%). An increase was seen in PRC from baseline to Week 28 Endpoint for

the treated population (1545.8%). An increase in the aldosterone levels (44.5%) was also observed.

Study SPP2344 – background

Figure 5: Study Design (Study SPP2344, Sponsor's Figure)



Study SPP2344 was a 36-week randomized, double-blind, parallel-group, multicenter, active-controlled, optional titration study comparing the efficacy and safety of an aliskiren-based regimen (with optional add-on HCTZ and amlodipine) to a Ramipril-based regimen (with optional add-on HCTZ and amlodipine) in patients ≥ 65 years old with systolic essential hypertension (msSBP ≥ 140 mmHg and < 180 mmHg). The study was comprised of 2 periods (washout and up to 36 weeks of double-blind treatment (Figure 5). For those patients whose BP was not adequately controlled with aliskiren/HCTZ or Ramipril/HCTZ, the optional titration of amlodipine was initiated after Week 22 of the study.

The primary efficacy variable was msSBP change from baseline. Key secondary endpoints included change in msDBP, BP control and response rates.

Of the 901 patients who were randomized, 896 patients received study medication. 51 patients received aliskiren/amlodipine/HCTZ and 68 patients received the Ramipril/amlodipine/HCTZ triple combination therapy.

Study SPP2344 - efficacy

At Week 28, 6 weeks after the escalation with aliskiren/amlodipine/HCTZ or ramipril/amlodipine/HCTZ triple combination therapy, clinically meaningful reductions in

msSBP were observed with the aliskiren-triple combination treatment (22.0 mmHg) compared to the ramipril-triple combination (19.1 mmHg). Similar results were seen in the msSBP at the Week 36 Endpoint for the aliskiren-triple and ramipril-triple combination therapies (-30.8 mmHg and -25.7 mmHg, respectively). The aliskiren-triple combination treatment also had greater msDBP reductions at Week 36 Endpoint.

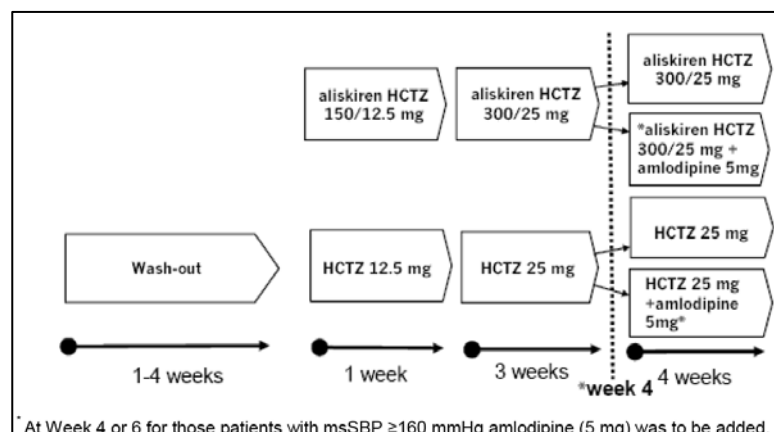
The percentage of patients achieving BP control (msSBP/msDBP <140/90 mmHg) was numerically greater for the group of patients with the aliskiren triple-combination treatment (38.5%) versus the group of patients with ramipril triple-combination treatment (28.4%) at Week 28. Similar trends were apparent for the aliskiren-triple and ramipril-triple combination at the Week 36 Endpoint (61.5% and 54.4%, respectively).

Table 4: Blood Pressure Endpoints in SPP2344 Stratified By Treatment Group (Reviewer's Table)

SPP 2344 (901 patients randomized, 896 received study med)		
	Aliskiren-based triple therapy (n=51)	Ramipril-based triple therapy (n=68)
Change From Baseline In msSBP At 36-Week Endpoint	-30.8 mmHg	-24.8 mmHg
Blood Pressure Control At 36-Week Endpoint	61.5%	54.4%

Study SPP2411 - background

Figure 6: Study Design (Study SPP2411, Sponsor's Figure)



Study SPP2411 was an 8-week randomized, double-blind, parallel-group, multicenter, active-controlled, dose-escalation study in older patients (≥ 55 years) with moderate to severe systolic hypertension (msSBP ≥ 160 mmHg and < 200 mmHg). The study evaluated the efficacy and safety of aliskiren/HCTZ combination vs. HCTZ. In patients whose BP was not controlled by aliskiren/HCTZ or HCTZ, amlodipine was added starting from Week 4. The study was conducted at 80 sites in the US. An overview of the study design is shown in Figure 6.

A total of 451 patients were randomized (228 in the aliskiren/HCTZ group and 223 in the HCTZ alone group). A total of 29 patients received aliskiren/amlodipine/HCTZ triple combination treatment.

Study SPP2411 – efficacy:

In Study SPP2411, the aliskiren/HCTZ group (with optional add-on of amlodipine) showed a clinically meaningful further reduction in msSBP/msDBP after receiving the triple combination therapy. The msSBP/msDBP reductions at Week 8 Endpoint were 33.2/11.2 mmHg, which were greater than in the HCTZ group (with optional add-on of amlodipine) (25.7/7.6 mmHg). BP control was 62.2% in the Aliskiren\HCTZ group (with optional add-on of amlodipine) versus 39.2% in the HCTZ (with optional add-on of amlodipine). BP response was 83.1% in the Aliskiren\HCTZ group (with optional add-on of amlodipine) versus 67.6% in the HCTZ (with optional add-on of amlodipine).

Table 5: Blood Pressure Endpoints in SPP2411 Stratified By Treatment Group (Reviewer's Table)

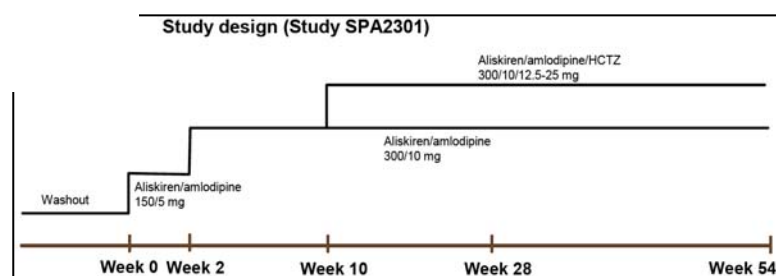
Blood Pressure Endpoints in SPP2411 Stratified By Treatment Group		
	Aliskiren/HCTZ (plus or minus Amlo)	HCTZ (plus or minus Amlo)
Change from baseline in mean sitting blood	-33.2 / -11.2	-25.7 / -7.6

pressure At 8-Week Endpoint		
Blood pressure control At 8-Week Endpoint	62.2%	39.2%
Blood pressure response At 8-Week Endpoint	83.1%	67.6%

Reviewer's comment: This study is hard to interpret in terms of the efficacy of triple therapy since patients were only uptitrated to triple therapy if they were not controlled on dual therapy alone. Moreover, the lack of placebo control makes for further challenge in interpreting these data. Finally, the fact the only 29 patients in this entire study were on Aliskiren-based triple therapy makes this is relatively non-contributory study for this particular application.

Study SPA2301 – background

Figure 7: Study Design (Study SPA2301, Sponsor's Figure)



Study SPA2301 assessed the long-term safety and efficacy of the aliskiren/amlodipine 300/10 mg combination. This was a 54-week open-label study in patients with essential hypertension (msDBP ≥ 90 mm Hg and < 110 mm Hg). For patients whose BP was not adequately controlled ($\geq 140/90$ mmHg) HCTZ was added starting from Week 10. An overview of the study design is shown in Figure 7.

SPA2301 was conducted at a total of 89 centers in 8 countries (Belgium, Switzerland, Germany, Denmark, Finland, India, Iceland, and US). A total of 86 patients received the aliskiren/amlodipine/HCTZ triple combination therapy of which 73 (84.9%) completed the study.

Study SPA2301 – efficacy:

Efficacy was a secondary objective. Overall, clinically meaningful mean reductions from baseline in msSBP (23.7 mmHg) and msDBP (14.2 mmHg) were seen at Week 54 Endpoint for those patients who had received the aliskiren/amlodipine/HCTZ triple therapy. Blood pressure control (msSBP/msDBP $< 140/90$ mmHg) at the Week 54

Endpoint was achieved by 58.1% of patients who received the aliskiren/amlodipine/HCTZ triple combination therapy during the study.

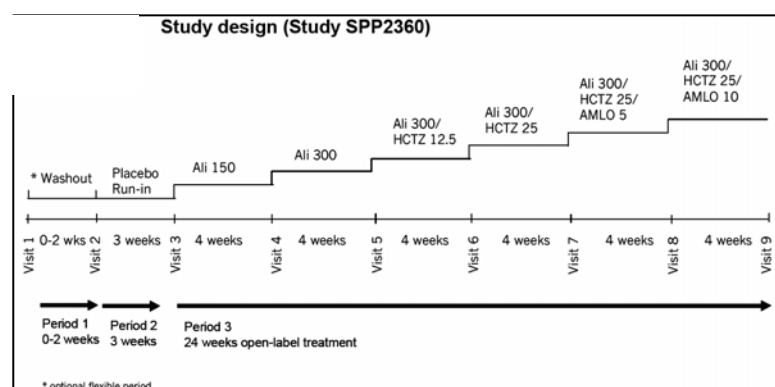
Table 6: SPA 2301 Blood Pressure Endpoints (Reviewer's Table)

SPA 2301 Blood Pressure Endpoints	
Patients on triple therapy (n=86)	
@54wks endpoint, ΔmsSBP	-23.7 / -14.2
@54wks endpoint, BP Control	58.1%

Reviewer's Comment: Since there was no comparator or control in this study, it is not possible to make efficacy conclusions from this study.

Study SPP2360 - background

Figure 8: Study Design (Study SPP2360, Sponsor's Figure)



Study SPP2360 was a 24-week open-label, non-comparative, multicenter study to assess the efficacy and tolerability of an aliskiren-based treatment algorithm in patients with mild to moderate hypertension. During the open-label active-treatment period, all patients initiated treatment with aliskiren 150 mg (up-titrated to aliskiren 300 mg), followed by the addition of HCTZ (12.5 mg up-titrated to 25 mg) and amlodipine (5 mg up titrated to 10 mg), as necessary to achieve the BP goal. Patients who met the relevant BP target were judged to be completers and terminated from the study. An overview of the study design is shown in Figure 8.

A total of 256 patients received the study treatment (119 patients in the aliskiren/amlodipine/HCTZ treatment step) at 29 centers in 4 countries (France, Hungary, Romania, and Slovakia).

Study SPP2360 – efficacy:

In SPP2360, clinically meaningful incremental reductions in msSBP/msDBP were seen from baseline in each treatment step (aliskiren monotherapy, 9.75/5.47 mmHg; aliskiren/HCTZ treatment, 17.98/7.75 mmHg; and aliskiren/amlodipine/HCTZ triple combination treatment, 27.99/13.59 mmHg), with the greatest reduction in msSBP/msDBP seen in the treatment step with the dose-escalation to aliskiren/amlodipine/HCTZ triple combination therapy.

The percentage of patients treated with the low- and high-dose aliskiren/amlodipine/HCTZ triple combination therapy who achieved BP target control (defined as msSBP/msDBP <140/90 mmHg for non-diabetic patients and msSBP/msDBP <130/80 mmHg for diabetic patients) was 31.1% (37 out of 119 patients) and 61.0% (47 out of 77 patients), respectively.

Reviewer's Comment: Since there was no comparator or control in this study, it is not possible to make efficacy conclusions from this study.

6 Review of Efficacy

Efficacy Summary

SAH2302 is the pivotal efficacy study for this application and will be the focus of discussion in Section 6 "review of efficacy".

SAH2302 was an 8-week, double-blind, randomized, parallel-group, active-controlled study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine/HCTZ in patients with moderate to severe hypertension (msSBP ≥ 160 mmHg and <200 mmHg and/or msDBP ≥ 100 mmHg and <120 mmHg).

A total of 1191 eligible patients were randomized to 1 of 4 treatment groups in a 1:1:1:1 ratio. Patient disposition was similar across all treatment groups. The majority of the patients in all treatment groups completed the study, 1106 patients (92.9%) in total.

Week 8 was the primary time point analyzed, and the primary endpoint was change from baseline of msSBP. For each patient, the last post-baseline measurement during the double-blind period was carried forward (LOCF) as the endpoint measurement. The primary comparisons performed were triple combination of (high-dose) aliskiren/amlodipine/HCTZ compared to the 3 dual combinations (aliskiren/HCTZ, aliskiren/amlodipine, and amlodipine/HCTZ). An analysis of covariance (ANCOVA) model was used for the primary analyses in the Full Analysis Set (FAS).

At the Week 8 endpoint, the LOCF analysis for the FAS showed that the (high-dose) triple combination of aliskiren/amlodipine/HCTZ had significantly greater reductions in msSBP (37.92 mmHg) than the aliskiren/amlodipine (31.37 mmHg), aliskiren/HCTZ

(27.99 mmHg), and amlodipine/HCTZ (30.77 mmHg) combination groups. Triple therapy reduced msSBP more than Aliskiren\Amlodipine by 6.55mmHg, more than Aliskiren\HCTZ by 9.93 mmHg, and more than Amlodipine\HCTZ by 7.15mmHg. Similar results were seen in the reduction in msDBP with triple combination use. MMRM and OC analyses showed similar results.

Reviewer's comment: Since there was no placebo control arm in this study, the reductions in blood pressure achieved in the various arms may very well represent overestimates of treatment effect.

Blood pressure (BP) control (<140/90 mmHg) was achieved by a significantly higher proportion of patients in the aliskiren/amlodipine/HCTZ combination group (62.3%) than compared to the dual combinations of aliskiren/HCTZ (33.1%), aliskiren/amlodipine (41.3%), and amlodipine/HCTZ (39.0%).

At Week 4 Endpoint (which marked the end of the low-dose period), statistically greater reductions in msSBP were also demonstrated with the triple combination of aliskiren/amlodipine/HCTZ (30.69 mmHg) than the aliskiren/amlodipine (25.14 mmHg), aliskiren/HCTZ (21.99 mmHg), and amlodipine/HCTZ (24.47 mmHg) combination groups. Triple therapy reduced msSBP more than Aliskiren\Amlodipine by 5.55 mmHg, more than Aliskiren\HCTZ by 8.70 mmHg, and more than Amlodipine\HCTZ did by 6.22 mmHg.

Reviewer's comment: Per comment above, since there was no placebo control arm in this study, the reductions in blood pressure achieved in the various arms may very well represent overestimates of treatment effect.

Similar trends were seen in the reduction in msDBP with triple combination use at the Week 4 Endpoint. The BP control rate at Week 4 Endpoint with the low-dose triple combination therapy (41.2%) was also statistically significantly greater ($p<0.001$) than each of the respective dual combinations of aliskiren/HCTZ (16.9%), aliskiren/amlodipine (23.7%), and amlodipine/HCTZ (20.7%).

In severe hypertension patient subpopulations (≥ 180 mmHg msSBP), the aliskiren/amlodipine/HCTZ triple combination produced statistically significant, and numerically greater reductions in msSBP/msDBP of 49.53/22.53 mmHg at the Week 8 endpoint compared to each of the respective dual combinations.

The 24-hour ABPM at the end of the 8-week treatment period showed that the triple combination (25.29 mmHg) resulted in a statistically superior reduction in mean 24-hour ambulatory SBP from baseline when compared to the aliskiren/amlodipine (20.30 mmHg), aliskiren/HCTZ (16.27 mmHg), and amlodipine/HCTZ (18.67 mmHg) combination groups. A greater decrease in mean ambulatory SBP and DBP with the

aliskiren/amlodipine/HCTZ triple combination group over the respective dual combinations was seen at every hour throughout the entire 24-hour period.

Reviewer's comment: The ability of the triple therapy to reduce ambulatory SBP over baseline to a greater extent than that achieved by the various dual therapies in each hour over the entire 24-hour period, i.e. the inter-dosing interval, lends support to once-daily dosing regimen proposed by this development program.

Plasma Renin Activity (PRA) was reduced by aliskiren/amlodipine and aliskiren/HCTZ dual-combinations (63% and 64%, respectively) and the aliskiren/amlodipine/HCTZ triple combination (34%). In contrast, amlodipine/HCTZ produced a significant increase in PRA (170%). All treatment groups produced an increase in PRC with the greatest increase seen with aliskiren/amlodipine/HCTZ triple combination (1419%) compared to the aliskiren/amlodipine (716%), aliskiren/HCTZ (721%), and amlodipine/HCTZ (158%) dual combinations.

6.1 Indication

- This product is indicated for the treatment of hypertension.
- This product is not indicated for initial therapy of hypertension.
- This product is being approved for once-daily dosing.
- The product is being approved for use as an add-on\switch therapy to provide additional blood pressure lowering for patients not adequately controlled with any two of the following antihypertensive components: aliskiren, calcium channel blockers and diuretics.
- The product is being approved as replacement therapy for patients receiving aliskiren, amlodipine and hydrochlorothiazide from separate tablets who may instead wish to receive a single fixed combination tablet containing the same component doses.

Objectives:

The primary objective of the study was to demonstrate that a once daily dosing regimen of the triple combination of aliskiren/amlodipine/HCTZ is superior to the double combinations of aliskiren/amlodipine, aliskiren/HCTZ and amlodipine/HCTZ in lowering mean sitting systolic blood pressure (msSBP) in patients with moderate to severe hypertension.

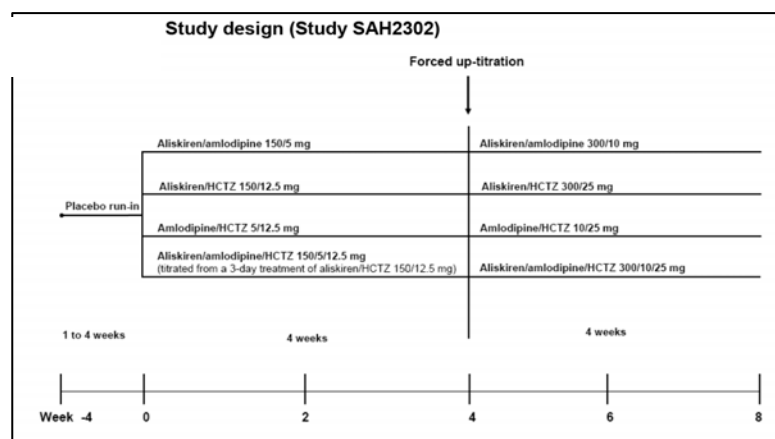
The secondary objectives include: To demonstrate that a once daily dosing regimen of the triple combination is superior to all the double combinations in lowering mean sitting diastolic blood pressure (msDBP); To evaluate the BP control rates (msSBP/msDBP < 140/90 mmHg) of the triple combination in comparison to the double combinations; To evaluate the DBP responder rates (msDBP < 90 mmHg and/or ≥ 10 mmHg reduction from baseline) of the triple combination in comparison to the double combinations; To evaluate the SBP responder rates (msSBP < 140 mmHg and/or ≥ 20 mmHg reduction

from baseline) of the triple combination to the double combinations; To evaluate the decrease in 24-hour mean ambulatory diastolic (MADBP) and systolic (MASBP) blood pressures produced by the triple combination in comparison to the double combinations in patients with moderate to severe hypertension.

6.1.1 Methods

SAH2302 is the pivotal efficacy study for this application. SAH2302 was an 8-week, double-blind, randomized, parallel-group, active-controlled, multicenter study to evaluate the efficacy and safety of the combination of aliskiren/amlodipine/HCTZ in patients with moderate to severe hypertension (msSBP ≥ 160 mmHg and < 200 mmHg and/or msDBP ≥ 100 mmHg and < 120 mmHg). The study was comprised of a washout, a single-blind placebo run-in and a double-blind treatment phase. During the first four weeks of double-blind treatment, patients received low doses of either triple combination aliskiren/amlodipine/HCTZ or double combinations of aliskiren/amlodipine, aliskiren/HCTZ, and amlodipine/HCTZ. Patients were forced to up titrate to higher doses after 4 weeks for additional 4 weeks of double-blind treatment.

Figure 9: Study Design (Study SAH2302, Sponsor's Figure)



A total of 1191 eligible patients were randomized to 1 of 4 treatment groups in a 1:1:1:1 ratio. Patient disposition was similar across all treatment groups. The majority of the patients in all treatment groups completed the study, 1106 patients (92.9%) total.

Selection of study population:

- A sample size of 984 completed patients was targeted (246 per treatment arm). Assuming a drop-out rate of 15%, 1160 patients were planned to be randomized. The sample size was calculated for the primary variable, change from baseline of msSBP, assuming a standard deviation of 15 mmHg (based on previous data). The objective was to show that the triple combination was statistically superior to all the

three corresponding double combination treatments. To achieve this objective with an overall power of 90%, the sample size was calculated to simultaneously detect a treatment difference of at least 5 mmHg for all three corresponding pairwise treatment comparisons (triple combination versus double combination), at a two-sided significance level of 0.05. Since it was necessary to show that the triple combination was statistically superior to all three double combination treatments, no multiple-comparisons adjustment of the type 1 error was needed. 1191 were randomized as follows: 287 to aliskiren/amlodipine, 298 to aliskiren/HCTZ, 296 to amlodipine/HCTZ, and 310 to aliskiren/amlodipine/HCTZ.

- Approximately 2400 male and female patients, with moderate to severe hypertension (msSBP of ≥ 160 mmHg and < 200 mmHg, and/or msDBP ≥ 100 mmHg and < 120 mmHg) were planned to be screened worldwide in order to randomize approximately 1160 patients (290 randomized patients per treatment group).
- A subset of the study population was studied for ambulatory BP. For this ambulatory BP analysis, a sample size of 592 completed patients was targeted. Assuming a drop-out rate of 15%, a total of at least 700 patients was necessary. 576 patients completed.

Inclusion criteria were as follows:

- Outpatients 18 years of age or older
- Male or female patients were eligible
- msDBP and msSBP requirements:
 - i. Diagnosis of moderate to severe hypertension (msSBP ≥ 160 mmHg and < 200 mmHg, and/or msDBP ≥ 100 mmHg and < 120 mmHg) at Visits 4, 5 or 6 (Qualifying BP visit)
 - ii. In addition, at the visit immediately prior to the above qualifying visit, patients were also to have msSBP ≥ 145 mmHg and < 200 mmHg and msDBP ≥ 95 mmHg and < 120 mmHg) at Visits 3, 5 or 5
 - iii. Patients had to meet the above two sets of requirements at subsequent adjacent visits, i.e. either Visits 3 and 4, Visits 4 and 5, or Visits 5 and 6.

OR

- i. msSBP ≥ 180 mmHg and < 200 mmHg with msDBP ≥ 95 mmHg and < 120 mmHg, or msDBP ≥ 110 mmHg and < 120 mmHg with msSBP ≥ 150 mmHg and < 200 mmHg after at least one week of treatment with placebo (Visit 3 and on).
- For patients requiring tapering off their previous antihypertensive medication, they had to meet the above criteria and completely discontinue all antihypertensive treatment prior to entering the treatment phase (placebo period) of the study.

Duration of treatment: After withdrawal of previous antihypertensive medication, if applicable, eligible patients entered a single-blind run-in placebo period of one to four weeks in duration. They were then randomized in a double-blind fashion to one of four treatment groups: aliskiren 150 mg/amlodipine 5 mg, aliskiren 150 mg/HCTZ 12.5 mg,

amlodipine 5 mg/HCTZ 12.5 mg, and aliskiren 150 mg/amlodipine 5 mg/ HCTZ 12.5 mg. After four weeks on these medications, patients were force titrated upward to aliskiren 300 mg/amlodipine 10 mg, aliskiren 300 mg/HCTZ 25 mg, amlodipine 10 mg/HCTZ 25 mg, and aliskiren 300 mg/amlodipine 10 mg/HCTZ 25 mg for another four weeks. Other dose variation was not permitted during this study.

Week 8 Endpoint was the primary endpoint analyzed. The primary endpoint was the change from baseline in msSBP (trough). For each patient, the last post-baseline measurement during the double-blind period was carried forward (LOCF) as the endpoint measurement. The primary comparisons performed were triple combination of (high-dose) aliskiren/amlodipine/HCTZ compared to the 3 dual combinations (aliskiren/HCTZ, aliskiren/amlodipine, and amlodipine/HCTZ). An analysis of covariance (ANCOVA) model with treatment and region as two factors, and baseline as a covariate was used for the primary analyses in the FAS. Three pair-wise treatment comparisons (triple combination versus the three dual therapies) were made based on the primary model. The triple combination was considered more effective than the dual therapies if all pair-wise comparisons were statistically significant in its favor. The statistical test for each of the pair-wise comparisons was made at the two-sided significance level of 0.05.

A supplementary model with treatment-by-region and treatment-by-baseline terms added to the primary model, with treatment and region as two factors, and the baseline as covariate, was used to assess treatment-by-region and treatment-by-baseline interactions.

Demographics

Baseline demographics for patients in the pivotal efficacy trial (SAH2302) were as follows (see also Table 7 below).

Age:

Mean age 55.1 years. 80.9% of patients were less than 65 years old and 19.1% were $\geq$ 65. 3.5% of all patients were $\geq$ 75 years old. Percentage of patients in each age group was similar across treatment groups.

Sex:

More male patients than female patients participated in the study (60.5% vs. 39.5%). Distribution of sexes was similar across all treatment groups.

Race:

Caucasian patients accounted for the majority (84.1%) of the study population followed by Black patients (10.0%). The number of patients of other races was small (5.9%).

Ethnicity:

The majority of the population (approximately 91%) was from 'Other' ethnicity, though 6.4% of the study population was Hispanic/ Latino in ethnicity.

BMI:

Approximately half of the patients (48.8%) were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) with the majority (85.1%) of patients having a $\text{BMI} \geq 25 \text{ kg/m}^2$.

Diabetes:

14.4% of all patients had a diagnosis of diabetes.

Renal metrics:

4.2% of patients had a glomerular filtration rate (eGFR) between 30 and 60 ml/min/1.73m² and 59.1% had an eGFR between 60 and 90 ml/min/1.73m². The remainder of patients (36.7% of total study population) had a rate $\geq 90 \text{ ml/min/1.73m}^2$.

Hypertension (mean duration):

The patients in this population had a mean duration of hypertension of 9.4 years, which was similar between treatment groups (mean duration was between 9.1 and 9.7 years).

Table 7: Demographics By Treatment Group (Randomized Set) Group B: Study SAH2302; short term, double blind, all controlled studies (Sponsor's Table)

Treatment Group	Number of patients	Age (yrs) Mean (SD)	Sex n (%)	
			Male	Female
Ali/Aml	287	54.4 (11.33)	172 (59.9)	115 (40.1)
Ali/HCTZ	298	55.5 (10.75)	175 (58.7)	123 (41.3)
Aml/HCTZ	296	55.1 (10.86)	186 (62.8)	110 (37.2)
Ali/Aml/HCTZ	310	55.4 (10.54)	187 (60.3)	123 (39.7)
Total	1191	55.1 (10.86)	720 (60.5)	471 (39.5)

Treatment Group	Race n (%)					
	Caucasian	Black	Asian	Native American	Pacific islander	Other
Ali/Aml	244 (85.0)	26 (9.1)	10 (3.5)	0 (0.0)	0 (0.0)	7 (2.4)
Ali/HCTZ	251 (84.2)	31 (10.4)	10 (3.4)	1 (0.3)	0 (0.0)	5 (1.7)
Aml/HCTZ	244 (82.4)	35 (11.8)	10 (3.4)	0 (0.0)	0 (0.0)	7 (2.4)
Ali/Aml/HCTZ	263 (84.8)	27 (8.7)	12 (3.9)	1 (0.3)	1 (0.3)	6 (1.9)
Total	1002 (84.1)	119 (10.0)	42 (3.5)	2 (0.2)	1 (0.1)	25 (2.1)

Treatment Group	BMI status n (%)				Diabetes n (%)	
	BMI < 20 kg/m ²	20 ≤ BMI < 25 kg/m ²	25 ≤ BMI < 30 kg/m ²	BMI ≥ 30 kg/m ²	Yes	No
Ali/Aml	1 (0.3)	35 (12.2)	97 (33.8)	153 (53.3)	46 (16.0)	241 (84.0)
Ali/HCTZ	2 (0.7)	51 (17.1)	105 (35.2)	139 (46.6)	40 (13.4)	258 (86.6)
Aml/HCTZ	2 (0.7)	40 (13.5)	117 (39.5)	137 (46.3)	53 (17.9)	243 (82.1)
Ali/Aml/HCTZ	0 (0.0)	43 (13.9)	114 (36.8)	152 (49.0)	33 (10.6)	277 (89.4)
Total	5 (0.4)	169 (14.2)	433 (36.4)	581 (48.8)	172 (14.4)	1019 (85.6)

Treatment Group	eGFR (ml/min/1.73 m ²) n(%)		
	30 ≤ GFR < 60 ml/min/1.73m ²	60 ≤ GFR < 90 ml/min/1.73 m ²	GFR ≥ 90 ml/min/1.73 m ²
Ali/Aml	10 (3.5)	174 (60.6)	103 (35.9)
Ali/HCTZ	11 (3.7)	168 (56.4)	119 (39.9)
Aml/HCTZ	11 (3.7)	186 (62.8)	99 (33.4)
Ali/Aml/HCTZ	18 (5.8)	176 (56.8)	116 (37.4)
Total	50 (4.2)	704 (59.1)	437 (36.7)

6.1.3 Subject Disposition

In the pivotal efficacy study, SAH2302, 1909 patients were enrolled, of which 1191 were randomized to the double blind study, two of whom were randomized erroneously. Overall, of the 1191 randomized, 1106 completed (92.9%) and 83 discontinued (7.0%). This pattern was mimicked in all treatment groups. Completion and discontinuation rates for the various treatment arms were as follows: Aliskiren\Amlodipine was 92.7% and 7.3%, Aliskiren\ HCTZ was 92.6% and 7.0%, Amlodipine \ HCTZ was 94.3% and 5.7%, and triple therapy was 91.9% and 7.7%. Discontinuations due to AEs were slightly more frequent in the aliskiren/amlodipine/HCTZ group (3.5%) compared to the aliskiren/amlodipine (2.4%), aliskiren/HCTZ (0.7%) and amlodipine/HCTZ (2.7%) groups. (See Table 8 below for more details on patient disposition.)

Reviewer's comment: completion and discontinuation rates were similar across all treatment groups. The overall discontinuation rate of 7.0% seems reasonable for an 8-week study.

Table 8: Patient Participation And Withdrawal, Group B: Study SAH2302, Short-Term, Double-Blind, All Controlled Studies (Sponsor's Table)

Treatment Group	Randomized	Treated n (%)	Completed n (%)	Discontinued n(%)			
				Total	Safety	Lack of efficacy	Other
Ali/Aml	287	287 (100.0)	266 (92.7)	21 (7.3)	8 (2.8)	2 (0.7)	11 (3.8)
Ali/HCTZ	298 *	297 (99.7)	276 (92.6)	21 (7.0)	5 (1.7)	3 (1.0)	13 (4.4)
Aml/HCTZ	296	295 (99.7)	279 (94.3)	17 (5.7)	10 (3.4)	1 (0.3)	6 (2.0)
Ali/Aml/HCTZ	310 *	309 (99.7)	285 (91.9)	24 (7.7)	13 (4.2)	2 (0.6)	9 (2.9)

Safety = Adverse event(s), death, abnormal laboratory values, abnormal test procedure result(s).
Other = Administrative problems, subject's condition no longer requires study drug, lost to follow up, subject withdrawal consent, protocol deviation or other.

6.1.4 Analysis of Primary Endpoint(s)

Primary endpoint was msSBP (trough) at study endpoint (8 weeks). At the Week 8 Endpoint, the (high-dose) triple combination of aliskiren/amlodipine/HCTZ showed significantly greater reductions from baseline in msSBP (37.92 mmHg) as compared to aliskiren/amlodipine (31.37 mmHg), aliskiren/HCTZ (27.99 mmHg), and amlodipine/HCTZ (30.77 mmHg). Subtracting these outcomes from one another demonstrates that triple therapy reduced msSBP more than Aliskiren\Amlodipine by 6.55mmHg, more than Aliskiren\HCTZ by 9.93 mmHg, and more than Amlodipine\HCTZ by 7.15mmHg. (These data can be found in Table 10 below.) Similar results were seen in the reduction in msDBP with triple combination use.

Reviewer's Comments: Using the Full Analysis Set provided by the sponsor, the reviewer confirmed the efficacy results for the primary endpoint of the change from baseline of msSBP at the end of Week 8 for LOCF analysis data. The reviewer also

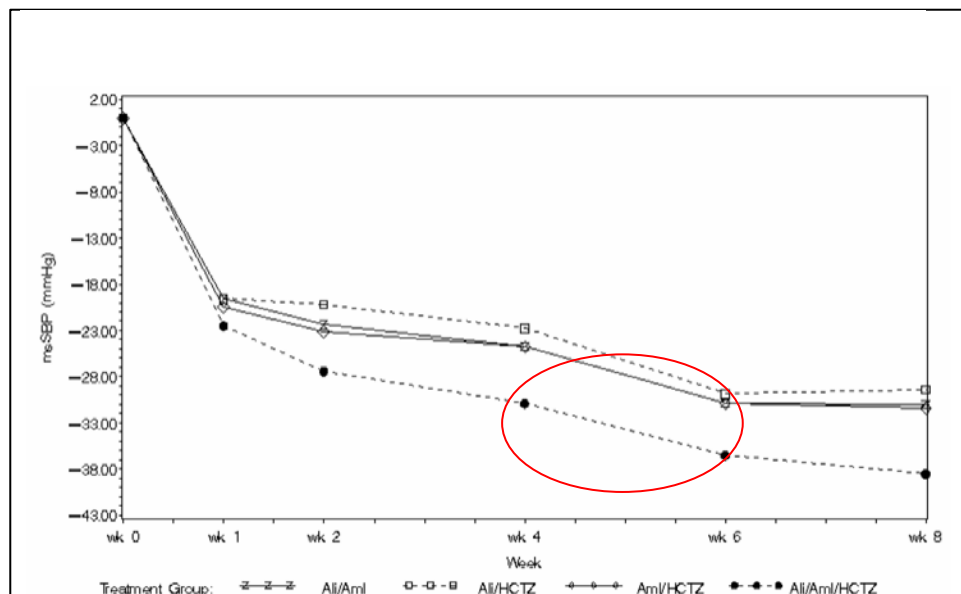
derived the efficacy results for the observed case (OC) analysis data and that derived using the mixed model repeated measurement (MMRM) procedure at Week 8. These methods also gave statistically significant results, supporting the LOCF analyses. This is not surprising given the missing data are not heavy (about 7%). From the reviewer's findings, the statistical superiority of the triple combination over all the dual combinations was confirmed for Weeks 6 and 8. The OC and MMRM analysis results are similar to those depicted in Table 9 which was derived using LOCF analysis. Notice that Week 4 is the time at which all the patients received higher dose of medications, so the efficacy results at Week 4 do not represent the true treatment effect, therefore are not considered here.

Reviewer's comment: Since there was no placebo control arm in this study, the reductions in blood pressure achieved in the various arms may very well represent overestimates of treatment effect. Nevertheless, the subtracted reductions demonstrate that triple therapy was significantly more effective in lowering msSBP than any of the dual therapies.

Table 9: Efficacy Results For The Change From Baseline In Mean Sitting Systolic Blood Pressure At Week 8 Endpoint (Full Analysis Set) (Reviewer's Table).

Pairwise Comparison	LSM differences in change from baseline (SE)	95% CI for LSM difference	P-value
OC Analysis			
Ali/Aml/HCTZ vs Ali/Aml	-7.09 (1.20)	(-9.44, -4.73)	<0.001
Ali/Aml/HCTZ vs Ali/HCTZ	-9.98 (1.19)	(-12.31, -7.65)	<0.001
Ali/Aml/HCTZ vs Aml/HCTZ	-7.63 (1.19)	(-9.97, -5.30)	<0.001
MMRM Analysis			
Ali/Aml/HCTZ vs Ali/Aml	-7.06 (1.20)	(-9.41, -4.71)	<0.001
Ali/Aml/HCTZ vs Ali/HCTZ	-10.05 (1.19)	(-12.38, -7.73)	<0.001
Ali/Aml/HCTZ vs Aml/HCTZ	-7.61 (1.18)	(-9.93, -5.29)	<0.001

Figure 10: Mean Change From Baseline In msSBP by treatment group and week (FAS)-Study SAH2302 (Sponsor's Figure)



Reviewer's comment: In Figure 10 above, high dose therapy begins at Week 4. Note that significant reduction in BP occurs over the succeeding two weeks. Note further that additional reductions in BP occur in the two weeks following that. This suggests that maximal reductions in BP may need more than two weeks on high dose triple combination therapy.

Protocol Deviation #1:

It came to FDA's attention, late in the review process, that conduct of SAH2302 was flawed at times in regards to the manner in which msSBP measurements were collected. Specifically, according to protocol, three msSBP measurements were to be taken at each visit where msSBP is collected, spaced apart by 1-2 minutes. Moreover, if any msSBP reading was ≥ 10 mmHg different from one of the other two readings then another set of readings was to be taken. If this second set of readings produced another aberrant set, then this aberrant set was considered acceptable and was to be used as the reading for that study visit. However, in reviewing their site data late in the review calendar, sponsor has discovered that there were occasions where this rule of taking a second set of readings on aberrancy in the first set was not universally enforced. However, since aberrant readings are acceptable readings if they were collected during the second reading, it is unknown what fraction of aberrant readings are legitimate second-set readings versus which are illegitimate first-set readings. What is known is that 33-39% of baseline readings were aberrant and 24-32% of study endpoint readings were as well. To address this concern, sponsor conducted an analysis of msSBP data with the full analysis set and a separate analysis of msSBP

data excluding all patients who had aberrant msSBP readings in their baseline and 8-week endpoint readings. Sponsor successfully demonstrates that triple therapy achieved a statistically significant win over all the dual therapies in both the FAS and the analysis that excludes individuals with aberrancy at both baseline and study endpoint. The same analysis was conducted on these two populations (the FAS and the population that excluding aberrant readings) for msDBP. See Table 10 and Table 11 below for the data.

Reviewer's Comment: The issue of aberrant readings getting accepted into the study is satisfactorily addressed by the sponsor since:

- 1. The study was well blinded, and the aberrancy was well distributed across the treatment groups.*
- 2. Primary endpoint was satisfied in a statistically significant manner even when excluding from analysis those patients who had aberrant readings at both baseline and study endpoint.*

Table 10: msSBP Endpoints In FAS versus FAS Excluding "Aberrant" patients (Reviewer's Table)

SYSTOLIC		
Δ msSBP from baseline to 8 weeks		
Treatment Group	FAS	FAS excluding patients who had aberrant readings at both baseline and endpoint
Ali/Aml 300/10 mg	-31.37	-30.8
Ali/HCTZ 300/25 mg	-27.99	-26.5
Aml/HCTZ 10/25 mg	-30.77	-29.0
TRIPLE THERAPY	-37.92	-39.1

SYSTOLIC		
Triple therapy vs Dual therapy - subtracted reductions in msSBP from baseline to 8 weeks		
	FAS	FAS excluding patients who had aberrant readings at both baseline and endpoint
Triple vs. Ali\Aml	-6.55	-8.3
Triple vs. Ali\HCTZ	-9.93	-12.6
Triple vs. Aml\HCTZ	-7.15	-10.1

Table 11: msDBP Endpoints In FAS versus FAS Excluding "Aberrant" patients (Reviewer's Table)

DIASTOLIC		
Δ msDBP from baseline to 8 weeks		

<i>Treatment Group</i>	<i>FAS</i>	<i>FAS excluding patients who had aberrant readings at both baseline and endpoint</i>
Ali/Aml 300/10 mg	-18.03	-19.2
Ali/HCTZ 300/25 mg	-14.32	-12.3
Aml/HCTZ 10/25 mg	-17.03	-16.4
TRIPLE THERAPY	-20.63	-20.6

<i>DIASTOLIC</i>		
<i>Triple therapy vs Dual therapy - subtracted reductions in msDBP from baseline to 8 weeks</i>		
	<i>FAS</i>	<i>FAS excluding patients who had aberrant readings at both baseline and endpoint</i>
Triple vs. Ali\Aml	-2.60	-1.4
Triple vs. Ali\HCTZ	-6.31	-8.3
Triple vs. Aml\HCTZ	-3.60	-4.2

Protocol Deviation #2:

Similar to the protocol deviation #1, very late in the review calendar, sponsor shared with FDA that they discovered a protocol deviation. Specifically, that a large number of patients were randomized into the SAH2302 without having proper inclusion criteria satisfied. This amounted to 13.5% of all randomized patients. Most of the errors surrounded the issue of BP criteria, which were highly complicated. In addition to these 13.5% ,there were 2.2% of randomized patients who were associated with other major protocol deviations. To address these issues of concern, sponsor conducted additional analyses of the primary endpoint looking at both the FAS as well as the population of patients excluding those that were associated with these major protocol deviations. Per **Table 13** below, which list the results of these analyses, primary endpoint was satisfied with statistical significance in either the FAS or the modified analysis.

Reviewer's Comment: Per my comment on protocol deviation #1, this deviation appears to be satisfactorily addressed by the sponsor since:

- 1. The study was well blinded, the deviations of concern occurred pre-randomization, so the deviations should be well distributed across the treatment groups.*
- 2. In the dataset provided by the sponsor, the PPS set contains 79.44% of a total of 1182 patients in the FAS population. That excludes the patients that did not satisfy the proper inclusion criteria. Excluding those who are not in the PPS, and those who had baseline and endpoint aberrant readings, the total number of patients is 493. The reviewers conducted the efficacy analyses on this data set for the primary endpoints msSBP and the secondary endpoint msDBP using the same statistical model as the primary efficacy analysis. The efficacy results are given in the following table. It shows that the primary endpoint was still*

statistically significant even after excluding those patients who associated with both protocol deviations.

Table 12: Efficacy Results For the Change From Baseline In Mean Sitting Systolic and Diastolic Blood Pressure At Week 8 Endpoint (PPS set after removing the Removing the Patients with Aberrant Readings) (Reviewer's Table).

Pairwise Comparison	LSM differences in change from baseline (SE)	95% CI for LSM difference	P-value
msSBP			
Ali/Aml/HCTZ vs Ali/Aml	-8.77 (1.66)	(-12.02, -5.52)	<0.001
Ali/Aml/HCTZ vs Ali/HCTZ	-13.21 (1.73)	(-16.60, -9.81)	<0.001
Ali/Aml/HCTZ vs Aml/HCTZ	-10.43 (1.67)	(-13.70, -7.15)	<0.001
msDBP			
Ali/Aml/HCTZ vs Ali/Aml	-3.05 (1.07)	(-5.16, -0.94)	<0.005
Ali/Aml/HCTZ vs Ali/HCTZ	-8.69 (1.11)	(-10.87, -6.50)	<0.001
Ali/Aml/HCTZ vs Aml/HCTZ	-4.79 (1.08)	(-6.91, -2.67)	<0.001

Table 13: Within And Between Treatment Analysis For Change From Baseline In Mean Sitting Systolic Blood Pressure (msSBP) At Week 8 Endpoint (Full Analysis Set And Per Protocol Set) (Sponsor's Table)

	N		Baseline Mean (SE)		Change from baseline Mean (SE)	
	FAS	PPS	FAS	PPS	FAS	PPS
Ali/Aml	282	225	171.52 (0.76)	171.86 (0.85)	-30.62 (0.92)	-31.72 (1.02)
Ali/HCTZ	296	234	173.25 (0.79)	174.52 (0.86)	-28.21 (0.98)	-30.11 (1.05)
Aml/HCTZ	295	233	173.25 (0.77)	173.75 (0.86)	-30.82 (0.94)	-32.12 (1.07)
Ali/Aml/HCTZ	308	247	171.77 (0.75)	172.14 (0.85)	-37.38 (1.02)	-39.40 (1.08)
Pair wise comparison			LSM difference in change from baseline (SE)		p-value	
			FAS	PPS	FAS	PPS
Ali/Aml/HCTZ vs Ali/Aml			-6.55 (1.22)	-7.51 (1.31)	< 0.001*	< 0.001*
Ali/Aml/HCTZ vs Ali/HCTZ			-9.93 (1.21)	-10.59 (1.30)	< 0.001*	< 0.001*
Ali/Aml/HCTZ vs Aml/HCTZ			-7.15 (1.21)	-8.04 (1.30)	< 0.001*	< 0.001*

SE – Standard Error
FAS – Full Analysis Set
PPS – Per Protocol Set (excluding major protocol deviations)
LSM – Least Square Mean
* indicates statistical significance at 0.05 level for the change from baseline

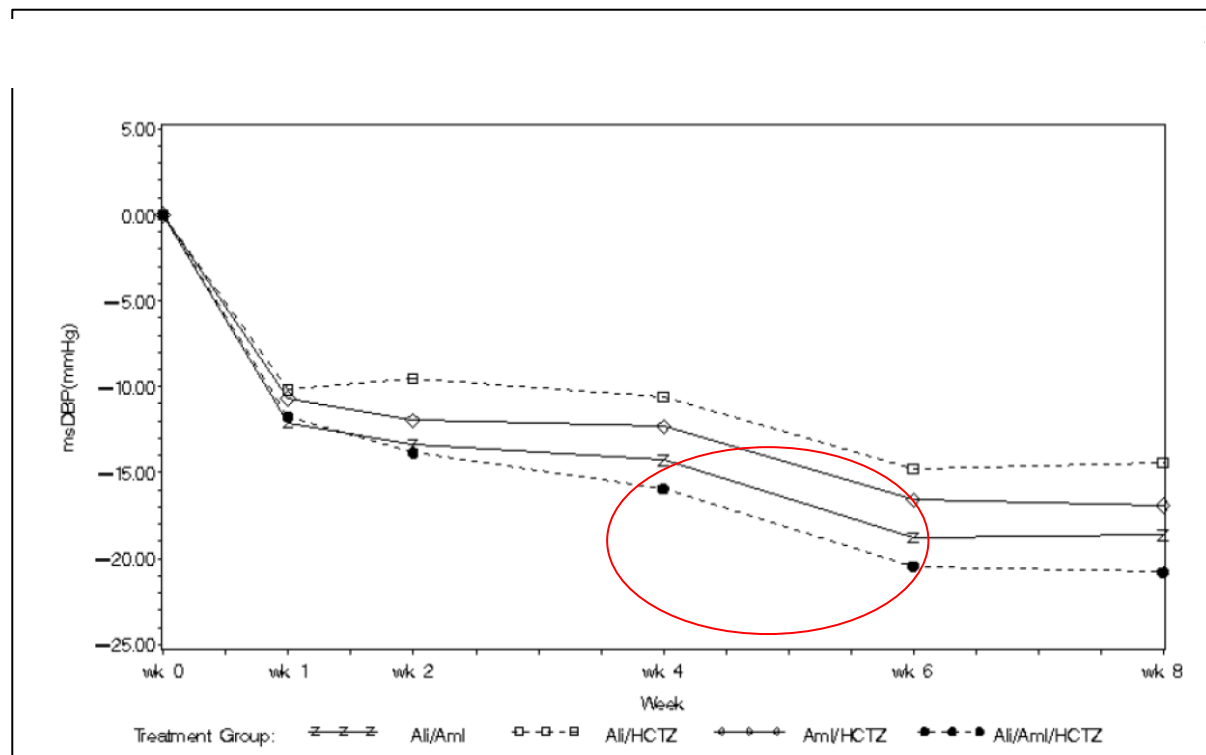
6.1.5 Analysis of Secondary Endpoints(s)

msDBP -- Change from baseline at 8-weeks:

At the Week 8 Endpoint, the (high-dose) triple combination of aliskiren/amlodipine/HCTZ showed significantly greater reductions from baseline msSBP (20.63 mmHg) as compared to aliskiren/amlodipine (18.03 mmHg), aliskiren/HCTZ (14.32 mmHg), and amlodipine/HCTZ (17.03 mmHg). Subtracting these outcomes from one another demonstrates that triple therapy reduced msSBP more than Aliskiren\Amlodipine by 2.60mmHg, more than Aliskiren\HCTZ by 6.30 mmHg, and more than Amlodipine\HCTZ by 3.59mmHg. (These data can be found in Figure 11 and Table 14 and Table 15.)

Reviewer's comment: The reviewer conducted similar statistical analysis and confirmed the sponsor's efficacy results. In addition, OC data analysis and MMRM procedure also give similar results that show some robustness of the efficacy results on the change from baseline of msDBP at Week 8.

Figure 11: Mean Change from Baseline in msDBP by treatment group and week (FAS)-Study SAH2302 (Sponsor's Figure)



Reviewer's comment: In Figure 11 above, patients begin high dose treatment at Week 4. It is clear that the majority, if not the entirety of the reduction in msDBP brought upon by the high dosing is achieved by Week 6, with only negligible subsequent reduction taking place from Week 6 to 8. This is in distinction to the msSBP profile described above in Section 6.1.4 where further reductions do in fact take place from Week 6 to Week 8.

Table 14: Subtracted Reduction From Baseline in msDBP At Week 8 Endpoint (Reviewer's Table)

Subtracted reduction in msDBP (@8wk over baseline)	
Treatment Group	Subtracted reduction in msDBP at 8wk over baseline (mmHg)
Triple therapy vs Ali\Aml	-2.60
Triple therapy vs Ali\HCTZ	-6.30
Triple therapy vs Aml\HCTZ	-3.59

Reviewer's comment: Note that the benefit of triple therapy over Aliskiren\Amlodipine in terms of msDBP is a reduction of only 2.60 mmHg. Comparing this figure to the effect of food on Aliskiren (as discussed in Section 4.4.3 above) yields an interesting observation. Per Section 4.4.3 above, our analysis of Aliskiren's food effect data shows that food diminishes the effects of Aliskiren on msDBP by approximately 2mmHg. Therefore, the 2.6mmHg benefit (in terms of msDBP) of switching from Aliskiren\Amlo dual therapy to triple therapy may essentially be achieved by simply staying on Aliskiren\amlo and switching from fed to fasting administration (again, assuming one's administration was fed).

Had diastolic BP been the primary endpoint of this trial, I would say that this endpoint failed in terms of triple therapy versus Aliskiren\Amlo. However, diastolic BP is not the primary endpoint of this trial. Rather, msSBP is the primary. And, as discussed above, the margin of demonstrated efficacy for msSBP is satisfactory. Therefore, overall I support approving the benefit of triple therapy for those uncontrolled on Aliskiren\amlo.

Reviewer's comment: As evidenced in Table 14, triple therapy is superior to each dual therapy (by -2.60 to -6.30 mmHg). This margin of superiority is not as large in magnitude as that demonstrated for msSBP (see Table 10 above), which ranged from -6.55 to -9.93 mmHg. Nonetheless, the pattern is the same with triple therapy demonstrating superiority on both endpoints.

Table 15: Reduction From Baseline in msDBP At Week 8 Endpoint (Reviewer's Table)

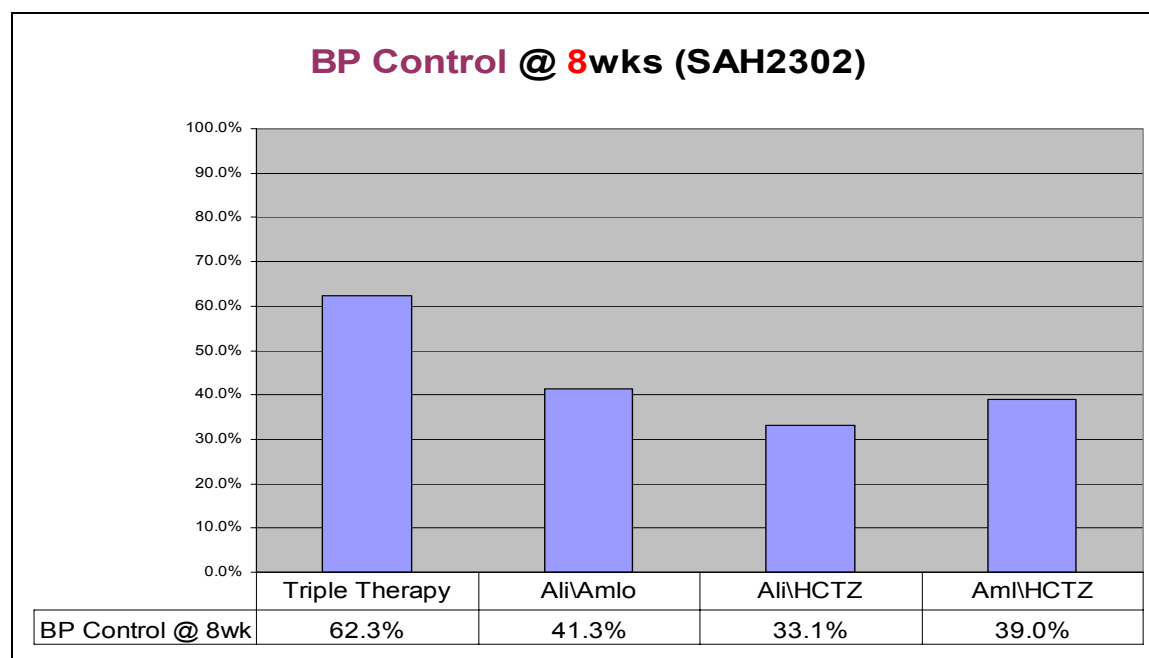
Change in msDBP (@8wk over baseline)	
Treatment Group	Δ msDBP from baseline, @8wk
Ali/Aml 300/10 mg	-18.03
Ali/HCTZ 300/25 mg	-14.32
Aml/HCTZ 10/25 mg	-17.03
Ali/Aml/HCTZ 300/10/25 mg	-20.63

BP control at 8 weeks:

Blood pressure (BP) control (<140/90 mmHg) was achieved by a significantly higher proportion of patients in the aliskiren/amlodipine/HCTZ combination group (62.3%) compared to the dual combinations of aliskiren/HCTZ (33.1%), aliskiren/amlodipine (41.3%), and amlodipine/HCTZ (39.0%). Both chi-square test and logistic regression adjusted for the baseline blood pressure give statistically significant results indicating that the triple combination group of aliskiren/amlodipine/HCTZ improves all three dual combination groups in increasing the percentage of blood control at Week 8 with both LOCF and OC data.

Reviewer's comment: Though triple therapy did demonstrate superiority over all the dual therapies in terms of BP control, since Brandname is being approved as add-on or switch therapy rather than an initial therapy, the endpoint of BP control is not particularly relevant.

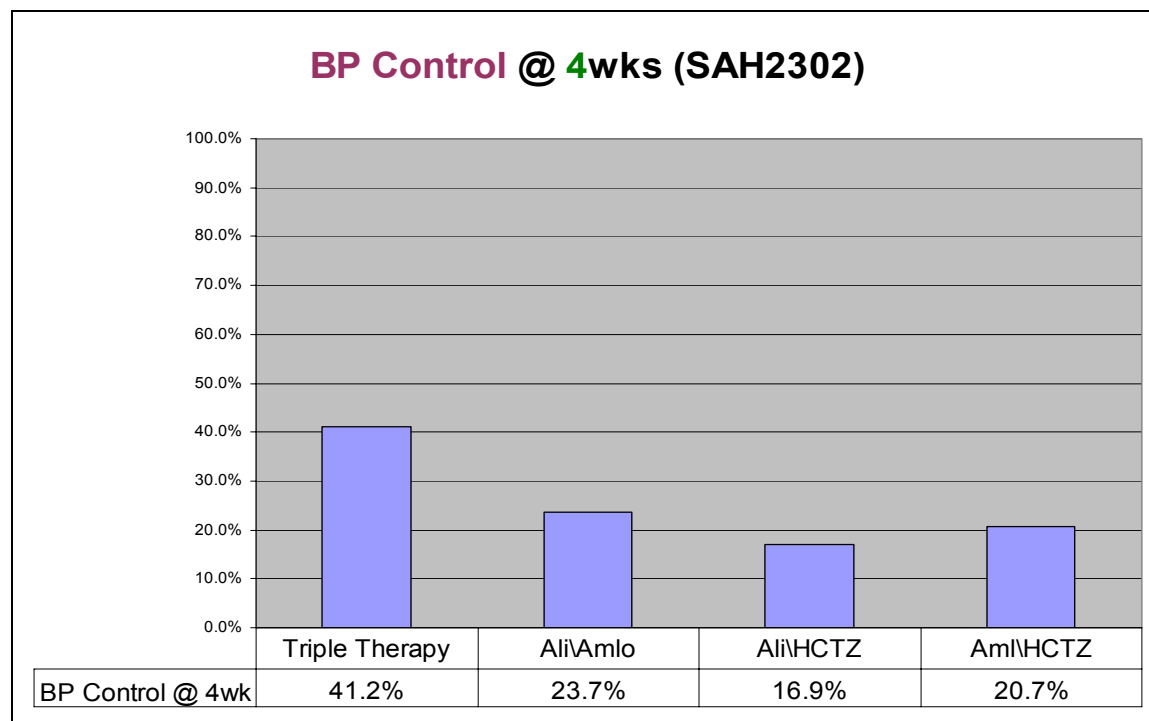
Figure 12: Blood Pressure Control at Week 8 Endpoint (SAH2302, Reviewer's Figure)



BP control at 4 weeks:

Blood pressure (BP) control (<140/90 mmHg) was achieved by a significantly higher proportion of patients in the aliskiren/amlodipine/HCTZ combination group (41.2%) than compared to the dual combinations of aliskiren/HCTZ (23.7%), aliskiren/amlodipine (16.9%), and amlodipine/HCTZ (20.7%).

Figure 13: Blood Pressure Control at Week 4 Endpoint (SAH2302, Reviewer's Figure)



msSBP at 4-weeks:

At Week 4 Endpoint during the low-dose triple combination period, statistically greater reductions in msSBP were also demonstrated with the triple combination of aliskiren/amlodipine/HCTZ (30.69 mmHg) than the aliskiren/amlodipine (25.14 mmHg), aliskiren/HCTZ (21.99 mmHg), and amlodipine/HCTZ (24.47 mmHg) combination groups. Triple therapy reduced msSBP more than Aliskiren\Amlodipine by 5.55 mmHg, more than Aliskiren\HCTZ by 8.70 mmHg, and more than Amlodipine\HCTZ did 6.22 mmHg.

Reviewer's comment: Per comment above, since there was no placebo control arm in this study, the reductions in blood pressure achieved in the various arms may very well represent overestimates of treatment effect.

Figure 14: Change From Baseline in msSBP at Week 4 Endpoint (SAH2302, Reviewer's Figure)

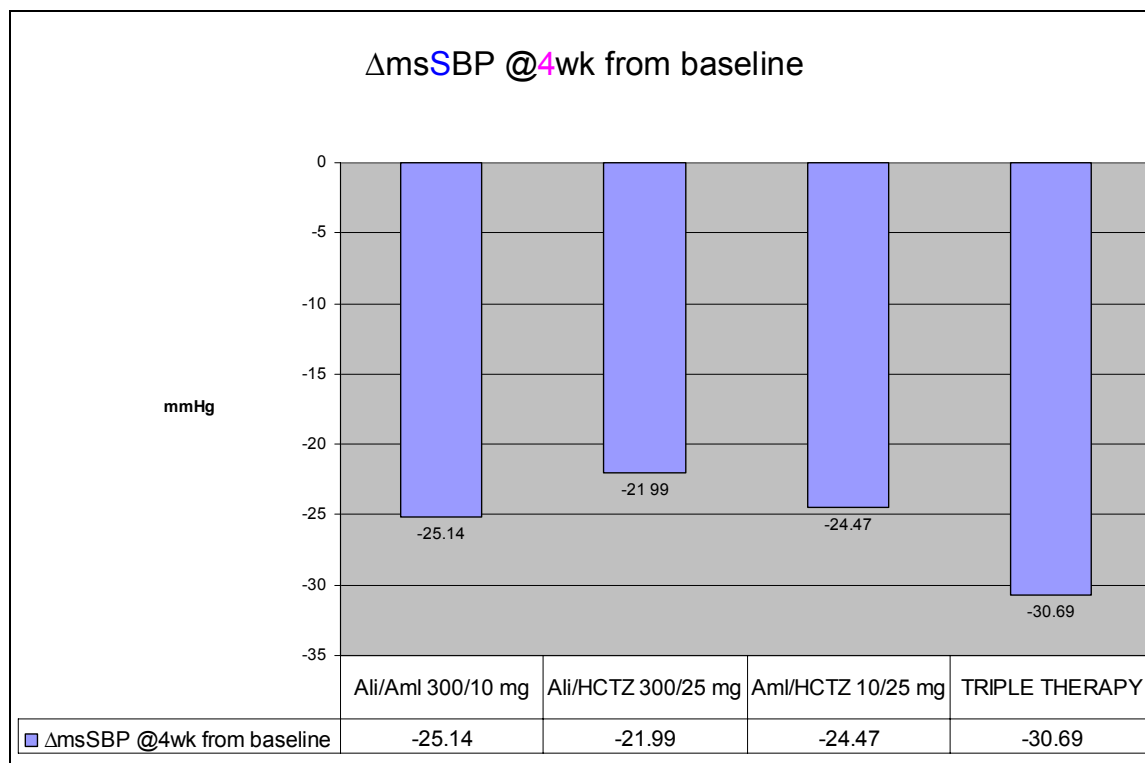


Table 16: Subtracted Reduction From Baseline in msSBP At Week 4 Endpoint (Reviewer's Table)

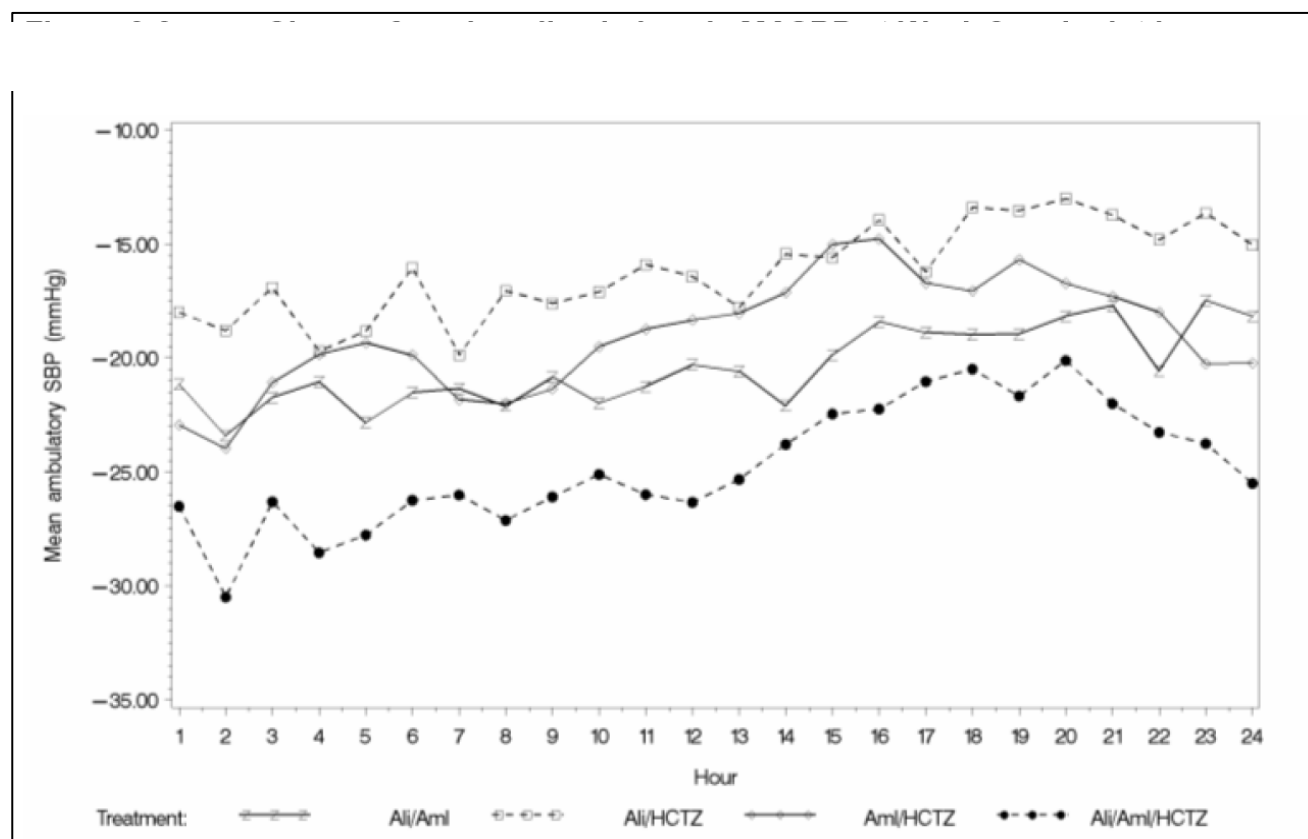
Subtracted reduction in msSBP (@4wk over baseline)	
Treatment Group	Subtracted reduction in msSBP at 4wk over baseline (mmHg)
Triple therapy vs Ali\Aml	-5.55
Triple therapy vs Ali\HCTZ	-8.70
Triple therapy vs Aml\HCTZ	-6.22

Similar trends were seen in the reduction in msDBP with triple combination use at the Week 4 Endpoint. The BP control rate at Week 4 Endpoint with the low-dose triple combination therapy (41.2%) was also statistically significantly greater ($p < 0.001$) than each of the respective dual combinations of aliskiren/HCTZ (16.9%), aliskiren/amlodipine (23.7%), and amlodipine/HCTZ (20.7%).

Ambulatory BP:

The 24-hour ABPM at the end of the 8-week treatment period showed that the triple combination resulted in a statistically superior ($p < 0.001$) reduction in mean 24-hour ambulatory SBP from baseline (25.29 mmHg) than each of the aliskiren/amlodipine (20.30 mmHg), aliskiren/HCTZ (16.27 mmHg), and amlodipine/HCTZ (18.67 mmHg) combination groups. A greater decrease in mean ambulatory SBP and DBP with the aliskiren/amlodipine/HCTZ triple combination group over the respective dual combinations was seen at every hour throughout the entire 24-hour period.

Figure 15: Change from Baseline in hourly mean ambulatory systolic blood pressure (MASBP) at Week 8 endpoint by post-dosing hour and treatment (FAS) – Study SAH2302 (Sponsor’s Figure)



Reviewer’s comment: The ability of the triple therapy to reduce ambulatory SBP over baseline to a greater extent than that achieved by all the dual therapies in each hour over the entire 24-hour period, i.e. the inter-dosing interval, lends support to once-daily dosing regimen proposed by this development program.

6.1.6 Other Endpoints

PRA was reduced by aliskiren/amlodipine and aliskiren/HCTZ dual-combinations (63% and 64%, respectively) and the aliskiren/amlodipine/HCTZ triple combination (34%). In contrast amlodipine/HCTZ produced a significant increase in PRA (170%). All treatment groups produced an increase in PRC with the greatest increase seen with aliskiren/amlodipine/HCTZ triple combination (1419%) compared to the aliskiren/amlodipine (716%), aliskiren/HCTZ (721%), and amlodipine/HCTZ (158%) dual combinations.

Figure 16: Plasma Renin Activity (PRA) (Reviewer's Figure)

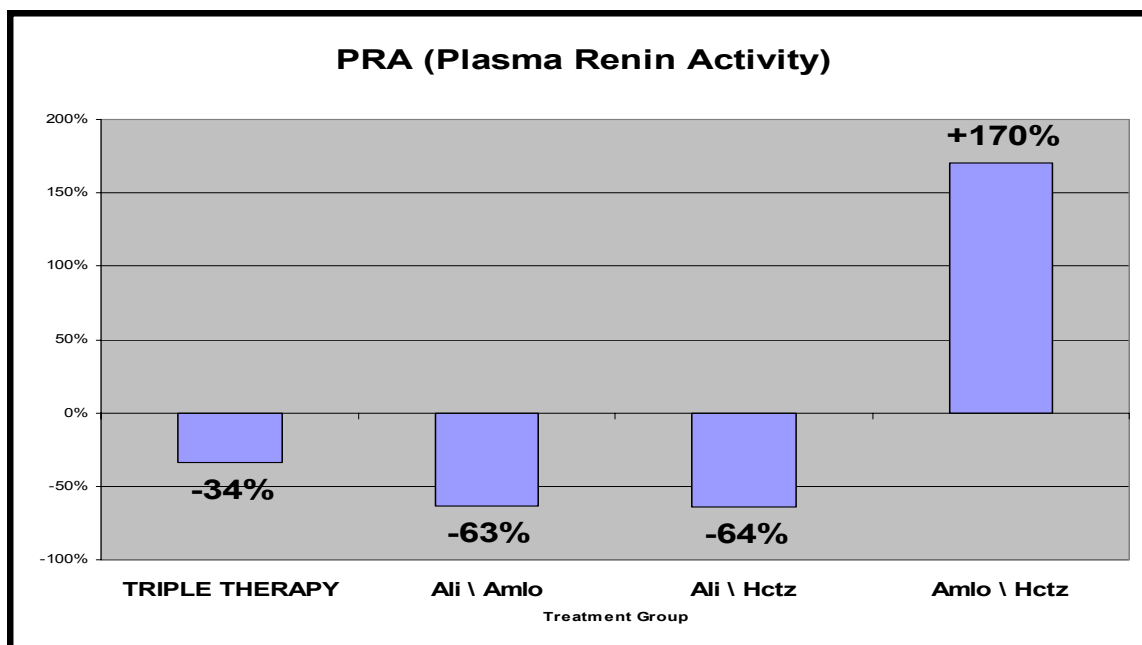
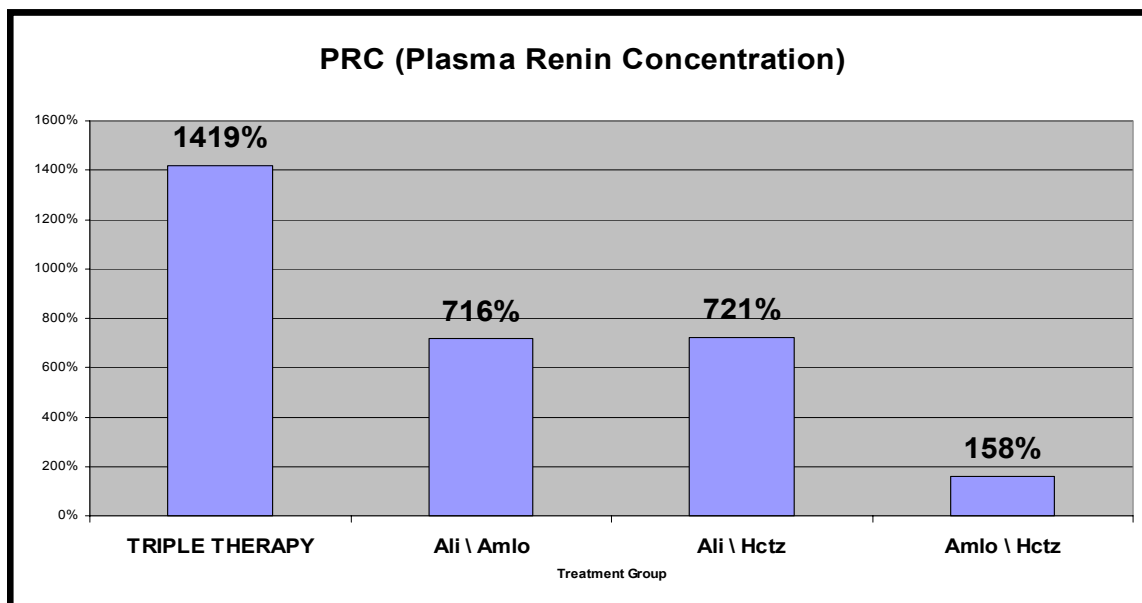


Figure 17: Plasma Renin Concentration (Reviewer's Figure)



Reviewer's comment: The presumed mechanism for Aliskiren's reduction of PRA is as follows: Aliskiren binds renin, thereby reducing renin activity. Binding to Aliskiren renders renin inactive. However, it does not diminish renin's concentration. In fact, the binding of renin by Aliskiren may trigger greater production of renin, to compensate for the inactivated renin. The net effect is that Aliskiren will dramatically reduce renin activity (PRA) but will raise renin concentration (PRC).

6.1.7 Subpopulations

Age:

The patients were separated into three age groups: less than 65, 65 to 75, and greater than 75 years of age. They contained 954 (80.9%), 186 (19.1%) and 42 (3.5%) patients, respectively. In the ANCOVA analysis for comparing triple therapy with dual therapies for the change from baseline of msSBP at Week 8, age group as a factor was statistically significant, indicating the differences of the treatment effect over age groups. The triple therapy group was consistently superior in reducing msSBP as compared to each dual therapy, regardless of age group, as depicted in Table 17 below,

Table 17: Efficacy Results For The Change From Baseline In Mean Sitting Systolic Blood Pressure At Week 8 Endpoint For Age Groups (LOCF Analysis In Full Analysis Set) (Reviewer's Table).

Pairwise Comparison	LSM differences in change from baseline (SE)	95% CI for LSM difference
<65 Years		
Ali/Aml/HCTZ vs Ali/Aml	-6.25 (1.33)	(-8.86, -3.64)
Ali/Aml/HCTZ vs Ali/HCTZ	-9.59 (1.32)	(-12.18, -7.01)
Ali/Aml/HCTZ vs Aml/HCTZ	-6.27 (1.33)	(-8.88, -3.66)
From 65 to 75 Years		
Ali/Aml/HCTZ vs Ali/Aml	-5.73 (3.43)	(-12.51, 1.05)
Ali/Aml/HCTZ vs Ali/HCTZ	-10.56 (3.47)	(-17.42, -3.71)
Ali/Aml/HCTZ vs Aml/HCTZ	-8.49 (3.20)	(-14.81, -2.17)
Above 75 Years		
Ali/Aml/HCTZ vs Ali/Aml	-14.82 (7.25)	(-29.60, -0.05)
Ali/Aml/HCTZ vs Ali/HCTZ	-15.53 (6.82)	(-29.43, -1.64)
Ali/Aml/HCTZ vs Aml/HCTZ	-20.59 (8.04)	(-36.97, -4.21)

“Race”:

The patient population consists of 5 different races: Caucasian (996 patients, 84.1%), Black (118 patients, 10.0%), Asian (41 patients, 3.5%), Native American (2 patients, <1%), Pacific Islander (1 patient, <1%) and Others (24 patients, 2%). Since the sizes of the last three groups are too small, we only compare the triple therapy group with the dual therapy groups in the first three race groups. In the ANCOVA analysis for the comparison of triple therapy with dual therapies for the change from baseline of msSBP at Week 8, race as a factor was statistically significant, indicating the difference of the treatment effect over race groups. As depicted in Table 18 below, triple therapy was significantly superior in reducing msSBP as compared to each dual therapy in these three race groups.

Table 18: Efficacy Results For The Change From Baseline In Mean Sitting Systolic Blood Pressure At Week 8 Endpoint For Age Groups (LOCF Analysis In Full Analysis Set) (Reviewer's Table).

Pairwise Comparison	LSM differences in change from baseline (SE)	95% CI for LSM difference
Caucasian		
Ali/Aml/HCTZ vs Ali/Aml	-6.69 (1.33)	(-9.30, -4.07)
Ali/Aml/HCTZ vs Ali/HCTZ	-9.41 (1.32)	(-12.00, -6.82)
Ali/Aml/HCTZ vs Aml/HCTZ	-6.34 (1.33)	(-8.95, -3.72)
Black		

Ali/Aml/HCTZ vs Ali/Aml	-5.61 (4.03)	(-13.59, 2.37)
Ali/Aml/HCTZ vs Ali/HCTZ	-10.36 (3.81)	(-17.92, -2.82)
Ali/Aml/HCTZ vs Aml/HCTZ	-9.80 (3.71)	(-17.15, -2.45)
Asian		
Ali/Aml/HCTZ vs Ali/Aml	-2.92 (7.37)	(-17.89, 12.05)
Ali/Aml/HCTZ vs Ali/HCTZ	-19.06 (7.26)	(-33.81, -4.31)
Ali/Aml/HCTZ vs Aml/HCTZ	-9.01 (7.43)	(-24.12, 6.10)

Ethnicity:

6.4% of the study population was Hispanic/Latino in ethnicity. The majority of the population (approximately 91%) was from 'Other' ethnicity. As shown in Figure 18 below, triple therapy beat all dual therapies in lowering msSBP for "other ethnicity" and "Hispanic\Latino" ethnicities. (Several other ethnicities were too small in number to be meaningfully included in this analysis.)

Table 19: Subtracted Reduction From Baseline in msSBP (mmHg) At Week 8 Endpoint, SAH2302, Latino\Hispanic vs other (Reviewer's Table)

<i>Subtracted Reduction From Baseline in msSBP (mmHg) At Week 8 Endpoint, SAH2302, Latino\Hispanic vs other</i>		
	<i>Other ethnicity (n=1078)</i>	<i>Latino\Hispanic (n=76)</i>
Triple vs. Ali\Aml	-6.7	-9.4
Triple vs. Ali\HCTZ	-8.6	-17.4
Triple vs. Aml\HCTZ	-6.4	-5.0

Sex

Notice there are 715 (60.5%) male patients and 467 (39.5%) female patients. In the ANCOVA analysis for the comparison of triple therapy with dual therapies for the change from baseline of msSBP at Week 8, sex as a factor was statistically significant, indicating the difference of the treatment effect between male and female groups. Conducting the comparisons separately, the triple therapy group was superior in reducing msSBP as compared to each dual therapy in both male and female groups, as depicted in Table 20 below.

Table 20: Efficacy Results For The Change From Baseline In Mean Sitting Systolic Blood Pressure At Week 8 Endpoint For Sexes (LOCF Analysis In Full Analysis Set) (Reviewer's Table).

Pairwise Comparison	LSM differences in change from baseline (SE)	95% CI for LSM difference
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Male		
Ali/Aml/HCTZ vs Ali/Aml	-5.68 (1.49)	(-8.61, -2.76)
Ali/Aml/HCTZ vs Ali/HCTZ	-8.28 (1.49)	(-11.19, -5.36)
Ali/Aml/HCTZ vs Aml/HCTZ	-7.08 (1.47)	(-9.95, -4.20)
Female		
Ali/Aml/HCTZ vs Ali/Aml	-7.73 (1.94)	(-11.55, -3.91)
Ali/Aml/HCTZ vs Ali/HCTZ	-12.43 (1.90)	(-16.16, -8.69)
Ali/Aml/HCTZ vs Aml/HCTZ	-6.54 (1.95)	(-10.37, -2.71)

Region

The study was conducted in six different regions consisting of a total of 12 countries. In the efficacy analyses, these 12 countries were grouped into 6 regions: USA, Canada, Germany, North West Europe, North East Europe and Rest of Europe and Australia. In the ANCOVA analysis for the comparison of the triple therapy with dual therapies for the change from baseline of msSBP at Week 8, region as a factor was statistically significant, indicating the difference of the treatment effect over region groups. We further separate the regions into US and non-US, and conduct the comparisons separately, the triple therapy group was superior in reducing msSBP as compared to each dual therapy in both US and non-US regions, as depicted in Table 21 below.

Table 21: Efficacy Results For The Change From Baseline In Mean Sitting Systolic Blood Pressure At Week 8 Endpoint For US And Non US Patients (LOCF Analysis In Full Analysis Set) (Reviewer's Table).

Pairwise Comparison	LSM differences in change from baseline (SE)	95% CI for LSM difference
US		
Ali/Aml/HCTZ vs Ali/Aml	-7.03 (2.27)	(-7.03, -2.57)
Ali/Aml/HCTZ vs Ali/HCTZ	-9.93 (2.24)	(-14.33, -5.52)
Ali/Aml/HCTZ vs Aml/HCTZ	-9.31 (2.25)	(-13.74, -4.88)
Non-U.S.		
Ali/Aml/HCTZ vs Ali/Aml	-6.26 (1.50)	(-9.20, -3.33)
Ali/Aml/HCTZ vs Ali/HCTZ	-9.90 (1.48)	(-12.80, -7.00)
Ali/Aml/HCTZ vs Aml/HCTZ	-6.30 (1.48)	(-9.21, -6.54)

Severe Hypertensives:

In severe hypertension patients (≥ 180 mmHg msSBP), the aliskiren/amlodipine/HCTZ triple combination produced reductions in msSBP/msDBP of 49.53/22.53 mmHg at the Week 8 endpoint which was statistically significant compared to each of the respective dual combinations. The efficacy result for the severe hypertensive patients for both the change from baseline of msSBP and msDBP are given in Table 22 and Table 23, respectively. Severe hypertensives receiving triple therapy reached BP control at a

lower rate than all hypertensives receiving triple therapy (57.5% vs. 62.3%, respectively).

Table 22: Between Treatment Analysis For Change From Baseline In Mean Sitting Systolic Blood Pressure At Week 8 Endpoint – Severe Hypertension Patients (Sponsor’s Table)

Table 11-9 Between treatment analysis for change from baseline in mean sitting systolic blood pressure at Week 8 endpoint – Severe hypertension patients (Full analysis set)			
Treatment group	N	LSM change from baseline (SE)	
Alii/Aml 300/10 mg	83	-38.10 (1.82)	
Alii/HCTZ 300/25 mg	111	-33.22 (1.59)	
Aml/HCTZ 10/25 mg	108	-39.94 (1.61)	
Alii/Aml/HCTZ 300/10/25 mg	106	-49.53 (1.61)	
Pairwise comparison	LSM difference in change from baseline (SE)	95% CI for LSM difference	p-value
Alii/Aml/HCTZ vs Alii/Aml	-11.42 (2.40)	(-16.14, -6.71)	<0.001*
Alii/Aml/HCTZ vs Alii/HCTZ	-16.31 (2.22)	(-20.68, -11.9)	<0.001*
Alii/Aml/HCTZ vs Aml/HCTZ	-9.58 (2.24)	(-13.98, -5.19)	<0.001*
SE = standard error; LSM = least squares mean; CI = confidence interval. Least squares means, confidence intervals, and p-values were from an ANCOVA model containing treatment, region and baseline. P-Values and treatment comparisons were evaluated at the average baseline level. * indicates statistical significance at 0.05 level.			

Table 23: Efficacy results for the change from baseline in mean sitting diastolic blood pressure at Week 8 endpoint for the severe hypertension group (Full analysis set). (Reviewer’s Table)

Pairwise Comparison	LSM differences in change from baseline (SE)	95% CI for LSM difference	P-value
Alii/Aml/HCTZ vs Alii/Aml	-4.92 (1.39)	(-7.66, 2.19)	<0.001
Alii/Aml/HCTZ vs Alii/HCTZ	-8.20 (1.29)	(-10.73, -5.66)	<0.001
Alii/Aml/HCTZ vs Aml/HCTZ	-4.76 (1.29)	(-7.31, -2.22)	<0.001

The proportion of severe hypertensive patients with BP control at Week 8 endpoint was greater and statistically significant ($p < 0.001$) in the aliskiren/amlodipine/HCTZ 300/10/25 mg triple combination compared to each of the double combination groups. The proportion of patients achieving BP control in the aliskiren/amlodipine/HCTZ triple combination group was 57.5% compared to 16.2% to 25.0% in the double combination groups.

Reviewer's comment: In the subgroup analysis for severe hypertensives ($180 \leq \text{msSBP} < 200$), triple therapy beat all dual therapies on the endpoint of msSBP and msDBP. This is relevant because severe hypertensives are perhaps more likely than mild or moderate hypertensives to require triple therapy to control or reduce their hypertension.

Reviewer's comment: BP control by Week 8 was better in all patients (62.3%) than in severe hypertensives (57.5%). But this is to be expected as the starting BP in the hypertensives is higher to begin with, by definition.

Diabetics:

There were a total of 171 diabetic patients and 1011 non-diabetic patients. In the ANCOVA analysis for the comparison of the triple therapy with dual therapies for msSBP at Week 8, being diabetics as a factor was highly statistically significant, but not the interaction between treatment indicator and diabetic factor. This may indicate a high diabetic effect but not a big difference in the superiority of the triple therapy over the dual therapies in the diabetic and non-diabetic groups. Triple therapy beat all double therapies in reducing msSBP at Week 8 from baseline for non-diabetics, but for diabetics the superiority of the triple therapy is only statistically significant in Ali/HCTZ, not in the other two dual therapies, see the following table. Due to the similarity of the magnitude of the effect of triple therapy over the dual therapies in both diabetic and non-diabetic groups, the lack of significance could be due to the smaller sample size.

Table 24: Efficacy Results For The Change From Baseline In Mean Sitting Systolic Blood Pressure At Week 8 Endpoint In Diabetic And Non-Diabetic Patients (LOCF Analysis In Full Analysis Set) (Reviewer's Table).

Pairwise Comparison	LSM differences in change from baseline (SE)	95% CI for LSM difference
Diabetics		
Ali/Aml/HCTZ vs Ali/Aml	-3.12 (3.96)	(-10.95, 4.71)
Ali/Aml/HCTZ vs Ali/HCTZ	-10.27 (4.10)	(-18.37, -2.17)
Ali/Aml/HCTZ vs Aml/HCTZ	-4.09 (3.85)	(-11.70, 3.51)
Non-diabetics		
Ali/Aml/HCTZ vs Ali/Aml	-6.51 (1.27)	(-9.00, -4.02)
Ali/Aml/HCTZ vs Ali/HCTZ	-9.62 (1.24)	(-12.05, -7.19)
Ali/Aml/HCTZ vs Aml/HCTZ	-7.01 (1.26)	(-9.48, -4.53)

BMI:

Approximately half of the patients (48.8%) were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) with the majority (85.1%) of patients having a $\text{BMI} \geq 25 \text{ kg/m}^2$.

At week 8 endpoint, triple therapy beat all dual therapies in lowering msSBP, in all BMI subgroups.

Table 25: Subtracted Reduction From Baseline in msSBP (mmHg) At Week 8 Endpoint Stratified by BMI, SAH2302 (Reviewer's Table)

	20<BMI<25		25<BMI<30		BMI≥30	
	subtracted reduction in msSBP (mmHg)	n	subtracted reduction in msSBP (mmHg)	n	Subtracted reduction in msSBP (mmHg)	n
Triple vs. AliAml	-10.0	43 vs. 34	-4.9	114 vs. 96	-6.8	151 vs. 151
Triple vs. AliHCTZ	-14.1	43 vs. 51	-10.0	114 vs. 105	-7.4	151 vs. 138
Triple vs. AmlHCTZ	-12.6	43 vs. 39	-9.2	114 vs. 117	-6.2	151 vs. 137

Reviewer's comment: triple therapy appears to be successful in reducing msSBP regardless of BMI subgroup, with the exception of BMI<20, for which insufficient data was present (there were only 5 patients with BMI<20 in the entire study).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Regulatory approval is being sought for the aliskiren/amlodipine/HCTZ fixed combination dose strengths of 150/5/12.5, 300/5/12.5, 300/5/25, 300/10/12.5 and 300/10/25mg. Dosing schedule is to be once daily. The pivotal study (SAH2302) assessed both the lowest- (150/5/12.5 mg) and highest-doses(300/10/25 mg) of aliskiren/amlodipine/HCTZ triple combination therapy. The key long-term safety study (SAH2301) evaluated the triple combination at the highest dose of 300/10/25 mg. In other supportive studies, additional doses of 300/5/25 mg and 300/10/12.5 were also received by certain patients. All studies used once daily dosing. All of these individual component drugs and dose strengths are already approved via their respective monotherapy programs. Moreover, all three component drug products (Aliskiren, Amlodipine, HCTZ) are already approved for once daily dosing.

Regulatory approval is being sought for the fixed-dose triple combinations to be replacement therapy for the titrated components. In addition, a patient whose BP is not adequately controlled by either dual component alone is to be switched to the aliskiren/amlodipine/HCTZ combination once-daily to achieve BP control. Finally, for patients on combination therapy, if BP remains uncontrolled, this approval would allow for the dose(s) of one or all of the components to be increased.

Reviewer's comment: I am inclined to support approval of these dosages and approval of once daily dosing for several reasons. One, the fact that all three drug components are already approved for once daily dosing. Two, the fact the highest and lowest dosage combination have been tested in the pivotal efficacy trial

(SAH2302). Three, the fact that all the monotherapy dosages are already approved and are already approved for once daily dosing. Four, the fact that this is not being approved as initial therapy.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Mean ambulatory blood pressure measurements were taken in a subset of patients in the pivotal efficacy study (SAH2302). This demonstrated a significantly greater reduction (at 8week endpoint over baseline) in ambulatory systolic blood pressure at every hour of the day for the full 24 hours inter-dosing interval for triple therapy as compared to each dual therapy (see Figure 15 above).

Persistence of effect over long term was tested to some extent in the pivotal safety trial, SAH2301. SAH2301 examined the efficacy of the aliskiren/amlodipine/HCTZ triple combination in patients with essential hypertension (msDBP ≥ 100 and < 120 mmHg, and/or msSBP ≥ 160 and < 200 mmHg) up to a 54-week treatment period. A total of 497 patients were treated with aliskiren/amlodipine/HCTZ triple combination therapy for at least 6 months (≥ 180 days) and 182 patients for at least 1 year (≥ 360 days). As early as 2 weeks after the patients had received the full dose of the triple combination of aliskiren/amlodipine/HCTZ, significant reductions in msSBP and msDBP were observed as was BP control. These were maintained throughout the 54 week Endpoint.

The effect on treatment withdrawal was not studied with triple therapy.

Reviewer's comment: Given that a withdrawal study was not conducted, (b) (4)

6.1.10 Additional Efficacy Issues/Analyses

n/a.

7 Review of Safety

Safety Summary

The safety analysis was based on analysis of the six clinical studies supporting this NDA. These studies are listed in Table 2. The safety profile of this combination drug is acceptable for the following reasons.

- The safety profile for aliskiren/amlodipine/HCTZ was consistent with that previously known for aliskiren, amlodipine, or HCTZ when used as monotherapy or as dual combination.

- There were no unexpected safety findings in the clinical program. There were no deaths in any patients who took triple therapy.
- The incidence and severity of total and individual adverse events for aliskiren/amlodipine/HCTZ treatment were generally similar to the component dual combination treatments.
- Peripheral edema, a known side effect of amlodipine, occurred more in treatment groups containing amlodipine. The aliskiren/amlodipine/HCTZ showed slightly less reported peripheral edema than aliskiren/amlodipine treatment. Peripheral edema were mostly mild to moderate in severity and rarely led to patient discontinuation.
- With the exception of peripheral edema, there was no increase in AE incidence and severity when the dose of aliskiren/amlodipine/HCTZ was increased from 150/5/12.5 mg to 300/10/25 mg. AEs potentially related to low blood pressure such as hypotension, orthostatic hypotension, syncope and dizziness occurred at low incidence and rarely led to patient discontinuation in patients treated with aliskiren/amlodipine/HCTZ.
- Hyperkalemia occurred uncommonly with the treatment of aliskiren/amlodipine/HCTZ triple combination with the incidence similar to the component dual combinations. No case of angioedema was reported in the entire clinical program.
- Aliskiren/amlodipine/HCTZ was generally well-tolerated regardless of gender, age or race.
- Changes in laboratory parameters observed with aliskiren/amlodipine/HCTZ were generally minor and consistent with the known effect of aliskiren, amlodipine, or HCTZ. There were no meaningful differences between aliskiren/amlodipine/HCTZ triple combination and component dual combinations.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Six completed clinical trials are being used to support this NDA. All six were completed prior to submission of the NDA and all six were analyzed in this safety review. See section 5.1 for a listing of the six trials. Of the six studies supporting this NDA, two (SPP2344 and SPA2301) were submitted as part of prior FDA submissions; the remaining four were submitted as part of this submission.

Table 26: Summary of Efficacy and Safety Studies (Reviewer's Table)

Summary of Efficacy and Safety Studies							
#	Study	N (treated)	Design	Duration	Drugs	Control	Endpoint

1	MAJOR PIVOTAL TRIAL (SAH2302)	1188	double blind, active-controlled, four-group, parallel study, evaluating efficacy of triple therapy vs dual therapies	8wk	Aliskiren, Amlodipine, HCTZ	Active Control	Δfrom baseline msSBP
2	MAJOR SAFETY TRIAL (SAH2301)	564	open label, evaluating long term safety of triple therapy	28wk-54wk	Aliskiren, Amlodipine, HCTZ	No control	Δfrom baseline msDBP, msSBP
3	(supportive study) SPP2344	896 (only 51 on triple therapy)	double blind, active controlled study evaluating Ali-based regimen vs Ramipril based regimen in elderly hypertensives	36wk	Aliskiren, Amlodipine, HCTZ, Ramipril	Active Control	Δfrom baseline msSBP
4	(supportive study) SPP2411	450 (only 29 on triple therapy)	double blind, parallel group, active controlled dose escalation study evaluation Ali\HCTZ vs HCTZ	8wk	Aliskiren, Amlodipine, HCTZ	Active Control	Δfrom baseline msSBP
5	(supportive study) SPA2301	556 (only 86 on triple therapy)	open label study evaluating long term safety and efficacy of al\amlo with optional HCTZ	54wk	Aliskiren, Amlodipine, HCTZ	Active Control	Δfrom baseline msDBP, msSBP
6	(supportive study) SPP2360	256 (119 on triple therapy)	open label, non-comparative study, patients treated with Ali-based regiment, with optional add-on of HCTZ and amlo	24wk	Aliskiren, Amlodipine, HCTZ	No control	Proportion of patients who reached the BP target

7.1.2 Categorization of Adverse Events

Information about AEs and SAEs was collected in all clinical trials. An AE was defined as any undesirable sign, symptom or medical condition occurring after starting study

drug even if the event was not considered to be related to study drug. AEs could be volunteered by the subject, discovered during general questioning by the investigator or detected through physical examination, laboratory test or other means. Medical conditions/diseases present before starting study treatment were only considered AEs if they worsened after starting study treatment.

AEs occurring before starting study treatment but after signing the informed consent form were recorded on the Medical History/Current Medical Conditions Case Report Form (CRF). As far as possible, each AE was also described by its duration (start and end dates), the severity grade (mild, moderate, severe), its relationship to the study drug (suspected/not suspected), the actions taken, and the outcome.

An SAE was defined as an event which was fatal or life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability or incapacity, constituted congenital anomaly or a birth defect, or was medically significant in that it may have jeopardized the subject and could have required medical or surgical intervention to prevent one of the outcomes listed above.

The AE terms used were the preferred terms included in the Medical Dictionary for Drug Regulatory Affairs (MedDRA). The incidence of AEs (new or worsened) was summarized by primary system organ class, preferred term, severity, and relationship to study drug.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety population is comprised of all patients from the six aforementioned clinical trials who received at least one dose of study drug. Studies were pooled in the following manner.

Populations were organized into 3 groups (see Table 27) according to the type of clinical trial. This grouping system is a standard Novartis procedure.

Table 27: Population Groupings For Safety Assessment (Sponsor's Table)

Database	Studies	Total number of patients treated (safety population)/ No. of patients treated with aliskiren/amlodipine/HCTZ
Safety Dataset Group B (short-term, double-blind, all controlled)	SAH2302	1188/ 309
Safety Dataset Group C (all long-term, open-label studies)	SAH2301, SPA2301	1120/ 647
Safety Dataset Group D (long-term, double-blind study)	SPP2344	896/ 51

- Group A comprises the safety population from placebo controlled trials. Since no such trials exist in this NDA, this Group is empty.
- Group B comprises the pooled safety populations from the short-term, double-blind, active controlled studies (SAH2302)
- Group C comprises the pooled safety populations from the long-term, open-label studies (SAH2301, SPA2301)
- Group D comprises the pooled safety populations from the long-term, double-blind study (SPP2344)

Only four of the six clinical studies (SAH2302, SAH2301, SPA2301, SPP2344) were assigned to the various groupings above. Studies SPP2360 and SPP2411 were not included in these groupings because of particular study design attributes which made it inappropriate to pool them with any of the groupings in Table 27. SPP2360's unique attribute was its open-label forced termination of patients with BP control prior to add-on of aliskiren/amlodipine/HCTZ. SPP2411's unique attribute was the short duration of aliskiren/amlodipine/HCTZ treatment (2-4 weeks). As a result, safety analysis of these two studies will be addressed independent from the safety analysis conducted on groups B\C\D. This approach of excluding these two studies from the B\C\D groupings was agreed upon by FDA in a letter from DCRP dated 9\29\2009.

Reviewer's comment: I find this pooling scheme to be reasonable given that:

- *the groupings in Table 27 above are logical groupings based on study design*
- *it was agreed upon in advance between sponsor and FDA*
- *Novartis practices this grouping method with other applications and did not devise this schema solely for this application*

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, 3910 patients were included in this development program. Of these, 1155 were exposed to triple therapy. 568 were exposed to triple therapy for 6 months, and 182 for 12 months. (See Figure 18 and Table 28 below.)

Reviewer's comment: ICH E1 (1995) requires that any new chemical entity have:

- *at least 1500 patients have short term exposure to the test drug*
- *at least 300-600 patients be exposed to the test drug for at least 6 months*
- *some number of patients be exposed to the drug for at least 12 months (though no specific number is given for this milestone).*

While this development program clearly satisfies the second of third of these requirements (568 patients exposed to test drug for 6 months, and 182 for 12 months), there is an insufficient number of patients exposed to triple therapy for

short term exposure (only 1155 instead of the requisite 1500). However, I am inclined to allow this exception given that this drug is not a purely new chemical entity; it is, rather, a fixed combination of three approved drugs. Moreover, the individual monotherapies that comprise this "new" drug product have had hundreds of thousands to millions of doses sold, giving a very large post-marketing safety base for the constituent monotherapy programs. (b) (4)

Figure 18: Number of Patients On Triple Therapy For Given Duration (days) - All Studies (Reviewer's Figure)

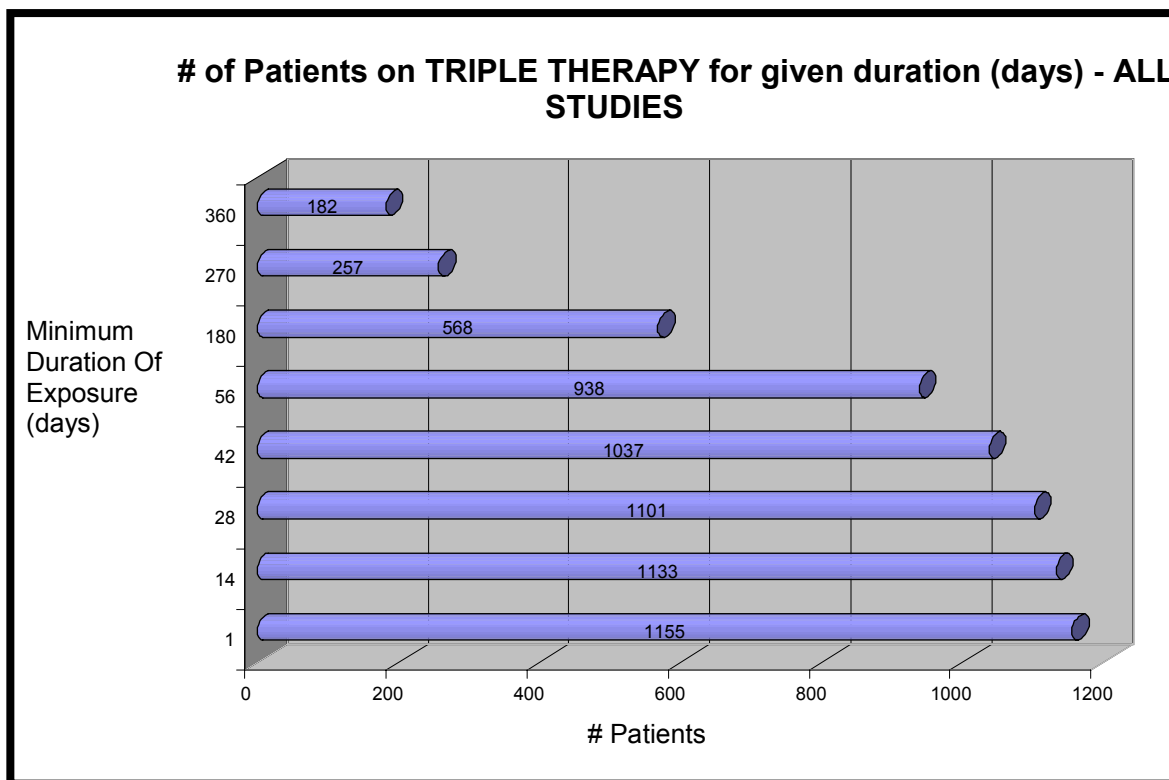


**Table 28: Duration Of Exposure To Study Drug (Safety Set), All Studies
(Sponsor's Table)**

Duration of Exposure (days)	Ali/Aml/ HCTZ N=1155	Ali/Aml N=843	Ali/HCTZ N=1490	Mono Ali N=708	Ramipril/Aml/ HCTZ N=68
≥ 1	1155 (100.0)	843 (100.0)	1490 (100.0)	708 (100.0)	68 (100.0)
≥ 14	1133 (98.1)	827 (98.1)	902 (60.5)	676 (95.5)	68 (100.0)
≥ 28	1101 (95.3)	818 (97.0)	877 (58.9)	651 (91.9)	65 (95.6)
≥ 42	1037 (89.8)	800 (94.9)	814 (54.6)	622 (87.9)	65 (95.6)
≥ 56	938 (81.2)	736 (87.3)	686 (46.0)	576 (81.4)	58 (85.3)
≥180	568 (49.2)	412 (48.9)	4 (0.3)	172 (24.3)	0 (0.0)
≥270	257 (22.3)	394 (46.7)	0 (0.0)	3 (0.4)	0 (0.0)
≥360	182 (15.8)	372 (44.1)	0 (0.0)	0 (0.0)	0 (0.0)
Statistics					
n	1155	843	1490	708	68
Mean	159.3	211.1	45.3	108.9	82.5
SD	120.99	155.54	43.22	82.99	24.21
Median	126.0	138.0	55.0	83.0	97.0
Minimum	2	1	1	1	16
Maximum	392	407	195	284	125

Duration of Exposure (days)	Ramipril/ HCTZ N=244	Aml/HCTZ N=345	Mono Ramipril N=443	HCTZ N=223	Total N=3910
≥ 1	244 (100.0)	345 (100.0)	443 (100.0)	223 (100.0)	3910 (100.0)
≥ 14	237 (97.1)	342 (99.1)	424 (95.7)	216 (96.9)	3799 (97.2)
≥ 28	235 (96.3)	321 (93.0)	410 (92.6)	207 (92.8)	3720 (95.1)
≥ 42	231 (94.7)	285 (82.6)	399 (90.1)	162 (72.6)	3633 (92.9)
≥ 56	225 (92.2)	219 (63.5)	390 (88.0)	134 (60.1)	3286 (84.0)
≥180	4 (1.6)	0 (0.0)	135 (30.5)	0 (0.0)	1693 (43.3)
≥270	0 (0.0)	0 (0.0)	4 (0.9)	0 (0.0)	678 (17.3)
≥360	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	637 (16.3)
Statistics					
n	244	345	443	223	3910
Mean	119.9	51.8	132.0	48.3	160.8
SD	49.47	13.26	81.74	14.16	124.72
Median	139.5	56.0	88.0	56.0	88.0
Minimum	1	3	1	7	1
Maximum	244	84	288	69	407

Demographics of target populations:

The demographics of the target populations are analyzed according to their groupings (group B, C, and D), as laid out in section 7.1.3 above. As mentioned above, the 6 clinical trials were pooled into the 3 safety groupings based on their clinical trial design: groups B, C, and D. As 2 of the 6 clinical trials were deemed inappropriate for pooling into any of the three groupings (as agreed upon by sponsor and FDA), their demographics analysis will be addressed independent from the demographics of the other 4 trials.

Demographics of group B:

Group B includes all short term, double blind, controlled studies. Only one of the six clinical studies qualified for inclusion into this group -- SAH2302. SAH2302 is the pivotal efficacy study of this development program. A summary of the baseline demographics for this population is presented in Table 29 below.

Table 29: Demographics By Treatment Group (Randomized Set) Group B: Study SAH2302; Short-Term, Double-Blind, All Controlled Studies (Sponsor's Table)

Treatment Group	Number of patients	Age (yrs) Mean (SD)	Sex n (%)	
			Male	Female
Ali/Aml	287	54.4 (11.33)	172 (59.9)	115 (40.1)
Ali/HCTZ	298	55.5 (10.75)	175 (58.7)	123 (41.3)
Aml/HCTZ	296	55.1 (10.86)	186 (62.8)	110 (37.2)
Ali/Aml/HCTZ	310	55.4 (10.54)	187 (60.3)	123 (39.7)
Total	1191	55.1 (10.86)	720 (60.5)	471 (39.5)

Treatment Group	Race n (%)					
	Caucasian	Black	Asian	Native American	Pacific islander	Other
Ali/Aml	244 (85.0)	26 (9.1)	10 (3.5)	0 (0.0)	0 (0.0)	7 (2.4)
Ali/HCTZ	251 (84.2)	31 (10.4)	10 (3.4)	1 (0.3)	0 (0.0)	5 (1.7)
Aml/HCTZ	244 (82.4)	35 (11.8)	10 (3.4)	0 (0.0)	0 (0.0)	7 (2.4)
Ali/Aml/HCTZ	263 (84.8)	27 (8.7)	12 (3.9)	1 (0.3)	1 (0.3)	6 (1.9)
Total	1002 (84.1)	119 (10.0)	42 (3.5)	2 (0.2)	1 (0.1)	25 (2.1)

Treatment Group	BMI status n (%)				Diabetes n (%)	
	BMI < 20 kg/m ²	20 ≤ BMI < 25 kg/m ²	25 ≤ BMI < 30 kg/m ²	BMI ≥ 30 kg/m ²	Yes	No
Ali/Aml	1 (0.3)	35 (12.2)	97 (33.8)	153 (53.3)	46 (16.0)	241 (84.0)
Ali/HCTZ	2 (0.7)	51 (17.1)	105 (35.2)	139 (46.6)	40 (13.4)	258 (86.6)
Aml/HCTZ	2 (0.7)	40 (13.5)	117 (39.5)	137 (46.3)	53 (17.9)	243 (82.1)
Ali/Aml/HCTZ	0 (0.0)	43 (13.9)	114 (36.8)	152 (49.0)	33 (10.6)	277 (89.4)
Total	5 (0.4)	169 (14.2)	433 (36.4)	581 (48.8)	172 (14.4)	1019 (85.6)

Treatment Group	eGFR (ml/min/1.73 m ²) n(%)		
	30 ≤ GFR < 60 ml/min/1.73m ²	60 ≤ GFR < 90 ml/min/1.73 m ²	GFR ≥ 90 ml/min/1.73 m ²
Ali/Aml	10 (3.5)	174 (60.6)	103 (35.9)
Ali/HCTZ	11 (3.7)	168 (56.4)	119 (39.9)
Aml/HCTZ	11 (3.7)	186 (62.8)	99 (33.4)
Ali/Aml/HCTZ	18 (5.8)	176 (56.8)	116 (37.4)
Total	50 (4.2)	704 (59.1)	437 (36.7)

Age:

Mean age of patients in each treatment group was very similar (54.4-55.5 years). Mean age overall was 55.1 years.

Gender:

More male patients than female patients participated in the study overall (60.5% vs. 39.5%). This ratio was relatively constant across all treatment groups. In the various treatment groups, males were 58.7% to 62.8% of the population, while females were 37.2% to 41.3%.

“Race”:

Caucasian patients accounted for the majority (approximately 84%) of the study population followed by Black patients (approximately 10%). The number of patients of other “races” was small. These ratios were maintained relatively closely across all the treatment groups. In the various treatment groups, Caucasians were 82.4% to 85.0% of the population, whilst black patients were 8.7% to 11.8%.

Ethnicity:

Approximately 6% of the study population was Hispanic/ Latino in ethnicity. The majority of the population (approximately 91%) was from ‘Other’ ethnicity. This relative distribution was observed in every treatment group.

BMI:

Approximately half of the patients (48.8%) were obese (BMI ≥ 30 kg/m²) with the majority (85.1%) of patients having a BMI ≥ 25 kg/m².

Diabetes:

14.4% of all patients had a diagnosis of diabetes.

eGFR:

4.2% of patients had a glomerular filtration rate (eGFR) which was between 30 and 60 ml/min/1.73m² and 59.1% had an eGFR between 60 and 90 ml/min/1.73m².

History of hypertension:

The patients in this population had a mean duration of hypertension of 9.4 years, which was similar between treatment groups (mean duration was between 9.1 and 9.7 years).

Reviewer’s comment: As is evident from Table 29 and from my summary of the demographics data, the demographics were very similar across the treatment groups in Group B – as they should be given that this was a randomized trial. Moreover, there was good representation of the intended target population: i.e. individuals with a history of hypertension, overweight and obese individuals, people with various GFR statuses, diabetic and non-diabetic populations, and both Caucasian and black populations.

Demographics of group C:

Group C includes all long-term, open-label studies. This includes two of the six clinical studies that comprise this development program – SAH2301 (the major safety trial of this program) and SPA2301. A summary of the baseline demographics for this population is presented in Table 30 below.

Table 30: Demographics By Treatment Group (Safety Set) Group C: Studies SAH2301 and SPA 2301, Long-Term, Open-Label Studies (Sponsor's Table)

Treatment Group	Number of patients	Age (yrs) Mean (SD)	Sex n (%)		
			Male	Female	
Ali/Aml	470	54.2 (11.66)	274 (58.3)	196 (41.7)	
Ali/Aml/HCTZ	650	55.9 (11.33)	382 (58.8)	268 (41.2)	
Race n (%)					
Treatment Group	Caucasian	Black	Asian	Native American	Other
Ali/Aml	406 (86.4)	15 (3.2)	37 (7.9)	0 (0.0)	12 (2.6)
Ali/Aml/HCTZ	579 (89.1)	50 (7.7)	15 (2.3)	1 (0.2)	5 (0.8)
BMI status n(%)					
Treatment Group	BMI < 20 kg/ m ²	20 ≤ BMI < 25 kg/ m ²	25 ≤ BMI < 30 kg/m ²	BMI ≥ 30 kg/ m ²	
Ali/Aml	7 (1.5)	83 (17.7)	163 (34.7)	216 (46.0)	
Ali/Aml/HCTZ	8 (1.2)	54 (8.3)	239 (36.8)	347 (53.4)	
Diabetes n(%)					
Treatment Group	Diabetes n(%)		eGFR (mL/min/1.7m^2) n(%)		
	Yes	No	30 ≤ GFR < 60 ml/min/1.73m ²	60 ≤ GFR < 90 ml/min/ 1.73m ²	GFR ≥ 90 ml/min/ 1.73m ²
Ali/Aml	73 (15.5)	397 (84.5)	16 (3.4)	234 (49.8)	220 (46.8)
Ali/Aml/HCTZ	138 (21.2)	512 (78.8)	50 (7.7)	407 (62.6)	193 (29.7)

Age:

The mean age of patients in the aliskiren/amlodipine/HCTZ group was 55.9 years. The majority of patients (76.5%) were less than 65 years of age in the aliskiren / amlodipine / HCTZ treatment group. 23.5% of patients were ≥ 65 years and 4.9% of patients ≥ 75 years.

Gender:

More male patients than female patients were represented in the population (58.8% vs. 41.2%) in the aliskiren/amlodipine/HCTZ treatment group.

“Race”:

Caucasian patients accounted for the majority (89.1%) of the aliskiren/amlodipine/HCTZ treatment group followed by Black patients (7.7%). The number of patients of other races was small.

Ethnicity:

There were 6.5% patients in the aliskiren/amlodipine/HCTZ treatment group who were Hispanic/ Latino in ethnicity. The majority of the population (92.2%) were 'Other' ethnicity.

Reviewer's comment: The "racial" and ethnic distributions observed in Group C were relatively the same as those observed in group B.

BMI:

Approximately half of the patients (53.4%) in the aliskiren/amlodipine/HCTZ group were obese (BMI ≥ 30 kg/m²) with the majority (90.2%) of patients having a BMI ≥ 25 kg/m².

Diabetes:

21.2% of the triple therapy is group had a diagnosis of diabetes.

eGFR:

Patients with $30 \leq$ glomerular filtration rate(eGFR) < 60 ml/min/1.73m² comprised 7.7% of the aliskiren/amlodipine/HCTZ treatment group and those with an eGFR of between 60 and 90 ml/min/1.73m² comprised 62.6%.

Hypertension history:

The mean duration of hypertension history in the aliskiren/amlodipine/HCTZ treatment group was 9.1 years.

Demographics in Group D:

Group D includes all long-term, double-blind studies in this development program. Of the 6 clinical studies that comprise this program only one qualified for inclusion into this grouping – Study SPP2344. A summary of the baseline demographics for this long-term, double-blind study is shown in Table 31 below.

Table 31: Demographics By Treatment Group (Randomized Set) Group D: Study SPP2344; Long-Term Double-Blind Study (Sponsor's Table)

Treatment Group	Number of Patients	Age (yrs) Mean (SD)	Sex n (%)		Race n (%)		
			Male	Female	Caucasian	Black	Other
Ali/Aml/HCTZ	52	71.2 (4.96)	31 (59.6)	21 (40.4)	43 (82.7)	6 (11.5)	3 (5.8)
Ramipril/Aml/HCTZ	68	71.2 (5.62)	31 (45.6)	37 (54.4)	56 (82.4)	7 (10.3)	5 (7.4)
Total Ali	457	72.0 (5.56)	222 (48.6)	235 (51.4)	389 (85.1)	34 (7.4)	34 (7.4)
Total Ramipril	444	72.2 (5.62)	207 (46.6)	237 (53.4)	378 (85.1)	38 (8.6)	28 (6.3)

Treatment Group	Number of Patients	Age (yrs) Mean (SD)	BMI status n (%)				Diabetes n (%)		eGFR (mL/min/1.73 m ²)		
			BMI < 20 kg/m ²	20 ≤ BMI < 25 kg/m ²	25 ≤ BMI < 30 kg/m ²	BMI ≥ 30 kg/m ²	Yes	No	30 ≤ eGFR < 60	60 ≤ eGFR < 90	eGFR ≥ 90
Ali/Aml/HCTZ	52	71.2 (4.96)	1 (1.9)	7 (13.5)	21 (40.4)	23 (44.2)	14 (26.9)	38 (73.1)	7 (13.5)	32 (61.5)	13 (25.0)
Ramipril/Aml/HCTZ	68	71.2 (5.62)	2 (2.9)	16 (23.5)	20 (29.4)	30 (44.1)	11 (16.2)	57 (83.8)	12 (17.6)	38 (55.9)	18 (26.5)
Total Ali	457	72.0 (5.56)	11 (2.4)	77 (16.8)	185 (40.5)	183 (40.0)	99 (21.7)	358 (78.3)	78 (17.1)	285 (62.4)	91 (19.9)
Total Ramipril	444	72.2 (5.62)	10 (2.3)	91 (20.5)	160 (36.0)	179 (40.3)	87 (19.6)	357 (80.4)	77 (17.3)	286 (64.4)	79 (17.8)

Age:

This study was conducted in patients of age 65 years or older. The mean age of patients in the aliskiren/amlodipine/HCTZ treatment group was 71.2 years of age. Patients of 75 years or older accounted for 28.8% of the aliskiren/amlodipine/HCTZ treatment group. The percentages of patients for each age group were similar across treatment groups.

Reviewer's comment: representation of those older than 65 and of those older than 75 is appropriate since the target hypertension population is certainly in both of those age cohorts.

Gender:

There were similar numbers of females and males in each treatment group with slightly more females (total aliskiren group 51.4% female, 48.6% male, total ramipril group 53.4% female and 46.6% male), apart from the aliskiren/amlodipine/HCTZ group where there were slightly more males (59.6% males, 40.4% females).

“Race” & Ethnicity:

In the aliskiren/amlodipine/HCTZ treatment group Caucasian patients accounted for the majority (82.7%) of the study population followed by Black patients (11.5%). The number of patients of other “races” was small. As for ethnicity, 3.8% of the aliskiren/amlodipine/HCTZ treatment group were Hispanic/ Latino in ethnicity, while the majority (94.2%) was from ‘Other’ ethnicity.

BMI:

44.2% of the aliskiren/amlodipine/HCTZ treatment group were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) with the majority (84.6%) of patients having a $\text{BMI} \geq 25 \text{ kg/m}^2$.

Diabetes:

26.9% of patients in the aliskiren/amlodipine/HCTZ treatment group had a diagnosis of diabetes.

eGFR:

In the aliskiren/amlodipine/HCTZ treatment group, patients with $30 \leq \text{eGFR} < 60 \text{ ml/min/1.73m}^2$ comprised 13.5%, $60 \leq \text{eGFR} < 90 \text{ ml/min/1.73m}^2$ comprised 61.5%, and >90 comprised 25%.

Demographics in the remaining two studies:

Two of the six clinical studies supporting this NDA, studies SPP2360 and SPP2411, were not pooled into the B\C\D grouping schema, as outlined in section 7.1.4 above. The demographics underlying those two studies will be described here.

Demographics of Study SPP2360:

SPP2360 had a population with mild to moderate hypertension, an intended target population for this drug product. 20.7% of the study population was 65 years of age or older. 4.7% were 75 years or older. In the aliskiren/amlodipine/HCTZ group, 24.4% were 65 years or older and 5.0% were 75 years or older. There was a slightly greater proportion of males than females in the overall population (55.9% vs 44.1% in the total, with 59.7% vs 40.3% in the aliskiren/amlodipine/HCTZ treatment group). In terms of “race”, for the overall study population the vast majority were Caucasian (99.2%, also 99.2% for the aliskiren/amlodipine/HCTZ group). In terms of ethnicity, the vast majority were of non-specified (“other”) ethnicity (“other”: 97.3% of the total population and 99.2% of the aliskiren/amlodipine/HCTZ group). 37.1% of the total population (41.2% of the aliskiren/amlodipine/HCTZ group) were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$), 34.4% of the total population (42.0% of the aliskiren/amlodipine/HCTZ group) were diabetic and 7.4% of the total (9.2% of the aliskiren/amlodipine/HCTZ group) had some degree of renal impairment ($\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$). Patients with evidence of renal impairment as specified by creatinine $> 1.5 \times \text{ULN}$ were excluded from the study.

Demographics of Study SPP2411:

For SPP2411, patient baseline demographics were generally similar between groups. This study selected for patients ≥ 55 years old. The mean age of all patients was 64.8 years (64.0 years in the aliskiren/amlodipine/HCTZ group). 46.6% of patients in the study population were at least 65 years (37.9% in the aliskiren/amlodipine/HCTZ group) and 11.8% were at least 75 years (10.3% of the aliskiren/amlodipine/HCTZ group). Of the 451 patients in the randomized set 29 were escalated to the aliskiren/amlodipine/HCTZ combination. There was some variation of proportions of males and females between the treatment groups with overall a similar proportion of males and females (49.7% male: 50.3% female overall; 62.1% male and 37.9% female in the aliskiren/amlodipine/HCTZ group). There was a lower proportion of Caucasians (62.1%) and higher proportion of Black patients (31.0%) in the aliskiren/amlodipine/HCTZ treatment group, compared to the total group (78.3% and 16.9% respectively) and a higher proportion of Hispanic/Latino patients compared to the total population (20.7% vs. 12.2%). There was a similar proportion of patients in the treatment groups who were obese (BMI ≥ 30 kg/m²); 51.7% in the total population and 55.2% in the aliskiren/amlodipine/HCTZ group. 19.7% of patients overall had diabetes (13.8% in the aliskiren/amlodipine/HCTZ group).

7.2.2 Explorations for Dose Response

See Sections 7.3.4, 7.4.1, and 7.5.1.

7.2.3 Special Animal and/or In Vitro Testing

No specific animal testing or in vitro testing were conducted in connection with this application.

7.2.4 Routine Clinical Testing

The key clinical testing for this drug product for this product included monitoring of BP changes and monitoring for adverse events (such as peripheral oedema and electrolyte derangement) known to be associated with the three component drugs products that comprise this combination product. The clinical trials comprising this development program were well structured to record and analyze these metrics.

QT study and post-baseline ECG were not studied in this program as the monotherapy programs supporting the three drug products comprising this combination product did not warrant such study. For further discussion of electrocardiology, see section 7.4.4 below.

7.2.5 Metabolic, Clearance, and Interaction Workup

Pharmacokinetic data in support of this application was obtained 5 different studies.

- Two relative bioavailability studies (SAH2104 and SAH2105)

- One pivotal bioequivalence study (SAH2101)
- One food effect study (SAH2101)
- One pivotal efficacy study SAH2302 (of which a subset was used for population PK data.

ADME:

Following oral co-administration of 300 mg of aliskiren, 5 mg or 10 mg of amlodipine, and 25 mg HCTZ, either as a free combination or fixed combination, peak plasma concentrations of aliskiren, amlodipine, and HCTZ were reached in 1.5 to 2 hours, 8 hours, and 2 to 3 hours (median values), respectively. The mean apparent terminal elimination half-lives of aliskiren, amlodipine, and HCTZ are 55 to 66 hours, 48 to 55 hours, and 9.5 to 11 hours, respectively. The rate and extent of absorption, including elimination half-life of aliskiren, amlodipine, and HCTZ from the fixed combination tablets are similar to those of aliskiren, amlodipine, and HCTZ when administered as free combination (see Figure 19, Figure 20, Figure 21, and Table 32 below).

Figure 19: Mean Concentration time profiles of aliskiren following single dose administration of 300 mg aliskiren, 10 mg amlodipine, and 25 mg HCTZ in a fixed dose combination formulation variant 002 or as a free combination (Sponsor's Figure)

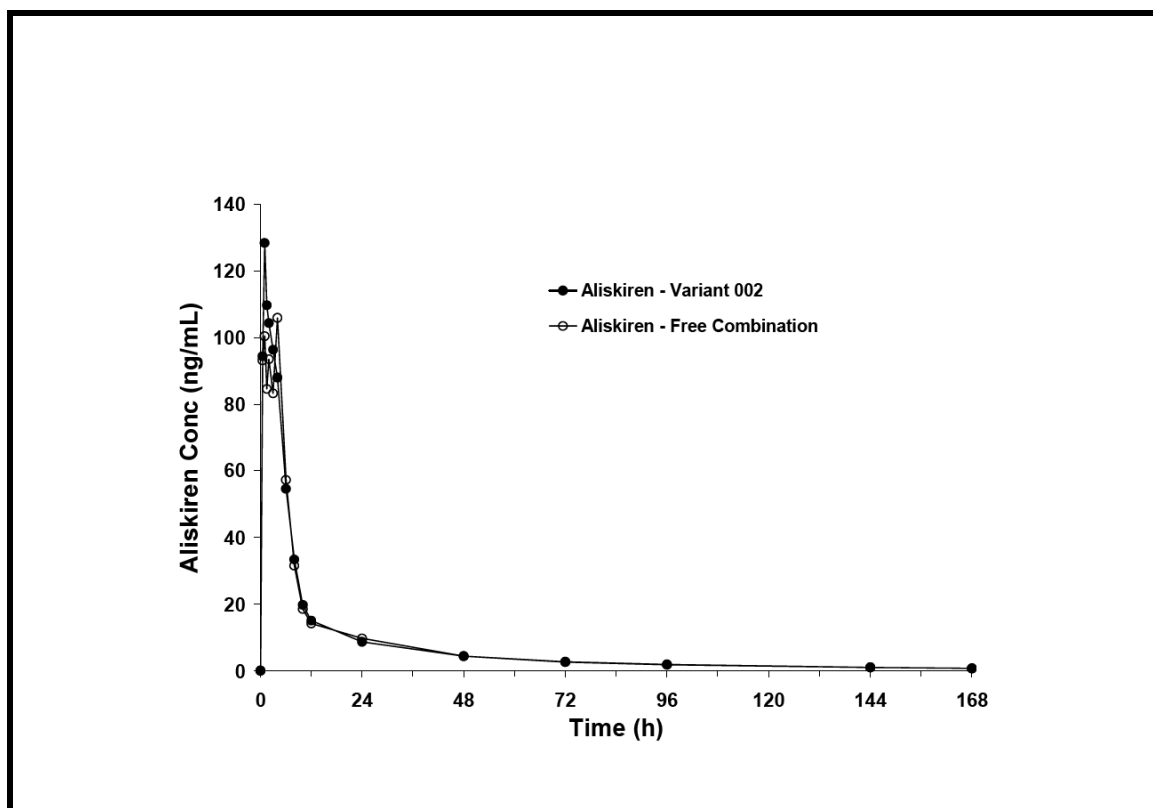


Figure 20: Mean Concentration time profiles of amlodipine following single dose administration of 300 mg aliskiren, 10mg amlodipine, and 25 mg HCTZ in a fixed dose combination formulation variant 002 or as a free combination (Sponsor's Figure)

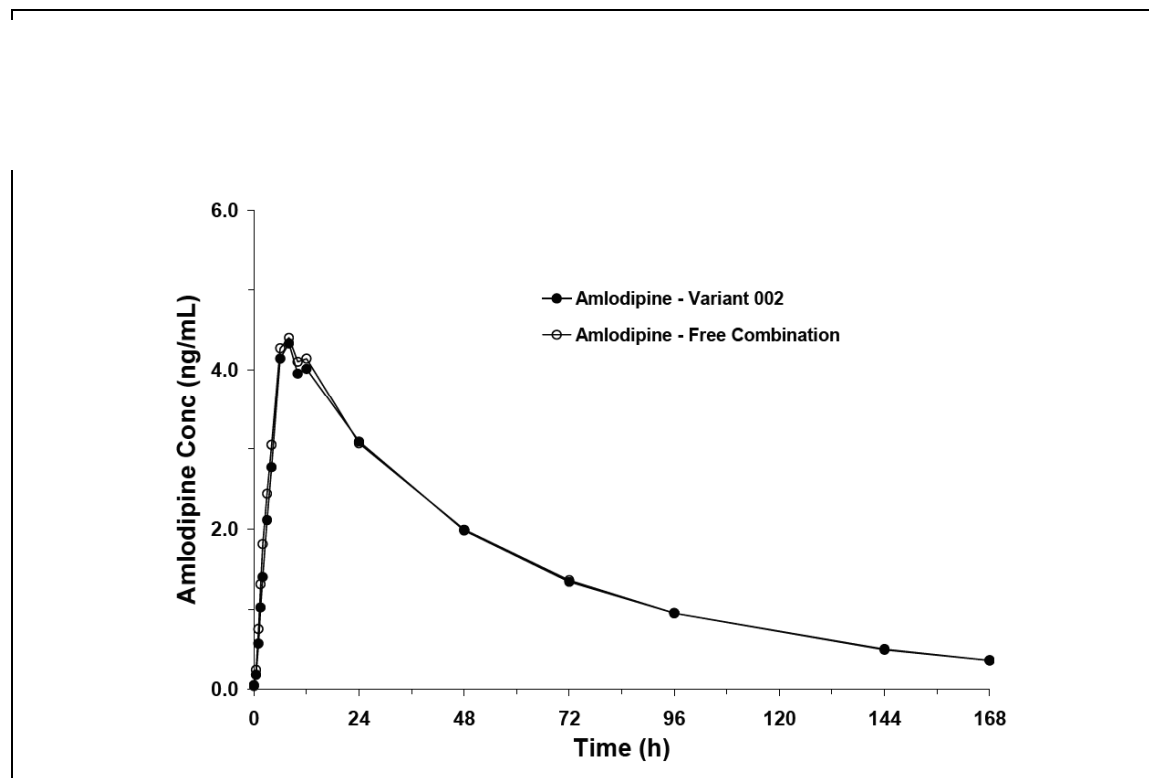


Figure 21: Mean Concentration time profiles of HCTZ following single dose administration of 300 mg aliskiren, 10mg amlodipine, and 25 mg HCTZ in a fixed dose combination formulation variant 002 or as a free combination (Sponsor's Figure)

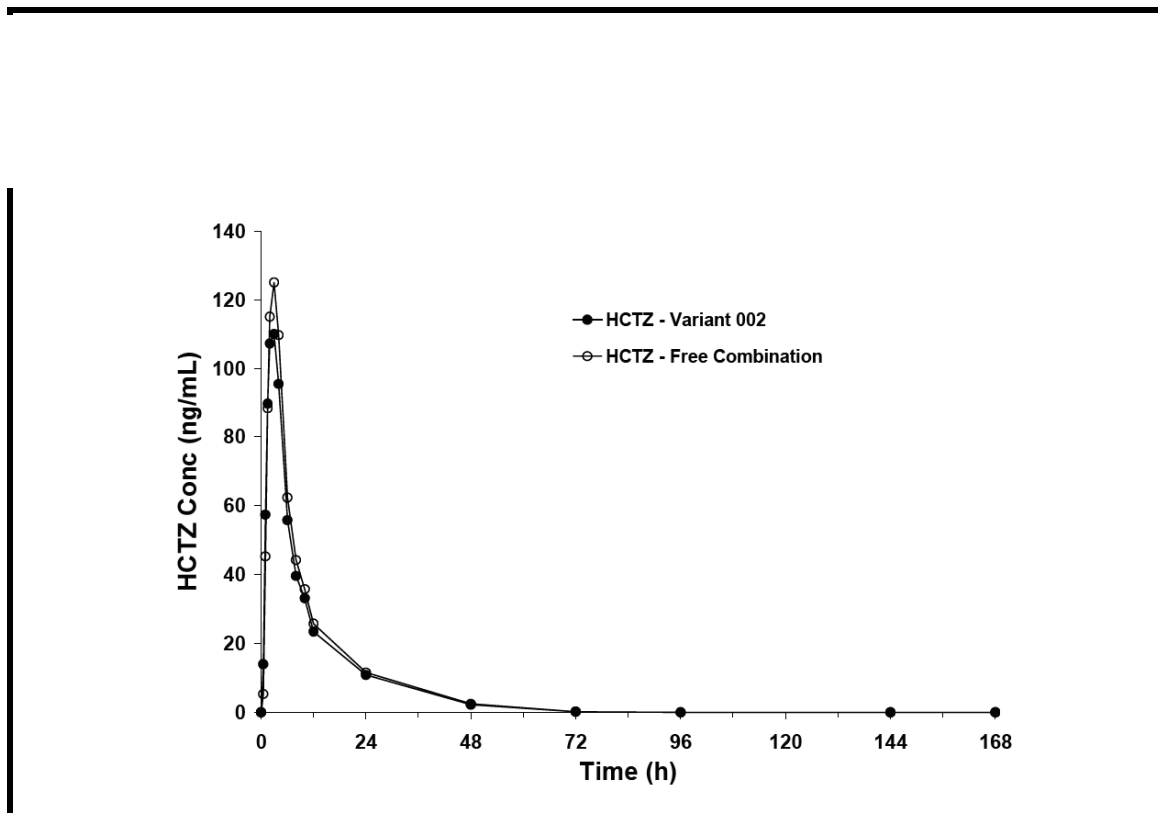


Table 32: Statistical Evaluation Of Pharmacokinetic Parameters Of Aliskiren, Amlodipine, And HCTZ Following Single Dose Administration Of 300 Mg Aliskiren, 10 Mg Amlodipine, And 25 Mg HCTZ As A Fixed Dose Combination Formulation Variant 002 Or As A Free Combination (CSAH100A2104) (Sponsor's Table)

Geometric Mean ratio (90% CI)		
Analyte	PK parameter	Variant 002 vs Free Combination
Aliskiren	AUClast	0.97 (0.88 – 1.07)
	AUCinf	0.98 (0.89 – 1.08)
	Cmax	1.02 (0.89– 1.18)
Amlodipine	AUClast	0.99 (0.97– 1.02)
	AUCinf	0.99 (0.97– 1.02)
	Cmax	0.99 (0.96 – 1.02)
HCTZ	AUClast	0.92 (0.88 – 0.95)
	AUCinf	0.91 (0.88 – 0.95)
	Cmax	0.90 (0.86 – 0.94)

CI: Confidence interval
Variant 002: Fast aliskiren release monolayer tablet

Drug-drug interactions (DDI):

DDI was measured in the context of study SAH2302, mentioned above. In SAH2302, triple therapy was compared to all the possible dual therapies. Population PK in a subset of this study was used as a means of testing DDI. The population of SAH2302 was a mild to moderate hypertension population, which is a primary intended population of this drug product. The population PK analysis showed that the patients on Aliskiren 300mg, amlodipine 10mg, and HCTZ 25mg, at steady state had the following variations in exposure when compared to the various dual therapies: the exposure of aliskiren decreased by 5 to 13%, amlodipine decreased by 6 to 22%, and HCTZ by 11%.

Reviewer's comment: though there does appear to be some loss in exposure secondary to the administration of triple therapy when compared to dual therapy, the magnitude of exposure is acceptable in my opinion given: one, the fact that there is great variability in exposure to begin with, in terms of Aliskiren especially; and, two, the fact that a significant efficacy benefit is achieved by the addition of the third drug component. Hence, the observed decrease in the exposure of aliskiren, amlodipine, and HCTZ does not appear to be clinically relevant.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events potentially caused by similar drugs in these classes of drugs were evaluated for. These include, for example, hypokalemia and hypotension that might be seen with thiazide diuretics or calcium derangement, palpitations, and peripheral edema that might be seen with calcium channel blockers. The side effect profile of this triple combination drug product did not show cause for concern on these grounds.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this clinical program amongst patients taking triple therapy. However, there still were deaths in the development program. 7 deaths occurred in the 6 completed studies that support this NDA, while an 8th death has occurred in an ongoing study (Study SPA2307), which was not complete by the time of this NDA submission. Of the 7 deaths in the six completed studies, four took place during placebo run-in while three more took place in patients not on triple therapy.

Reviewer's Comment: No deaths occurred in patients on triple therapy.

Table 33: Deaths in the Six Completed Clinical Studies (Reviewer's Table)

7 DEATHS in the Six Completed Clinical Studies					
ID	SAE	Study	Study medication	Cause	Narrative
0557/00010	death	SAH2302	PBO (run-in)	Unknown	39 year old black female. Died during PBO run-in before db, treatment phase. During run-in, patient called in and stated that she did not feel well. Nine days after she started pbo phase, investigator was informed that patient had passed away. Family did not respond to letter of inquiry. No other information available. The investigator did not suspect a relationship between the event and the study medication.
0557/00032	death	SAH2302	PBO (run-in)	Unknown Street Drug	48 year old black male. Died treatment phase. patient was discontinued from the placebo portion due to exclusionary blood pressure values. 18 days after last dose of pbo, patient was hospitalized and

					subsequently passed away with an unknown street drug in his body. No autopsy was performed. The investigator did not suspect a relationship between the event and the study medication.
0001/0003	death	SPP2360	PBO (run-in)	Unknown	48 year old white male. Patient died during placebo run-in phase, before taking any active study drug. Investigator did not suspect a relationship between this event and the placebo run-in drug.
0140/0013	death	SPP2360	PBO (run-in)	Sudden Cardiac Death	73 year old white male. Patient died during pbo run-in phase, before taking any active study medication. Patient had history of CAD and afib. Investigator: no relationship between study drug and death.
0522/0003	death	SPP2344	NOT TRIPLE THERAPY (Aliskiren 300mg)	CVA	66 year old white male. Died day 209. Awoke on day 208 with confusion, difficulty seeing and speaking. Diagnosed CVA. No autopsy performed. Sponsor does not attribute this to study drug. Investigator assessment not included.
0560/0001	death	SPP2344	NOT TRIPLE THERAPY. (Aliskiren 300 / Hctz 12.5)	Pancreatic Carcinoma	69 year old white male. Died day 279. The investigator did not suspect a relationship between the event and the study medication.
0514/0009	death	SPP2344	NOT TRIPLE THERAPY (Ramipril 10)	CAD	75 year old white female. Died day 237. History of CAD, AAA. coronary angioplasty. Found dead in home on day 237. The investigator did not suspect a relationship between the event and the study medication.

7.3.2 Nonfatal Serious Adverse Events:

In group B (which included all short term, double-blind, controlled studies, which included only SAH2302, the pivotal efficacy study, per discussion in section 7.1.3 above), there were 13 Serious Adverse Events (SAEs) during the treatment phase of the trial (8 additional SAE's occurred during the placebo run-in). 6 SAE's occurred in the triple therapy group, 4 of which led to discontinuations. The dual therapy groups had between 2 and 3 SAE's each, 2 of which led to discontinuations. A complete listing of all 21 SAE's is listed in Table 34 below.

The percentage of patients with any SAE was low in all treatment groups (0.7% to 1.9%). See chart XYZ below for a breakdown by treatment group. The six SAE's in the triple therapy group were: acute coronary syndrome (patient had history of smoking,

hypertension, and occurred on day 2 of study drug), supraventricular arrhythmia, goiter (patient had history of struma multinodosa), hypertension, psychosomatic disease and syncope (patient had history of seizure).

The following is a discussion of the 6 SAE's in the triple therapy group.

Canada site patient CAN/0150/00031 experienced the following SAE: hospitalization due to sever hypertension, treated in hospital and SAE resolved. *This does not appear to be attributable to triple therapy, which is an antihypertensive regimen.*

Israel site patient ISR/0177/00011 experienced the following SAE: syncope resulting in hospitalization; SAE resolved. Of note, patient had history of seizure in 2005. *Syncope was of unknown cause and could theoretically be attributed to a history of seizure or potentially to hypotensive effects of drug regimen. This should certainly be highlighted in the drug label.*

Germany site patient DEU/0265/00022 experienced the following SAE: hospitalization due to goiter. Patient had history of goiter. *Appears most likely that this condition was due to pre-existing condition, rather than anything attributable to test drug.*

Germany site patient DEU/0265/00023 experienced the following SAE: hospitalization due to psychosomatic syndrome. No further history of incident is related. *There does not appear to be reason to attribute this to test drug. Moreover, it's not even clear what the nature of this SAE was.*

USA site patient USA/0506/00004 experienced the following SAE: hospitalization due to acute coronary syndrome. Patient had history of hypertension and smoking. ACS occurred on 2nd day of taking test drug. *Likely due to history of hypertension and smoking rather than study drug, though acceleration of underlying disease process might potentially be attributable to study drug. This should be mentioned in the label.*

USA site patient USA/0552/00007 experienced the following SAE: hospitalization due to atrial fibrillation; condition resolved. No history of predisposing heart condition is given. *SAE could very well be due to study drug. This should be mentioned in label.*

A breakdown of SAE's leading to discontinuation can be seen in Table 36 below.

Table 34: List of SAE's in Group B: (Reviewer's Table)

SAE's in Group B							
	Study	ID	SAE	Study Medication	Recovery	Study Disposition	Investigator Suspect Relationship to Study Drug?

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						Discontinued	Completed	
1	SAH2302	0271 00005	Hospitalization due to Hypertensive crisis	Single Blind Placebo	YES	X		NO
2	SAH2302	0278 00007	Car accident	Single Blind Placebo	YES		X	NO
3	SAH2302	0304 00001	Hospitalization due to appendicitis	Single Blind Placebo	YES		X	NO
4	SAH2302	0543 00001	Hospitalization due to atypical chest pain	Single Blind Placebo	YES	X		NO
5	SAH2302	0544 00021	Hospitalization due to a fracture	Single Blind Placebo	Improving	X		NO
6	SAH2302	0554 00002	Hospitalization due to chest pain	Single Blind Placebo	YES	X		NO
7	SAH2302	0658 00004	Hospitalization due to gastroenteritis	Single Blind Placebo	YES	X		NO
8	SAH2302	0754 00016	Hospitalization due to vertiginous syndrome	Single Blind Placebo	YES	X		NO
9	SAH2302	CAN/0150/00031	Hospitalization due to severe Hypertension	Aliskiren / Amlodipine / HCTZ	YES	X		NO
10	SAH2302	ISR/0177/00011	Syncope resulting in hospitalization	Aliskiren / Amlodipine / HCTZ	YES		X	NO
11	SAH2302	DEU/0265/00022	Hospitalization due to struma (goiter)	Aliskiren / Amlodipine / HCTZ	YES		X	NO
12	SAH2302	DEU/0265/00023	Hospitalization due to psychosomatic syndrome	Aliskiren / Amlodipine / HCTZ	NO	X		NO
13	SAH2302	USA/0506/00004	Hospitalization due to Acute Coronary Syndrome	Aliskiren / Amlodipine / HCTZ	YES	X		NO
14	SAH2302	USA/0552/00007	Hospitalization due to Atrial flutter	Aliskiren / Amlodipine / HCTZ	YES	X		NO
15	SAH2302	LVA/0453/00022	Hospitalization due to Hepatitis A	Aliskiren /Amlodipine	n/a	X		NO

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16	SAH2302	TUR/0478/00005	Hospitalization due to Nasal Deviation	Aliskiren /Amlodipine	YES		X	NO
17	SAH2302	USA/0536/00057	Hospitalization due to ectopic tubal pregnancy	Aliskiren /Amlodipine	YES		X	NO
18	SAH2302	DEU/0268/00008	Hospitalization due to urinary stress incontinence	Aliskiren / HCTZ	Partial		X	NO
19	SAH2302	USA/0506/00005	Hospitalization due to right lower abdominal quadrant pain	Aliskiren / HCTZ	YES		X	NO
20	SAH2302	ISR/0177/00009	Hospitalization due to Cerebrovascular Accident, walking disturbances	Amlodipine / HCTZ	n/a	X		NO
21	SAH2302	DEU/0303/00002	Hospitalization due to Epistaxis	Amlodipine / HCTZ	YES		X	NO

Table 35: Rate of SAE's in Group B (Reviewer's Table)

Rate of SAE's in GROUP B			
<i>Aliskiren\Amlodipine</i>	<i>Aliskiren\Hctz</i>	<i>Amlodipine\Hctz</i>	<i>Triple Therapy</i>
1.0%	0.7%	0.7%	1.9% (n=6)

Table 36: Serious Adverse Events Leading To Discontinuation, By Primary System Organ Class And Treatment Groups (Safety Set), Group B: Study SAH2302, Short-Term, Double-Blind, All Controlled Study (Sponsor's Table)

System organ class	Ali/Aml N=287 n (%)	Ali/HCTZ N=297 n (%)	Aml/HCTZ N=295 n (%)	Ali/Aml/HCTZ N=309 n (%)	Total N=1188 n (%)
Any organ class	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.3)	6 (0.5)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Infections and infestations	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

In Group C (which included all long term, open label studies; defined in section 7.1.3 above as Studies SAH2301 and SPA2301), there 33 SAEs reported overall, of which only 15 were for patients taking triple therapy. All 33 SAEs are summarized in Table 37 below. SAE's were reported for 2.3% of patients in the aliskiren\amlodipine treatment group and 2.6% in the triple therapy group.

Of the 15 SAEs in the triple therapy population, seven led to discontinuation. In the Aliskiren\amlo population, three SAE's led to discontinuation. The SAE's that led to discontinuation in the triple therapy population were single reports of: atrial fibrillation, palpitations, osteoarthritis, cerebrovascular accident, drug dependence, interstitial lung disease, and hypotension.

Discussion of select SAE's in the triple therapy population follows.

Patient 0456-00003, on triple therapy, experienced heart palpitations that appeared to be related to study drug. Patient had 11-year history of hypertension. One day 26 of treatment in the study, patient presented with palpitations, was hypertensive and tachycardic. Patient was discontinued from study, resumed prior anti-hypertension medications and palpitations had resolved.

Patient 0501-00009 experiences atrial fibrillation. Cause was unclear.

Patient 0502-00001 experienced an SAE including: presyncope, non-cardiac chest pain, palpitations, headache, worsening sinusitis, renal insufficiency, thrombocytopenia. Investigator attributed the renal insufficiency and thrombocytopenia to the HCTZ component of the triple therapy. Patient discontinued HCTZ for last 37 days of therapy

in study, and renal insufficiency resolved on the day HCTZ was discontinued. Patient had a history of migraines, sinusitis, and iron deficiency anemia.

Patient 0700-00013 experienced an SAE of cerebrovascular accident (right basal ganglia infarct, severe). After treatment, patient's condition improved somewhat but residual hemiparesis did not resolve. Patient had history of diabetes mellitus Type II and ten year history of hypertension.

Reviewer's comment: The SAE's that had potential causal connection to study drug should be specifically pointed out in the label. I'm referring specifically to: heart palpitations, atrial fibrillation, renal insufficiency, thrombocytopenia, and cerebral vascular accident.

Table 37: SAE's in Group C: (Reviewer's Table)

SAE's in Group C								
	Study	ID	SAE	Study Medication	Recovery	Study Disposition		Did Investigator Suspect Relationship Study Drug?
						Discontinued	Completed	
1	SAH2301	0305-00001	stomach ache	screening phase	YES	X		n/a
2	SAH2301	0508-00005	heart attack	Washout Period	YES	X		NO
3	SAH2301	0307-00006	pain in the left arm	Triple Rx 300\5\12.5	YES		X	NO
4	SAH2301	0201-00007	phlebothrombosis cruix L.DX., hernia inguinalis L.Sin. incarcerated	Triple Rx 300\10\25	YES		X	NO

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5	SAH2301	0205-00009	cervical spinal channel stenosis, cervical myelopathy due to spinal channel stenosis	Triple Rx 300\10\25	Improving		X	NO
6	SAH2301	0256-00002	bronchitis	Triple Rx 300\10\25	YES		X	NO
7	SAH2301	0264-00007	worsening arthrosis left hip	Triple Rx 300\10\25	YES	X		NO
8	SAH2301	0401-00001	lumbar disk hernia	Triple Rx 300\10\25	YES		X	NO
9	SAH2301	0456-00003	heart palpitations	Triple Rx 300\10\25	YES	X		YES
10	SAH2301	0501-00007	critical stenosis right carotid artery, likely TIA	Triple Rx 300\10\25	YES		X	NO
11	SAH2301	0501-00009	atrial fibrillation	Triple Rx 300\10\25	YES	X		NO

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12	SAH2301	0502-00001	presyncope, non cardiac chest pain, palpitations, headache, worsening sinusitis, renal insufficiency, thrombocytopenia	Triple Rx 300\10\25	YES	X (omitted HCTZ for last 37 days of study, initially discontinued HCTZ because of renal insufficiency, which resolved)		YES (the renal insufficiency and thrombocytopenia were attributed to the triple therapy). Other SAE's: NO.
13	SAH2301	0506-00003	arthritis bilateral knees	Triple Rx 300\10\25	YES		X	NO
14	SAH2301	0508-00002	bilateral interstitial pneumonia	Triple Rx 300\10\25	YES	X		NO
15	SAH2301	0512-00012	Xanax dependence, Vicodin dependence	Triple Rx 300\10\25	YES	X		NO
16	SAH2301	0517-00006	ischemic 3rd digit right toe	Triple Rx 300\10\25	YES, following toe amputation		X	NO
17	SAH2301	0700-00013	CVA	Triple Rx 300\10\25	NO. improved but still residual hemiparesis.			YES

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18	SPA100A-2301	0043-00006	Rotator cuff syndrome	Ali 300 \ Amlo 10	YES		X	NO
19	SPA100A-2301	0045-00005	Prostate cancer metastatic	Ali 300 \ Amlo 10	n/a	X		NO
20	SPA100A-2301	0082-00006	Amebiasis, Gastroenteritis	Ali 300 \ Amlo 10	YES		X	NO
21	SPA100A-2301	0091-00002	Melanoma malignum	Ali 300 \ Amlo 10	NO		X	NO
22	SPA100A-2301	0124-00005	Right hip coxarthrosis	Ali 300 \ Amlo 10	n/a (underwent total endoprosthesis of right hip)		X	NO
23	SPA100A-2301	0141-00007	New decompensation diabetes mellitus / IDDM	Ali 300 \ Amlo 10	n/a (though patient was discharged following 15 days hospitalization)	X		NO
24	SPA100A-2301	0143-00005	Fell from roof	Ali 300 \ Amlo 10	n/a (though pt was discharged following 7 days hospitalization)		X	NO
25	SPA100A-2301	0203-00008	Acute exacerbation of asthma	Ali 300 \ Amlo 10	YES		X	NO
26	SPA100A-2301	0216-00004	Prostate adenocarcinoma	Ali 300 \ Amlo 10	YES	X		NO
27	SPA100A-2301	0506-00005	Dehydration due to diarrhea	Ali 300 \ Amlo 10	n/a (though pt was discharged following 2 days hospitalization)		X	NO

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28	SPA100A-2301	0523-00028	Gangrene left 4th toe	Ali 300 \ Amlo 10	YES (toe was amputated, some residual pain)			NO
29	SPA100A-2301	0524-00003	Symptomatic Hypotension	Ali 300 \ Amlo 10	YES	X		NO (But I consider the connection possible)
30	SPA100A-2301	0539-00004	Ischemic colon (abdominal pain, nausea, vomiting, diarrhea, dark stools and bright red rectal bleeding)	Ali 300 \ Amlo 10	YES		X	NO
31	SPA100A-2301	0540-00001	Atrial fibrillation	Ali 300 \ Amlo 10	NO	X		NO
32	SPA100A-2301	0542-00015	Attempted suicide (intentional over dose of 16 Tylenol tablets, worsening depression)	Ali 300 \ Amlo 10	YES	X		NO
33	SPA100A-2301	0544-00003	Pulm Embolism	Ali 300 \ Amlo 10	YES		X	NO

In Group D (which included all long term, double-blind studies; defined in section 7.1.3 above as only Study SPP2344), only one patient experience and SAE while on triple therapy. This was a case of bladder cancer which was not likely related to study drug, but was instead attributed to progression of underlying disease. Moreover, no patient on triple therapy had an SAE leading to discontinuation.

In the remaining two supportive studies, studies SPP2360 and SPP2411, there were no SAE's in patients on triple therapy.

7.3.3 Dropouts and/or Discontinuations

In group B (which included all short term, double-blind, controlled studies; defined in section 7.1.3 above), of the 1191 randomized patients, 1106 (92%) completed the study. Of the patients randomized to triple therapy, 91.9% completed the study. Completion rates for the other treatment groups ranged from 92.6% to 94.3%. All related data is listed in Table 38 below.

Reviewer Comments: completion rate was high in the triple therapy group and only marginally smaller than completion rates in the other treatment groups. This is acceptable.

7.7% of patients in the triple therapy group discontinued. 4.2% of patients in the triple therapy group discontinued due to safety reasons (AE, death, abnormal lb value, abnormal test result). Discontinuation due to safety in the other treatment arms ranged from 2.7% to 3.4%.

Reviewer's comments: Discontinuation due to safety in the triple therapy group was low (at 4.2%) and only marginally larger than the some of the rates in the dual therapy arms (3.4% in the amlodipine\HCTZ arm). This is acceptable.

Table 38: Patient Participation And Withdrawals, Group B: Study SAH2302, Short-Term, Double-Blind, All Controlled Studies (Sponsor's Table)

Treatment Group	Randomized	Treated n (%)	Completed n (%)	Discontinued n(%)			
				Total	Safety	Lack of efficacy	Other
Ali/Aml	287	287 (100.0)	266 (92.7)	21 (7.3)	8 (2.8)	2 (0.7)	11 (3.8)
Ali/HCTZ	298 *	297 (99.7)	276 (92.6)	21 (7.0)	5 (1.7)	3 (1.0)	13 (4.4)
Aml/HCTZ	296	295 (99.7)	279 (94.3)	17 (5.7)	10 (3.4)	1 (0.3)	6 (2.0)
Ali/Aml/HCTZ	310 *	309 (99.7)	285 (91.9)	24 (7.7)	13 (4.2)	2 (0.6)	9 (2.9)

Two patients were randomized in error and were assigned a randomization number (1 in the aliskiren/HCTZ group and 1 in the aliskiren/amlodipine/HCTZ group). Both patients were discontinued from the single-blind period without taking any double-blind study medication. Therefore, these patients were not counted as discontinued from the double-blind period. [\[SAH2302 CSR Section 10.1\]](#)

Safety = Adverse event(s), death, abnormal laboratory values, abnormal test procedure result(s).

Other = Administrative problems, subject's condition no longer requires study drug, lost to follow up, subject withdrawal consent, protocol deviation or other.

In Group C (which included all long term, open label studies; defined in section 7.1.3 above as Studies SAH2301 and SPA2301), 84.4% (n=1120) of all randomized patients completed the study, with a larger proportion of the triple therapy patients completing study (87.1%) compared to the double therapy patients (80.6%). Moreover, the rate for discontinuation due to safety reasons, was lower in the triple therapy group (7.2%) as compared to the dual therapy group (19.4%). See Table 39 below for full completion\discontinuation data.

Reviewer's Comment: It is reasonable for there to be a higher discontinuation rate in group C (84.4%) as compared to group B (91.9%) since group C encompasses long term studies, while group B only includes short term studies.

Table 39: Patient Participation And Withdrawals, Group C: Studies SAH2301 and SPA2301 Long-Term Open-Label Studies (Sponsor's Table)

Treatment Group	Treated n (%)	Completed n (%)	Discontinued n(%)			
			Total	Safety	Lack of efficacy	Other
Ali/Aml	470 (100.0)	379 (80.6)	91 (19.4)	60 (12.8)	1 (0.2)	30 (6.4)
Ali/Aml/HCTZ	650 (100.0)	566 (87.1)	84 (12.9)	47 (7.2)	5 (0.8)	32 (4.9)

Safety = Adverse event(s), death, abnormal laboratory values, abnormal test procedure result(s)
Other = Administrative problems, patient's condition no longer requires study drug, lost to follow up, patient withdrawal consent, protocol deviation, or other

In Group D (which included all long term, double-blind studies; defined in section 7.1.3 above as Study SPP2344), completion rates in the aliskiren-based triple therapy group was 98.1% (n=51) as compared to 75.3% in the aliskiren-based therapy group overall. See Table 40 below for full completion\discontinuation data.

Reviewer's Comment: completion rate comparison in this study between aliskiren-based triple therapy to aliskiren-based therapies overall is un-interpretable since aliskiren-based triple therapy was only administered conditionally if BP was uncontrolled. However, the number of patients in this study who took triple therapy (52) was very small compared to the numbers of patients (hundreds) from the pivotal studies underlying this application.

Table 40: Patient Participation And Withdrawals, Group D: Study SPP2344; Long-Term, Double-Blind Study (Sponsor's Table)

Treatment Group	Randomized	Treated (FAS) n (%)	Completed n (%)
Ali/Aml/HCTZ	52	52 (100.0)	51 (98.1)
Ramipril/Aml/ HCTZ	68	68 (100.0)	65 (95.6)
Total Ali	457	451 (98.7)	344 (75.3)
Total Ramipril	444	440 (99.1)	336 (75.7)

Treatment Group	Discontinued n (%)			
	Total	Safety	Lack of Efficacy	Other
Ali/Aml/HCTZ	1 (1.9)	1 (1.9)	0	0
Ramipril/Aml/ HCTZ	3 (4.4)	1 (1.5)	0	2 (2.9)
Total Ali	113 (24.7)	35 (7.7)	31 (6.8)	47 (10.3)
Total Ramipril	108 (24.3)	50 (11.3)	24 (5.4)	34 (7.7)

The mono aliskiren and mono ramipril and dual therapy treatment group data is provided in [\[SCS-PT-Table 2.7-1\]](#)
FAS (Full analysis set) consists of all randomized patients who had a baseline and at least one post-baseline efficacy measurement. Safety = Adverse event(s), death, abnormal laboratory values, abnormal test procedure result(s). Other = Administrative problems, patient's condition no longer requires study drug, lost to follow up, patient withdrew consent, protocol deviation or other.

The remaining two supportive studies to analyze for discontinuation rates are: SPP2360 and SPP2411.

In SPP2360, out of a total of 256 treated patients, the overall discontinuation rate was 9.4%. In the triple therapy cohort, 4 patients (3.4%) discontinued with 1 (0.8%) being due to an AE.

In study SPP2411, 451 patients were treated. 29 received aliskiren-based triple therapy, none of which discontinued early.

Reviewer's Comment: it is hard to interpret the relevance of safety data from study SPP2411 as patients only received triple therapy if their BP was uncontrolled. There was no proper control for the triple therapy patients. However, only 29 patients received triple therapy, so relevance of this study is minimal as compared to the safety data from the pivotal efficacy and safety studies, which are found in groups B and C above.

7.3.4 Significant Adverse Events

Peripheral edema, a known side effect of amlodipine, occurred more in treatment groups containing amlodipine. The aliskiren/amlodipine/HCTZ showed slightly less

reported peripheral edema than aliskiren/amlodipine treatment. Peripheral edema was mostly mild to moderate in severity and rarely led to patient discontinuation.

With the exception of peripheral edema, there was no increase in AE incidence and severity when the dose of aliskiren/amlodipine/HCTZ was increased from 150/5/12.5 mg to 300/10/25 mg. AEs potentially related to low blood pressure such as hypotension, orthostatic hypotension, syncope and dizziness occurred at low incidence and rarely led to patient discontinuation in patients treated with aliskiren/amlodipine/HCTZ.

Hyperkalemia occurred uncommonly with the treatment of aliskiren/amlodipine/HCTZ triple combination with the incidence similar to the component dual combinations. No case of angioedema was reported in the entire clinical program. Changes in laboratory parameters observed with aliskiren/amlodipine/HCTZ were generally minor and consistent with the known effect of aliskiren, amlodipine, or HCTZ. There were no meaningful differences between aliskiren/amlodipine/HCTZ triple combination and component dual combinations.

7.3.5 Submission Specific Primary Safety Concerns

There are no submission specific primary safety concerns. Per discussion in section 7.4.1 below, the safety profile of the triple therapy is similar to the safety profile of the various dual therapies, and is in line with the expected AE profile of the individual monotherapy components.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In group B (which included all short term, double-blind, controlled studies, which included only SAH2302, the pivotal efficacy study, per discussion in section 7.1.3 above), adverse events (AEs) that reached a threshold of 2% or more in any group are tallied in Table 41 below. AE rates were very similar in all the various treatment groups. In triple therapy, the rate of AE's was 36.2%; while the rate of AE's in the various dual therapy arms ranged from 32.3% to 33.6%. See Table 41 below for breakdown of most common AE's by treatment group.

Reviewer's comment: AE rates were very similar between the triple therapy arm (36.2%) and the dual therapy arms (32.3-33.6%). This is very supportive for safety profile of the triple therapy.

The most common AE was peripheral edema. Peripheral edema was highest in the treatment arms containing amlodipine, as amlodipine is well known to cause peripheral edema. Rate of peripheral edema in the triple therapy arm was 7.1%, while it 8.0% in the aliskiren\amlodipine arm. Peripheral edema was lowest, as expected, in the arm

containing no amlodipine, the aliskiren\ HCTZ arm (2.0%). All cases of peripheral edema were mild to moderate in severity.

Reviewer's comment: It's quite possible that the lower rate of peripheral edema observed in the triple therapy as compared to aliskiren\amlo is due to the addition of HCTZ, which may function as a counteracting force to amlodipine in effect on peripheral edema.

Other common AE's were dizziness, headache, nasopharyngitis, fatigue, and cough. Dizziness AE was 3.6% in the triple therapy arm; similar to the level observed in the aliskiren\amlo arm (3.4%). All cases of dizziness were mild to moderate; none was severe. The remaining AEs were observed at similar rates in triple therapy as compared to the dual therapy arms.

In Group B, the following percentage of patients discontinued from study due to AE's: 2.4% (n=7) of patients in the aliskiren\amlo group, 0.7% (n=2) in the aliskiren\ HCTZ group, 2.7% (n=8) in the amlodipine\ HCTZ group, and 3.6% (n=11) in the triple therapy group. Of note, none of the discontinuations in the triple therapy group were related to issues of dizziness, hypotension, or other AE's related to low blood pressure. Peripheral Edema was a common AE for discontinuation. This included one patient in the triple therapy arm, two in the aliskiren \ amlodipine arm and two in the amlodipine \ HCTZ arm.

Reviewer's Comment: The AE profile observed in triple therapy was similar to that observed in the dual therapy arms and was consistent with the AE profile expected from the individual monotherapy components.

Table 41: Number (%) Of Patients With Most Frequent AEs (At Least 2% For Any Group) By Preferred Term (Safety Set) Group B: Study SAH2302, Short-Term, Double-Blind, All Controlled Study (Sponsor's Table)

Preferred term	All Ali/Aml N=287 n (%)	All Ali/HCTZ N=297 n (%)	All Aml/HCTZ N=295 n (%)	All Ali/Aml/HCTZ N=309 n (%)
Any adverse experience	96 (33.4)	96 (32.3)	99 (33.6)	112 (36.2)
Oedema peripheral	23 (8.0)	6 (2.0)	12 (4.1)	22 (7.1)
Dizziness	7 (2.4)	10 (3.4)	5 (1.7)	11 (3.6)
Headache	9 (3.1)	12 (4.0)	15 (5.1)	11 (3.6)
Nasopharyngitis	2 (0.7)	6 (2.0)	10 (3.4)	8 (2.6)
Fatigue	1 (0.3)	6 (2.0)	4 (1.4)	6 (1.9)
Cough	4 (1.4)	0 (0.0)	6 (2.0)	1 (0.3)

In Group C (which included all long term, open label studies; defined in section 7.1.3 above as Studies SAH2301 and SPA2301), 647 patients received triple therapy, 324 (50.1%) of which experienced AEs. Of the 556 on aliskiren\ amlodipine dual therapy, 413 (74%) experienced AEs. The most common AEs were peripheral edema, headache, bronchitis, and nasopharyngitis. Peripheral edema was higher in the aliskiren \ amlodipine dual therapy group (20.5%) as compared to the triple therapy group (9.9%). This can possibly be attributed to the diuretic properties of HCTZ. Headache was also common, though, again, lower in the triple therapy group (3.9%) as compared to the dual therapy group (6.7%). These and the remaining AE's (all listed in Table 42 below) are shown to have the same profile: with the AE being of lower incidence in the triple therapy arm as compared to the dual therapy arm. Moreover, only 3.9% of AEs in the triple therapy arm were severe, while 7.2% of the dual therapy arm were severe.

Reviewer's comment: The prominence of peripheral edema in this AE profile (the commonest AE) is expected as all treatment arms included an amlodipine component, which is well known to cause peripheral edema. The remaining AEs are of acceptably low incidence. Moreover, the fact that incidence of AE's was so much higher in Group C as compared to Group B is clearly a function of Group C being comprised of term studies, while Group B being comprised a of short term study.

Reviewer's comment: the comparison of the triple therapy arm to the double therapy arm in Group C is un-interpretable since some of the patients on triple therapy in Group C only received triple therapy if their BP was uncontrolled on dual therapy. Therefore, these particular triple therapy patients were a different population than the dual therapy patients, and their AE rates cannot be compared.

Table 42: Number (%) Of Patients With Most Frequent AEs (At Least 2% For Any Group) By Preferred Term (Safety Set) In Group C: Studies SAH2301 and SPA2301 Long-Term Open-Label Studies (Sponsor's Table)

Preferred term	Ali/Aml N=556 n (%)	Ali/Aml/HCTZ* N=647 n (%)
Any adverse experience	413 (74.3)	324 (50.1)
Oedema peripheral	114 (20.5)	64 (9.9)
Headache	37 (6.7)	25 (3.9)
Bronchitis	30 (5.4)	24 (3.7)
Nasopharyngitis	26 (4.7)	22 (3.4)
Influenza	29 (5.2)	17 (2.6)
Back pain	25 (4.5)	16 (2.5)
Diarrhoea	15 (2.7)	15 (2.3)
Upper respiratory tract infection	37 (6.7)	15 (2.3)
Dizziness	28 (5.0)	12 (1.9)
Arthralgia	24 (4.3)	11 (1.7)
Cough	13 (2.3)	11 (1.7)
Pain in extremity	12 (2.2)	10 (1.5)
Fatigue	15 (2.7)	9 (1.4)
Nausea	13 (2.3)	9 (1.4)
Urinary tract infection	12 (2.2)	8 (1.2)
Sinusitis	21 (3.8)	7 (1.1)
Palpitations	12 (2.2)	6 (0.9)
Vertigo	13 (2.3)	6 (0.9)
Musculoskeletal pain	12 (2.2)	2 (0.3)
Joint swelling	17 (3.1)	1 (0.2)

* In [\[Study SAH2301\]](#) patients also received one week of treatment with aliskiren/HCTZ, prior to being force titrated to aliskiren/amlodipine/HCTZ; the AEs reported during this treatment are given in [\[SCS PT-Table 4.1-7\]](#)
Source: [\[SCS PT-Table 4.1-7\]](#)

In Group D (which included all long term, double-blind studies; defined in section 7.1.3 above as including only Study SPP2344). Of the 51 patients who received aliskiren-based triple therapy, 14 (27.5%) experienced AEs, with the three most common being cough, dizziness, and peripheral edema. All cases of peripheral edema were mild to moderate in severity. See Table 43 below for full listing of AEs.

Reviewer's Comment: These 51 patients were not randomized to aliskiren-based triple therapy. Rather, they were randomized to Aliskiren-based therapy overall. They only received aliskiren-based triple therapy if their BP was uncontrolled on mono and dual therapy.

Table 43: Number (%) Of Patients With Most Frequent AEs (At Least 2% For Any Group) By Preferred Term (Safety Set) In Group D: Study SPP2344, Long-Term Double-Blind Study (Sponsor's Table)

Preferred term	Ali/Aml/HCTZ (N=51) n (%)	Ramipril/Aml /HCTZ (N=68) n (%)	Total Ali (N=452) n (%)	Total Ramipril (N=444) n (%)
Any adverse experience	14 (27.5)	21 (30.9)	328 (72.6)	336 (75.7)
Cough	2 (3.9)	1 (1.5)	19 (4.2)	59 (13.3)
Dizziness	2 (3.9)	3 (4.4)	34 (7.5)	37 (8.3)
Oedema peripheral	2 (3.9)	1 (1.5)	22 (4.9)	18 (4.1)
Arthralgia	1 (2.0)	0	17 (3.8)	8 (1.8)
Back pain	1 (2.0)	0	21 (4.6)	15 (3.4)
Diarrhoea	1 (2.0)	0	30 (6.6)	22 (5.0)
Fatigue	1 (2.0)	1 (1.5)	28 (6.2)	20 (4.5)
Insomnia	1 (2.0)	3 (4.4)	16 (3.5)	15 (3.4)
Nasopharyngitis	1 (2.0)	0	23 (5.1)	20 (4.5)
Nausea	1 (2.0)	0	19 (4.2)	16 (3.6)
Sinusitis	1 (2.0)	0	15 (3.3)	12 (2.7)
Upper respiratory tract infection	1 (2.0)	1 (1.5)	35 (7.7)	28 (6.3)
Urinary tract infection	1 (2.0)	2 (2.9)	17 (3.8)	25 (5.6)
Bronchitis	0	0	7 (1.5)	16 (3.6)
Constipation	0	0	11 (2.4)	13 (2.9)
Headache	0	1 (1.5)	42 (9.3)	40 (9.0)
Rash	0	0	14 (3.1)	4 (0.9)

The remaining two supportive studies to analyze for AEs are: SPP2360 and SPP2411. In SPP2360, in the 119 patients who received the aliskiren-based triple therapy, the overall incidence of AEs was 6.7%, with none of these occurring at an incidence greater than or equal to 2% (in the triple therapy group). In SPP2411, there were 29 patients treated with aliskiren-based triple therapy and 4 patients had AEs (13.8%) compared to 50 patients treated with amlodipine/HCTZ where 14 patients had AEs (28.0%).

7.4.2 Laboratory Findings

Hematology:

Table 44, below, lists the thresholds used for laboratory data to determine whether results for “low” or “high”.

In group B (which included all short term, double-blind, controlled studies, which included only SAH2302, the pivotal efficacy study, per discussion in section 7.1.3 above), hemoglobin dropped an average of 1.9g/L from baseline in the triple therapy group; not as much of a drop, though, as occurred in one of the dual therapy groups (the Aliskiren\ amlodipine group), which experienced an average decrease of 2.8 g/L. See Table 45 below for data on all 4 arms. Moreover, an analysis of hemoglobin changes from baseline to post-baseline extreme value showed that shifts from normal to

low hemoglobin occurred in only 1.3% of patients on triple therapy, which was the smallest rate as compared to the dual therapy arms (aliskiren\ amlodipine was 3.2%, aliskiren\ HCTZ was 2.8%, and amlodipine\ HCTZ was 1.7%).

Reviewer's Comment: The triple therapy group's smaller average decrease in hemoglobin as compared to one of the dual therapy arms is supportive of the triple therapy safety profile, as is the lower rate of change from baseline to post-baseline extreme.

In terms of hematocrit, one patient (0.3%) in the triple therapy group experienced a decrease of greater than 20%. No patients in the dual therapy groups experienced a decrease of 20% or greater. In the triple therapy group, no patients discontinued treatment due to AE of anemia or any other abnormal lab value.

Table 44: Threshold For Laboratory Data Percentage Change From Baseline (Sponsor's Table)

Laboratory Variables	Low	High
Hematology		
Hemoglobin	>20% decrease	>50% increase
Hematocrit	>20% decrease	>50% increase
RBC count	>20% decrease	>50% increase
WBC count	>50% decrease	>50% increase
Platelet count	>50% decrease	>75% increase
Biochemistry		
Sodium	>5% decrease	
Potassium	>20% decrease	>20% increase
Chloride	>10% decrease	>10% increase
Calcium	>10% decrease	>10% increase
Creatinine		>50% increase
BUN		>50% increase
Glucose	>50% decrease	>50% increase
ALT (SGOT)		>150% increase
AST (SGPT)		>150% increase
Alkaline phosphatase		>100% increase
Total bilirubin		>100% increase
Uric acid		>50% increase
CK		>300% increase
In addition, criteria that are of clinical significance were identified for BUN, creatinine, and potassium: potassium (≥ 6 mmol/L, > 5.5 mmol/L, and < 3.5 mmol/L), blood urea nitrogen (BUN > 14.28 mmol/L), and creatinine (> 176.8 μ mol/L).		

Table 45: Change in Mean Hemoglobin By Treatment Arm (Reviewer's Table)

Treatment Arm	↓ mean Hgb (g/L)
Ali/Aml (N=287)	-2.8
Ali/HCTZ (N=297)	0.2
Aml/HCTZ (N=295)	-0.7
Ali/Aml/HCTZ(N=309)	-1.9

Group C and D:

In Group C (which included all long term, open label studies; defined in section 7.1.3 above as Studies SAH2301 and SPA2301), there was almost no change in mean hemoglobin from baseline to endpoint in the aliskiren\amlo\ HCTZ group (0.2g/L)

In Group D (which included all long term, double-blind studies; defined in section 7.1.3 above as Study SPP2344), the change in mean hemoglobin in the aliskiren-based triple therapy patients was -0.7 g/L, as compared to -1.5 g/L in the Ramipril-based triple therapy patients.

The percentage of patients with >20% decrease in hemoglobin at any post-baseline visit was low in Group C (2 patients, 0.3%, one in the normal range, one low) in the aliskiren/amlodipine/HCTZ group and 2 patients (0.4%, both low compared to the normal range) in the aliskiren/amlodipine group. There were no patients who discontinued treatment due to anemia in Group C or in Group D.

Hematology in the two remaining supportive studies (SPP2360 and SPP2411) demonstrated only small, non-clinically meaningful changes in hematologic parameters.

Clinical Chemistry:

For group B (which included all short term, double-blind, controlled studies, which included only SAH2302, the pivotal efficacy study, per discussion in section 7.1.3 above), summary of potassium, BUN, and creatinine can be found in Table 46 below. Hyperkalemia ($K > 5.5$ mmol/L) incidence was low in all groups though slightly higher in the aliskiren/amlodipine/HCTZ group (3.0% of patients). The incidence of hypokalemia ($K < 3.5$ mmol/L at any post baseline visit) was higher in treatment groups containing HCTZ. However, the treatment groups also containing aliskiren had a lower incidence (4.4% in aliskiren/HCTZ and 11.0% in aliskiren/amlodipine/HCTZ) than the amlodipine/HCTZ group (19.0%).

Reviewer's Comment: triple therapy's effect on potassium appears to be in line with the effect of the various dual therapies on serum potassium. Moreover, the fact that aliskiren\amlo\HCTZ had less hypokalemia than amlodipine\HCTZ suggests that HCTZ and aliskiren might have balancing effects on potassium.

BUN and Creatinine levels did not exceed the predetermined cutoffs in any patients on triple therapy. Uric acid increased in all treatment groups containing HCTZ. However, the increase in the aliskiren/amlodipine/HCTZ group (40.8 µmol/L) was less than in the aliskiren/HCTZ group (56.9 µmol/L).

Table 46: Summary Of Potassium, BUN, And Creatinine By Specified Criteria (Safety Set), Group B: Study SAH2302; Short-Term, Double-Blind, All Controlled Study (Sponsor's Table)

Laboratory test	Criterion		Alii/Aml (N=287)		Alii/HCTZ (N=297)		Aml/HCTZ (N=295)		Alii/Aml/HCTZ (N=309)	
			n	%	n	%	n	%	n	%
Potassium	≥ 6.0 mmol/L	Total No.	280	100	293	100	294	100	300	100
		No. of patients meeting criterion	1	0.4	0	0.0	3	1.0	3	1.0
	> 5.5 mmol/L	Total No.	280	100	293	100	294	100	300	100
		No. of patients meeting criterion	2	0.7	2	0.7	6	2.0	9	3.0
	< 3.5 mmol/L	Total No.	280	100	293	100	294	100	300	100
		No. of patients meeting criterion	6	2.1	13	4.4	56	19.0	33	11.0
Blood Urea Nitrogen (BUN)	> 14.28 mmol/L	Total No.	280	100	293	100	294	100	300	100
		No. of patients meeting criterion	0	0.0	2	0.7	0	0.0	0	0.0
Creatinine	> 176.8 umol/L	Total No.	280	100	293	100	294	100	300	100
		No. of patients meeting criterion	0	0.0	0	0.0	0	0.0	0	0.0

In Group C (which included all long term, open label studies; defined in section 7.1.3 above as Studies SAH2301 and SPA2301), most changes from baseline to endpoint were similar among the treatment groups. A small and not meaningful decrease in potassium was observed in the aliskiren/amlodipine/HCTZ group (-0.136 mmol/L) and aliskiren/amlodipine group (-0.031 mmol/L). Uric acid increased in the aliskiren/amlodipine/HCTZ group (30.9 µmol/L) while remained almost unchanged in the aliskiren/amlodipine group (-4.7 µmol/L).

Reviewer's comment: The increase in uric acid in aliskiren/amlodipine/HCTZ can plausibly be attributed to the known effect of HCTZ on decreasing excretion of uric acid.

The changes in creatinine from baseline, between the treatment groups, were minor and not clinically meaningful.

Table 47 below displays the number and percentage of patients meeting pre-specified criteria for certain potentially clinically significant laboratory parameters. Hyperkalemia ($K > 5.5$ mmol/L) incidence was similar in both groups (2.2% in the aliskiren/amlodipine group and 2.3% in the aliskiren/amlodipine/HCTZ group). It should be noted that in 3 of the 7 aliskiren/amlodipine/HCTZ treated patients with $K \geq 6$ mmol/L, the increase in K was caused by technical issues (uncentrifuged blood samples due to malfunction of centrifuge at one site). The potassium values at the subsequent visit for those 3 patients were within normal range. The incidence of hypokalemia ($K < 3.5$ mmol/L at any post baseline visit) was higher in the aliskiren/amlodipine/HCTZ treated patients compared to aliskiren/amlodipine treated patients, which might be expected due to the known potassium lowering effect of the HCTZ component. A small number of patients (0.3% for BUN and 0.2% for creatinine) met the specified criteria (Table 47) in the aliskiren/amlodipine/HCTZ group, whereas none did so in the aliskiren/amlodipine treatment group.

Table 47: Summary Of Potassium, BUN, And Creatinine By Specified Criteria (Safety Set), Group C: Studies SAH2301 And SPA2301 Long-Term, Open-Label Studies (Sponsor's Table)

Laboratory test	Criterion		Ali/Aml (N=470)		Ali/Aml/HCTZ (N=650)	
			n	%	n	%
Potassium	≥ 6.0 mmol/L	Total No.	463	100	640	100
		No. of patients meeting criterion	4	0.9	7	1.1
	> 5.5 mmol/L	Total No.	463	100	640	100
		No. of patients meeting criterion	10	2.2	15	2.3
	< 3.5 mmol/L	Total No.	463	100	640	100
		No. of patients meeting criterion	9	1.9	75	11.7
Blood Urea Nitrogen (BUN)	> 14.28 mmol/L	Total No.	463	100	640	100
		No. of patients meeting criterion	0	0.0	2	0.3
Creatinine	> 176.8 umol/L	Total No.	463	100	640	100
		No. of patients meeting criterion	0	0.0	1	0.2

In Group D (which included all long term, double-blind studies; defined in section 7.1.3 above as only Study SPP2344), a small decrease in potassium was seen in the

aliskiren/amlodipine/HCTZ group (-0.196 mmol/L) which was similar to the ramipril/amlodipine/HCTZ group (-0.168 mmol/L). Uric acid increase was seen with similar magnitude for aliskiren/amlodipine/HCTZ (58.9 µmol/L) and ramipril/amlodipine/HCTZ (56.8 µmol/L). Hyperkalemia ($K > 5.5$ mmol/L) incidence was low in all groups including aliskiren/amlodipine/HCTZ group (1 patient, 2.0%). The incidence of hypokalemia ($K < 3.5$ mmol/L at any post baseline visit) was slightly higher in the ramipril/amlodipine/HCTZ group (4.4%) than in the aliskiren/amlodipine/HCTZ group (3.9%). One patient (2.0%) met the specified criteria for BUN values in the aliskiren/amlodipine/HCTZ group.

Table 48: Summary Of Potassium, BUN, And Creatinine By Specified Criteria (Safety Set), Group D: Study SPP2344, Long-Term, Double-Blind, All Controlled Studies (Sponsor's Table)

	Ali/Aml /HCTZ (N=51) n %	Ramipril/ Aml/HCTZ (N=68) n %	Total Ali (N=452) n %	Total Ramipril (N=444) n %
Potassium				
Total	51	68	437	430
≥ 6.0 mmol/L	0	0	5 (1.1)	2 (0.5)
> 5.5 mmol/L	1 (2.0)	0	8 (1.8)	9 (2.1)
< 3.5 mmol/L	2 (3.9)	3 (4.4)	10 (2.3)	10 (2.3)
Blood Urea Nitrogen (BUN)				
Total	51	68	437	430
> 14.28 mmol/L	1 (2.0)	0	5 (1.1)	1 (0.2)
Creatinine				
Total	51	68	437	430
> 176.8 µmol/L	0	0	2 (0.5)	1 (0.2)

Clinical chemistry in the remaining two supportive studies, SPP2360 and SPP2411, follows.

For Study SPP2360, changes from baseline for each biochemistry parameter were small. Mean increases in creatinine were observed in all three treatment steps (for patients during the treatment step: aliskiren monotherapy 0.9 µmol/L, aliskiren/HCTZ 2.5 µmol/L, and aliskiren/HCTZ/amlodipine 5.3 µmol/L).

Reviewer's comment: These changes in creatinine do not appear to be clinically significant.

Mean increases in uric acid were observed in patients during the aliskiren monotherapy, aliskiren/HCTZ and aliskiren/HCTZ/amlodipine treatment steps (12.9 µmol/L, 33.2 µmol/L and 35.9 µmol/L, respectively). The minor shifts in BUN were not clinically

relevant. There were no clinically relevant changes in potassium(-0.1to -0.3 mmol/L) or uric acid (33.2 – 59.0 μ mol/L) in any of the treatment groups compared to baseline.

In Study SPP2411, a generally low proportion of patients had shifts from normal biochemistry values at baseline to values outside the normal range. There were no cases of hyperkalemia ($K > 5.5$ mmol/L) in the aliskiren/amlodipine/HCTZ treatment group.

Vital Signs:

There were no clinically significant changes from baseline in body weight or sitting and standing pulse rate in any of the treatment groups in the pooled populations.

Orthostatic blood pressure changes:

Orthostatic blood pressure change were defined as a decrease of at least 20mmHg in systolic blood pressure (SBP) or a decrease of at least 10mmHg in diastolic blood pressure (DBP) when a patient moved from a sitting position to a standing position.

For group B, the incidence of orthostatic BP changes is summarized by treatment group for SAH2302 in Table 49 below. In general, orthostatic BP change was similar or lower at individual post-baseline visits compared to baseline for all treatment groups. There is no increase in incidence of orthostatic BP with increase of the dose for the triple combination. When orthostatic BP changes at any visit post-baseline were considered, the incidence with aliskiren/amlodipine/HCTZ (15.3%) treatment was similar to both the aliskiren/amlodipine(15.5%) and amlodipine/HCTZ (15.3%).

Table 49: Incidence Of Orthostatic Blood Pressure Change (Safety Set), Group B: Study SAH2302; Short-Term, Double-Blind, All Controlled Study (Sponsor's Table)

	Alii/Aml N = 287			Alii/HCTZ N = 297			Aml/HCTZ N = 295			Alii/Aml/HCTZ N = 309		
	Total	n	(%)	Total	n	(%)	Total	n	(%)	Total	n	(%)
Baseline	280	16	(5.7)	294	30	(10.2)	291	18	(6.2)	303	22	(7.3)
Day 4	277	16	(5.8)	292	11	(3.8)	291	11	(3.8)	301	15	(5.0)
Week 1	275	12	(4.4)	290	6	(2.1)	289	7	(2.4)	300	10	(3.3)
Week 2	275	10	(3.6)	290	13	(4.5)	293	13	(4.4)	299	12	(4.0)
Week 4	277	11	(4.0)	282	9	(3.2)	290	10	(3.4)	297	6	(2.0)
Week 4 endpoint	283	11	(3.9)	296	10	(3.4)	294	10	(3.4)	307	6	(2.0)
Week 6	273	3	(1.1)	279	7	(2.5)	286	7	(2.4)	292	7	(2.4)
Week 8	267	7	(2.6)	277	6	(2.2)	277	16	(5.8)	288	4	(1.4)
Week 8 endpoint	283	7	(2.5)	296	8	(2.7)	294	17	(5.8)	307	4	(1.3)
Any visit (post-baseline)	283	44	(15.5)	296	35	(11.8)	294	45	(15.3)	307	47	(15.3)

Orthostatic blood pressure change was defined as a decrease of at least 20 mmHg in systolic blood pressure or a decrease of at least 10 mmHg in diastolic blood pressure when a patient moved from a sitting position to a standing position. Total is the number of patients evaluated at that visit.
Week 4/8 endpoint is the Week 4/8 value or LOCF

For Group C, incidence of orthostatic BP changes is summarized in Table 50 below. In aliskiren/amlodipine/HCTZ treated patients, orthostatic BP change was similar or lower at individual post-baseline visits compared to baseline. When orthostatic BP changes at any visit post-baseline were considered, the incidence with aliskiren/amlodipine/HCTZ treatment(16.6%) was similar to that observed in the short-term studies.

Table 50: Incidence Of Orthostatic Blood Pressure Change (Safety Set), Group C: Studies SAH2301 And SPA2301, Long-Term, Open Label Studies (Sponsor's Table)

Visit	Ali/Aml N=470		Ali/Aml/HCTZ N=650	
	Total	n (%)	Total	n (%)
Baseline	470	5 (1.1)	649	32 (4.9)
Week 1			563	28 (5.0)
Week 2	466	12 (2.6)	645	25 (3.9)
Week 4	459	11 (2.4)	637	21 (3.3)
Week 6	453	6 (1.3)	629	18 (2.9)
Week 10	440	8 (1.8)	86	3 (3.5)
Week 14	428	4 (0.9)	85	4 (4.7)
Week 16			531	22 (4.1)
Week 28	415	3 (0.7)	589	28 (4.8)
Week 41	396	4 (1.0)	280	4 (1.4)
Week 54	383	4 (1.0)	273	5 (1.8)
End point	467	4 (0.9)	650	28 (4.3)
Any visit (post-baseline)	467	40 (8.6)	650	108 (16.6)

For Group D, the incidence of orthostatic BP changes is summarized in Table 51 below. When orthostatic BP changes at any visit post-baseline were considered, the incidence with aliskiren/amlodipine/HCTZ (25.5%) was slightly higher than with ramipril/amlodipine/HCTZ (20.6%). The incidence of orthostatic BP change in all patients treated with the aliskiren regimen (18.4%) was similar to in all patients treated with the ramipril regimen (18.0%).

Table 51: Incidence Of Orthostatic Blood Pressure Change (Safety Set), Group D: Study SPP2344; Long-Term, Double-Blind Study (Sponsor's Table)

Visit	Ali/Aml/HCTZ (N=51) Total n (%)	Ramipril/Aml/HCTZ (N=68) Total n (%)	Total Ali (N=452) Total n (%)	Total Ramipril (N=444) Total n (%)
Baseline	51 2 (3.9)	68 2 (2.9)	451 20 (4.4)	442 13 (2.9)
Week 2	51 4 (7.8)	68 1 (1.5)	440 20 (4.5)	435 12 (2.8)
Week 4	51 3 (5.9)	68 1 (1.5)	416 20 (4.8)	418 8 (1.9)
Week 8	51 1 (2.0)	68 4 (5.9)	399 15 (3.8)	403 19 (4.7)
Week 12	51 2 (3.9)	68 2 (2.9)	378 16 (4.2)	389 18 (4.6)
Week 16	51 2 (3.9)	68 2 (2.9)	370 14 (3.8)	369 15 (4.1)
Week 22	51 2 (3.9)	68 3 (4.4)	359 11 (3.1)	362 17 (4.7)
Week 28	51 6 (11.8)	67 2 (3.0)	353 13 (3.7)	348 9 (2.6)
Week 36	51 1 (2.0)	66 3 (4.5)	344 8 (2.3)	337 11 (3.3)
Endpoint	51 1 (2.0)	68 4 (5.9)	445 13 (2.9)	439 17 (3.9)
Any visit	51 13 (25.5)	68 14 (20.6)	445 82 (18.4)	439 79 (18.0)

In terms of Study SPP2360, at baseline, 3.5% of the overall population had orthostatic BP changes. The incidence of patients with orthostatic changes at any visit ranged from 0.8%- 5.6%. The proportion of patients with orthostatic changes at any post-baseline visit was 11.2%. This information is tabulated in Table 52 below.

Table 52: Number (%) Of Patients With Orthostatic Blood Pressure, By Visit (Study SPP2360, Safety Set) (Sponsor's Table)

Visit	N=256	
	N	n (%)
Baseline	254	9 (3.5)
Visit 4	251	14 (5.6)
Visit 5	226	6 (2.7)
Visit 6	196	4 (2.0)
Visit 7	154	8 (5.2)
Visit 8	119	1 (0.8)
Visit 9	77	2 (2.6)
Any visit (post-baseline)	251	28 (11.2)

For Study SPP2411, the standing BP was not measured so orthostatic BP change was not assessed.

7.4.4 Electrocardiograms (ECGs)

No post-baseline electrocardiograms (ECGs) were performed in studies included in this submission. The effects of aliskiren on ECG intervals were studied during its development and it was demonstrated that aliskiren did not prolong the QT interval.

Moreover, amlodipine is not known to cause ECG changes either. HCTZ is not known to cause ECG changes either. However, in the case of electrolyte abnormalities secondary to the use of HCTZ, relevant ECG changes may occur.

7.4.5 Special Safety Studies/Clinical Trials

Special safety studies were not performed with the combination of aliskiren, amlodipine, and HCTZ.

7.4.6 Immunogenicity

The AE profile of the triple therapy did not show a pattern of increased adverse events of potentially immunogenic etiology. Moreover, Aliskiren, amlodipine, and HCTZ are all small molecules that by themselves should have little immunogenic potential.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The most common adverse event, peripheral edema, demonstrated a dose dependency in the pivotal efficacy study (SAH2302). In the low dose triple therapy period, only 1.6% (5 of 209) of triple therapy patients reported peripheral edema, while 6.1% (18 of 296) reported in the high dose triple therapy group. None of the other most common AEs demonstrated a dose-dependency. Rate of reported headaches went from 3.2% down to 0.7% when comparing low dose to high dose (respectively), and rate of dizziness was roughly flat, going from 1.9% to 1.7% respectively.

An analysis of the pivotal efficacy study, SAH2302, demonstrates that going from low dosage triple therapy to high dosage therapy did not increase discontinuations secondary to AEs. In fact, the opposite was observed. Discontinuations secondary to AEs went from 2.3% to 1.4% when comparing the low dose phase of the study to the high dose phase.

Reviewer's Comment: The label should indicate that dose-dependent peripheral edema was clearly observed.

7.5.2 Time Dependency for Adverse Events

No significantly time-dependent adverse events were observed with this product in either the pivotal efficacy study or the major safety study. Peripheral edema, for example, the most common AE in this study, demonstrated a well distributed time distribution in terms of the start date of the event in patients.

7.5.3 Drug-Demographic Interactions

Gender:

Peripheral Edema was the most common AE in this study. In Group C (which included the major safety study SAH 2301 as well as another long term open-label study, SPA2301), peripheral edema was reported in 45.8% of males and 56.2% of females who received triple therapy. This difference was driven by peripheral edema having higher incidence in females.

Race\Ethnicity:

There were no obvious differences in AE profile between races and ethnicities.

Age:

In the pivotal efficacy study, SAH2302, AE incidence for patients on triple therapy broke down as follows: <65 years old (34.4%, n=86), ≥65 years old (44.1%, n=26), >75 years old (18.2%, n=2). One of the main areas of concern in terms of AEs in the elderly is AE's related to hypotension. These include: dizziness, postural dizziness, presyncope, syncope, and hypotension. Analysis of Table 53 below clearly demonstrates that the triple therapy patients ≥65 years old had more AE's than the <65 year old subjects. Specifically, dizziness in triple therapy patients was reported in 2.8% of patients less than 65 years old and 6.8% of patients ≥ 65 years old. Similar disparities are seen for postural dizziness and hypotension. Similar disparities were seen in Group C, which included the long term open label studies. In group C, 6.4% of patients <65 years old discontinued due to AE's, 9.2% of patients ≥65 years old, and 12.5% of patients ≥75 years old. In terms of peripheral edema, in group C, for patients on triple therapy, 9.6% (77 of 615) of patients <75 years old reported peripheral edema, while 15.6% (5 of 32) was reported in patients ≥75 years old.

Reviewer's Comment: The Label should accordingly warn that:

- *AE's related to hypotension are more common in those ≥ 65 years old and should therefore be monitored more closely in that age group.*
- *Discontinuations due to AE's more common in patients ≥65 years old compared to those <65 and more common in those ≥75 than those < 75.*
- *Peripheral edema was reported in higher rate in patients ≥75 years old as compared to those <75 years old.*

Table 53: Number (%) Of Patients With AEs Potential Related To Low Blood Pressure, By Age Group, Group B, Study SAH2302 (Short Term, Double Blind, All Controlled Study) (Safety Population) (Sponsor's Table)

Age group Preferred term	Alii/Aml				Alii/HCTZ				Aml/HCTZ				Alii/Aml/HCTZ			
	< 65y N=237	≥ 65y N=50	≥ 75y N=10	Total N=287	< 65y N=241	≥ 65y N=56	≥ 75y N=13	Total N=297	< 65y N=232	≥ 65y N=63	≥ 75y N=8	Total N=295	< 65y N=250	≥ 65y N=59	≥ 75y N=11	Total N=309
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dizziness	7 (3.0)	0 (0.0)	0 (0.0)	7 (2.4)	7 (2.9)	3 (5.4)	0 (0.0)	10 (3.4)	5 (2.2)	0 (0.0)	0 (0.0)	5 (1.7)	7 (2.8)	4 (6.8)	0 (0.0)	11 (3.6)
Dizziness Postural	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.7)	0 (0.0)	2 (0.6)
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.3)

7.5.4 Drug-Disease Interactions

The overall frequency of AEs in Group C (which included the major long term open label safety study, SAH2301, as well as one other long term open label study) was similar for patients treated with triple therapy regardless of baseline renal function or baseline diabetic status.

Patients with moderate renal impairment comprised 5.9% of the population (66 of 1120 treated patients) in Group C (the long-term, open-label studies). The overall frequency of AEs in Group C was similar for all patients treated with aliskiren/amlodipine/HCTZ regardless of baseline renal function. For patients with GFR ≥ 30 and < 60 ml/min/1.73m², AE rate was 44.9% versus 50.1% in the overall population.

Similarly, diabetics in group C on triple therapy demonstrated an overall AE incidence rate (44.5%) similar to that demonstrated in the overall population (50.1%).

7.5.5 Drug-Drug Interactions

See Section 7.2.5 above.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Additional risk of the human carcinogenicity was not observed in the triple combination therapy group as compared to the dual therapy groups.

7.6.2 Human Reproduction and Pregnancy Data

There were two pregnancies during the major safety study (SAH2301). However, in neither case was the patient taking aliskiren/amlodipine/HCTZ.

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Aliskiren was not studied during pregnancy, and is not to be used in women who are pregnant or may become pregnant. There is also no clinical experience with amlodipine in pregnancy. Hydrochlorothiazide crosses the placenta. Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with fetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults. As a result, aliskiren/amlodipine/HCTZ is not recommended for use in pregnancy or in women planning to become pregnant.

It is not known whether aliskiren or amlodipine are excreted in human milk, though Aliskiren is secreted in the milk of lactating rats. Thiazides, however, are known to be excreted in breast milk. Therefore, because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue any thiazide-containing regimen (including this triple therapy product), taking into account the importance of the drug to the mother.

Reviewer's Comment: The above information should be (and is) included in the proposed label.

7.6.3 Pediatrics and Assessment of Effects on Growth

Sponsor did not conduct pediatric studies and did not submit pediatric data with this application. Sponsor requested that pediatric waiver be granted for this combination product. The Division previously waived the pediatric requirement for other aliskiren fixed dose combination products and it was largely on these grounds that sponsor requested a waiver of the pediatric requirement for this combination.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose:

There were no reports of overdose of aliskiren/amlodipine/HCTZ in the studies included in this submission, nor in a search of the Novartis Clinical Safety database. Nor was there any data available in this application related to aliskiren/amlodipine/HCTZ overdose in humans.

Abuse:

No specific abuse studies were conducted for triple therapy. However, preclinical and clinical studies have not indicated any potential for dependence with aliskiren or amlodipine or HCTZ, and there is no reason to suspect potential for abuse in humans.

Reviewer's Comment: Based on the known pharmacology of the monotherapy agents, no abuse potential is expected.

Withdrawal\Rebound:

The effect of treatment withdrawal was not studied specifically with the aliskiren/amlodipine/HCTZ combination. However, as described in the original aliskiren monotherapy submission, no withdrawal or rebound effects on efficacy of aliskiren monotherapy have been observed. With cessation of aliskiren monotherapy, BP gradually returned toward baseline levels over a period of several weeks (Andersen et al 2008). There was no evidence of rebound hypertension after abrupt cessation of aliskiren therapy. Moreover, there is no mention of withdrawal or rebound effects in the prescribing information for amlodipine or HCTZ.

Reviewer's Comment: Though it hasn't been studied explicitly, based on the existing data for the monotherapy components, there is no evidence of potential rebound effects with the aliskiren/amlodipine/HCTZ combination therapy.

7.7 Additional Submissions / Safety Issues

n/a.

8 Postmarket Experience

n/a.

9 Appendices

9.1 Literature Review/References

[Anderson K, Weinberger M, Egan B, et al (2008)] Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. J Hypertens; 26:589-599.

[Azizi M, Menard J, Bissery A, et al (2004)] Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II-renin feedback interruption. J Am Soc Nephrol; 15: 3126-3133.

[Bisognano J, McLaughlin T, Roberts CS, et al (2004)] Incremental effectiveness of amlodipine besylate in the treatment of hypertension with single and multiple medication regimens. Am J Hypertens; 17(8):676-683.

9.2 Labeling Recommendations

Labeling recommendations will be discussed separately.

9.3 Advisory Committee Meeting

No need arose for the convening of an advisory committee.

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

/s/

STEVEN T ARANOFF
11/23/2010

FANHUI KONG
11/23/2010

HSIEN MING J J HUNG
11/23/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 200-045

Applicant: Novartis

Stamp Date: 2/25/2010

Drug Name: (b) (4)

NDA/BLA Type: NDA 505(b)(2)

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			See eCTD module section 2.5, pages 49-53.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) RLD = Amlodipine Besylate, HCTZ
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	(See eCTD module section 2.5, page 18.) Sponsor did not conduct dose-ranging studies. Instead, sponsor selected dosage based on the approved and most commonly used dosages of the individual monotherapies.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: Study SAH2302 Indication: HTN  (b) (4) Safety Study: Study SAH2301 Indication: HTN	X			Pivotal [Study SAH2302] was a large, 8-week, double-blind, randomized, parallel-group, active-controlled trial to evaluate the efficacy and safety of the combination of aliskiren/amlodipine/HCTZ in patients with moderate to severe hypertension (mean sitting systolic blood pressure (msSBP) $\geq$160 mmHg and <200 mmHg and/or mean sitting diastolic blood pressure (msDBP) $\geq$100 mmHg and <120 mmHg). The study populations in [Study SAH2302] reflected the target populations of patients who were most likely to require combination therapy with 3 agents. The study included a large number of patients with severe hypertensive patients ($\geq$180 mmHg msSBP), therefore, it allowed the adequate assessment of the BP lowering effect for aliskiren/amlodipine/HCTZ triple combination therapy in this patient population. Long term safety study Study SAH2301 Study was a 28- to 54-week study evaluating the long-term efficacy and safety of the triple combination (aliskiren/amlodipine/HCTZ) in patients with moderate to severe hypertension. The study was comprised of 2 treatment periods. All patients had 28 weeks of treatment and approximately the first 200 patients completing the first 6 months of treatment continued in the study for an additional 26 weeks (a total of 54 weeks).
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Application appears to satisfy agreements made at pre-IND meeting between DCRP and sponsor. At the pre-IND meeting, we agreed to sponsor's study design (pivotal study 2302), patient selection (Stage 2 hypertensive patients based on either DBP or SBP), and the use of systolic blood pressure reduction as the primary efficacy endpoint in pivotal Study CSAH100A2302 as grounds for registration of the triple fixed combination with the following provisos: a. The triple combination must beat the double combinations by a clinically meaningful difference, i.e., 2 mm Hg. b. Sponsor must also show the effects of the combinations upon BP control throughout the interdosing interval. We suggested they provide such demonstration within an ABPM substudy.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Endpoints conform to previous agency agreements. See row 15 above. Also see "preNDA discussion".

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?		X		No post-baseline electrocardiograms (ECGs) were performed in studies included in this submission. Sponsor gave the following as justification: - The effects of aliskiren on ECG intervals were studied during its development and it was demonstrated that aliskiren did not prolong the QT interval. Please refer to the current aliskiren prescribing information. - Amlodipine does not change sinoatrial nodal function or atrioventricular (AV) conduction in intact animals or man. In clinical trials with angina patients, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks. Please refer to the current amlodipine prescribing information. - HCTZ is not known to cause ECG changes. However, in the case of electrolyte abnormalities secondary to the use of HCTZ, relevant ECG changes may occur.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Sponsor was not able to identify any triple combo studies outside of those conducted by sponsor. (see eCTD 2.5 p47.)
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?		X		At the pre-IND meeting, DCRP agreed to sponsor's proposal that a minimum of 800 patients would be exposed to the triple combination therapy, with 300 being exposed to the highest dose regimen for 6 months in study2301. Sponsor has satisfied this. (see eCDT module 2.5 p9). Throughout the clinical program, 1155 patients received at least 1 dose of any aliskiren/amlodipine/HCTZ combination, 568 patients received aliskiren/amlodipine/HCTZ combination for at least 180 days (6 months) and 182 patients received the combination for at least 360 days (1 year).
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	requested by the Division?				
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	I could not find it.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	I am not aware of any special study\data requests.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	This is not an application for Rx-to-OTC switch or direct-to-OTC.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested on the grounds that the Division previously waived the pediatric requirement for other aliskiren fixed dose combination products on the basis that data in pediatric patients will not be available for each of the components at the projected time of submission.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		X		(see eCTD Module 2.5, page 47.) Sponsor states that preclinical and clinical studies have not indicated any potential for dependence with aliskiren or amlodipine or HCTZ, and states that there is no reason to suspect potential for abuse in humans. Sponsor further states that based on the known pharmacology of the monotherapy agents, no abuse potential is expected. Specific investigations have therefore not been conducted.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	I'm not aware of any previous agreements on this issue.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			(See eCTD 2.5, p11.) Sponsor states that: - all studies: were conducted in full compliance with Good Clinical Practice (as stated in ICH Guideline E6 (1996)) and were closely monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it. - The choice of study design, controls, and efficacy criteria for the pivotal study in this submission followed international and regional guidelines.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer

Date

Clinical Team Leader

Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200045

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

/s/

STEVEN T ARANOFF
04/16/2010

ABRAHAM M KARKOWSKY
04/16/2010