

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200045Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA number	200045
Submission type	Standard 505(b)(2) , N_000
Submission date	02/25/2010, 07/30/2010
Applicant name	Novartis Pharmaceuticals Corporation
Proposed brand name	Not decided while writing this review
Generic name	Aliskiren/Amlodipine/Hydrochlorothiazide (Alis/Aml/HCTZ)
Dosage form	Film-coated tablet
Dosage strengths (Alis/Aml/HCTZ in mg)	300/10/25, 300/10/12.5, 300/5/25, 300/5/12.5, 150/5/12.5
Proposed indication	Hypertension (add-on and replacement therapy)
OCP division	Division of Clinical Pharmacology 1
OND division	Cardiovascular and renal products
Primary reviewer	Sudharshan Hariharan, Ph.D.
Secondary reviewer	Divya Menon-Andersen, Ph.D.
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1. EXECUTIVE SUMMARY

Novartis Pharmaceuticals Corporation is seeking approval via the 505(b)(2) pathway of Brandname, a fixed-dose combination (FDC) tablet of aliskiren /amlodipine/hydrochlorothiazide (Alis/Aml/HCTZ) for use as an add-on or replacement in the treatment of hypertension. Brandname will be marketed in five strengths for once daily administration.

The application contains four clinical pharmacology studies and six clinical studies in support of the sponsor's claims of efficacy and safety. These include two relative bioavailability studies (CSAH100A2104 and CSAH100A2105), one bioequivalence (BE) study (CSAH100A2102), one food effect study (CSAH100A2101), one pivotal active-controlled study for efficacy (SAH100A2302), one key long-term open-label study for efficacy and safety (SAH100A2301), two supportive active-controlled studies (SPP2344 and SPP2411) and two supportive long-term open-label studies (SPA2301 and SPP2360). A drug-drug interaction (DDI) sub-study was performed as a part of the pivotal efficacy trial (SAH100A2302).

1.1. Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) reviewed original NDA 200045 and recommends approval from a clinical pharmacology perspective.

1.2. Phase 4 Requirements / Commitments

There are no Phase 4 requirements or commitments.

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The components of Brandname are approved for use in hypertension, and their pharmacokinetic (PK) and pharmacodynamic (PD) properties were reviewed under submissions NDA 21-985 (aliskiren, Tekturna[®]), NDA 19-787 (amlodipine, Norvasc[®]) and NDA (b) (4) (hydrochlorothiazide, Esidrix[®]).

The Clinical Pharmacology and Biopharmaceutics program for Brandname was designed primarily to enable association of the efficacy and safety data of the monotherapies to the FDC. Of the four clinical pharmacology studies submitted to the NDA, one bioequivalence study, one relative bioavailability study and one food effect study were reviewed. The DDI sub-study performed as a part of pivotal efficacy trial was also reviewed.

The key clinical pharmacology and biopharmaceutics findings are listed below:

- ❖ The FDC of aliskiren/amlodipine/hydrochlorothiazide is bioequivalent to the free combination.
 - Bioequivalence was established in the relative bioavailability study (CSAH100A2104).
 - In the bioequivalence study (CSAH100A2102), the 90% CI for C_{max} of aliskiren (0.76, 0.93) was not contained within the pre-determined BE limits of 0.8 – 1.25. However, this is not clinically significant, because of a shallow exposure-response relationship¹.

¹ See Appendix for exposure-response analysis report

- ❖ There is no clinically relevant food effect on Brandname.
 - Systemic exposure to amlodipine and hydrochlorothiazide was not affected by food.
 - Systemic exposure to aliskiren was reduced by ~80% when Brandname 300/10/25 mg was administered with a high fat meal. This observation is consistent with prior findings for aliskiren and its fixed dose combinations, where this effect was judged to be clinically not significant². This is supported by the shallow exposure-response relationship of aliskiren. The current label(s) recommends establishing a routine pattern for taking aliskiren (and its fixed dose combinations) with regard to meals. Therefore, the same labeling language should be used for Brandname.
- ❖ There is no clinically relevant drug-drug interaction between aliskiren, amlodipine and hydrochlorothiazide when administered in combination.

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² Tekturna[®], Tekamlo[®] and Tekturna HCT[®] Package insert

2. QUESTION BASED REVIEW

This is an abridged version of the question based review.

2.1. General attributes of the individual components and the FDC

Brandname is a film coated, FDC tablet of aliskiren, amlodipine and hydrochlorothiazide. All three active pharmaceutical ingredient of Brandname have been previously approved for marketing in the US, for use in the treatment of hypertension. Dual combinations of aliskiren/amlodipine (Tekamlo[®]) and aliskiren/hydrochlorothiazide (Tekturna HCT[®]) have also been previously approved.

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

The physical and chemical properties have been summarized under OCP reviews of NDA 21-985 (DARRTS 01/11/2007) for aliskiren, NDA 19-787 (DFS/DARRTS 10/1/1990) for amlodipine and in the package insert for hydrochlorothiazide (Esidrix[®]).

Brandname is an immediate-release film-coated tablet. In addition to the active ingredients Brandname contains the following inactive excipients: microcrystalline cellulose, crospovidone, povidone, colloidal silicon dioxide, and magnesium stearate. (b) (4)

2.1.2. What are the proposed dosages and routes of administration?

Brandname will be formulated in five strengths of Alis/Aml/HCTZ for oral administration. These are 300/10/25, 300/10/12.5, 300/5/25, 300/5/12.5 and 150/5/12.5 mg.

The approved dosing range for use in hypertension is 150 and 300 mg for aliskiren, 5 and 10 mg for amlodipine and 12.5 and 25 mg for hydrochlorothiazide.

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

Brandname is indicated for use as an add-on or replacement therapy in the treatment of hypertension. Aliskiren is a direct rennin inhibitor, amlodipine is a calcium channel blocker and hydrochlorothiazide is a diuretic. Hence, Brandname is expected to exert its effect by a combination of three mechanisms of action.

2.2. General clinical pharmacology

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

A summary of the clinical pharmacology studies reviewed in this NDA are presented in Table 1. Individual study reports for the following studies are presented in Appendix 4.1.

Table 1: Key design features of the clinical and clinical pharmacology studies:

CLINICAL		
Type of Study	Design	Treatments
Short-term pivotal efficacy (SAH100A2302)	8 week, double-blind, four treatments, randomized, hypertensive patients	<ul style="list-style-type: none"> • 300/10 mg (Alis/Aml) • 300/25 mg (Alis/HCTZ) • 10/25 mg (Aml/HCTZ) • 300/10/25 mg (Alis/Aml/HCTZ) <p>Note: Up-titration to high dose from Alis 150 mg, Aml 5 mg and HCTZ 12.5 mg was done at end of week 4</p>
Key long-term safety (SAH100A2301)	28 to 54 weeks, open-label, hypertensive patients	<ul style="list-style-type: none"> • 300/10/25 mg (Alis/Aml/HCTZ)
CLINICAL PHARMACOLOGY		
Bioequivalence ³ (CSAH100A2102)	Healthy, crossover, two treatments, single-dose, N = 96	<ul style="list-style-type: none"> • FDC vs Free combination 300/5/25 mg
Relative bioavailability ³ (CSAH100A2104)	Healthy, crossover, five treatments, single-dose, N = 63	<ul style="list-style-type: none"> • Four different FDCs vs Free combination 300/10/25 mg
Food effect (CSAH100A2101)	Healthy, crossover, two treatments, single-dose, N = 36	<ul style="list-style-type: none"> • FDC in fed vs fasted state 300/10/25 mg
DDI sub-study ⁴	Hypertensive patients, parallel, four treatments, multiple-dose, 8-weeks N ~ 20 per arm Steady state PK collection at week 6	<ul style="list-style-type: none"> • 300/10 mg (Alis/Aml) • 300/25 mg (Alis/HCTZ) • 10/25 mg (Aml/HCTZ) • 300/10/25 mg (Alis/Aml/HCTZ)

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

Yes. Aliskiren, amlodipine and hydrochlorothiazide are the only active moieties in Brandname. Please refer to section 2.4 for details of the bioanalytical method.

2.2.3. Exposure-Response

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

Yes. Brandname is a FDC of aliskiren, amlodipine and hydrochlorothiazide. The approved dosing range for aliskiren, amlodipine and hydrochlorothiazide for use in hypertension are 150/300 mg, 5/10 mg and 12.5/25 mg, respectively. Brandname will be formulated in five strengths of Alis/Aml/HCTZ that span the approved dosing range of the individual components for oral administration.

³ DSI inspections were not performed

⁴ DDI study was a sub-study in the pivotal efficacy trial

2.2.3.2. What are the characteristics of the exposure-response relationship for efficacy?

The pivotal efficacy trial evaluated the highest strength of the triple combination. Hence a dose – response relationship for the efficacy or safety cannot be explored.

2.2.3.3. What are the key results from the pivotal efficacy trial?

Please refer Table 1 for study design (SAH100A2302). A significantly higher decrease in mean seated systolic blood pressure (primary analysis) was observed with the triple combination over all the three dual combination at the end of week 8 (Fig. 1). Similar results and trend was observed with mean seated diastolic blood pressure (secondary analysis).

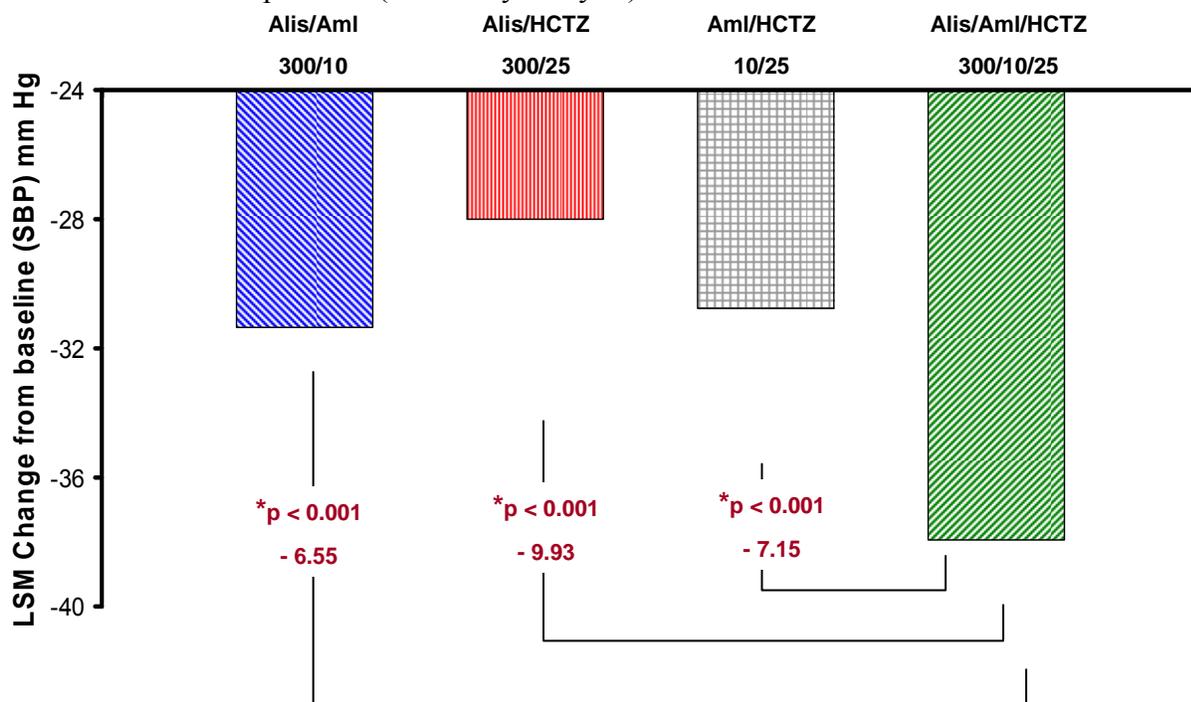


Figure 1: Mean change from baseline systolic blood pressure (primary analysis) for triple and dual combinations at week 8 (end of study).

2.2.4. What are the PK characteristics of the drug?

2.2.4.1. What are the single and multiple dose PK parameters?

The pharmacokinetic properties of aliskiren, amlodipine and hydrochlorothiazide have been reviewed and reported previously under NDAs 21-985, 19-787 and the package insert, respectively. Following administration of a single dose of Brandname 300/10/25 mg peak plasma aliskiren, amlodipine and hydrochlorothiazide concentrations were attained at about 1.25 h (range: 0.5 to 6 h), 8 h (range: 4 to 12 h) and 3 h (1.5 to 6 h), respectively. The mean (\pm SD) elimination half-life of aliskiren, amlodipine and hydrochlorothiazide were 60.2 (\pm 15.1) h, 48.4 (\pm 11.3) h and 10.8 (\pm 2.14) h, respectively. Mean clearance for FDC and free combination was about 294 and 293 L/h, 39 and 38 L/h, 25 and 23 L/h for aliskiren, amlodipine and hydrochlorothiazide, respectively. These observations are consistent with previous findings for aliskiren, amlodipine and hydrochlorothiazide.

2.2.5. Extrinsic Factors

2.2.5.1. What is the effect of food on the pharmacokinetics of the drugs in the FDC? What is its impact if any, on blood pressure reduction?

Systemic exposure to amlodipine and hydrochlorothiazide was not affected by food. Systemic exposure to aliskiren was reduced by ~80% when FDC at 300/10/25 mg was administered with a high fat meal (Fig. 2). This observation is consistent with prior findings for aliskiren⁵.

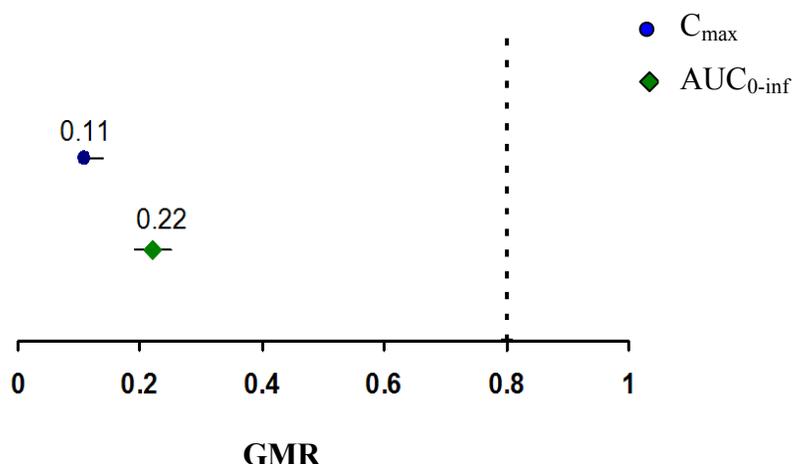


Figure 2: Results of the relative bioavailability of aliskiren when administered as a FDC in fed when compared to fasted state following a single oral dose of 300/10/25 mg. X-axis represents the geometric mean ratios. Data is represented as geometric mean ratio of the BE metrics (C_{max} , AUC_{0-inf}) with 90% CI around the point estimate.

From the exposure-response relationship (naïve pooled log-linear regression analysis, Appendix 4.1.5) of aliskiren (Fig. 3), it is observed that a 100-fold increase in aliskiren plasma concentration results in only 13 mm Hg drop for systolic blood pressure, indicating that the relationship is shallow. This is particularly evident when the x-axis is represented on a linear scale where the relationship flattens out at higher concentrations, reaching a plateau (Fig. 2 in Appendix 4.1.5).

The expected difference in blood pressure reduction between administration of aliskiren in the fed and fasted state was estimated using the E-R relationship and aliskiren plasma concentration data observed in the current food effect study. As seen in figure 3, there is a mean difference of -2.57 mm Hg (95% CI: -2.07 to -3.07 mm Hg) in SBP and -1.81 mm Hg (95% CI: -1.45 to -2.16 mm Hg) difference in DBP in fed vs fasted state following once daily 300 mg dose. However, these predictions do not take into account the variability in blood pressure response. Hence, the predicted effect of food on blood pressure response is overly conservative, and can only be used to provide a sense for the food effect on blood pressure for the aliskiren plasma concentrations reported in the food effect study (CSAH100A2101). Further, this is a cross-study comparison.

In addition, no dose adjustments are recommended for aliskiren or its fixed dose combinations. Patients are advised to establish a routine for taking aliskiren or its fixed dose combinations with regard to meals. Considering the above, no dose adjustments are warranted for Brandname when taken with food.

⁵ Tekturna[®], Tekamlo[®] and Tekturna HCT[®], Package insert

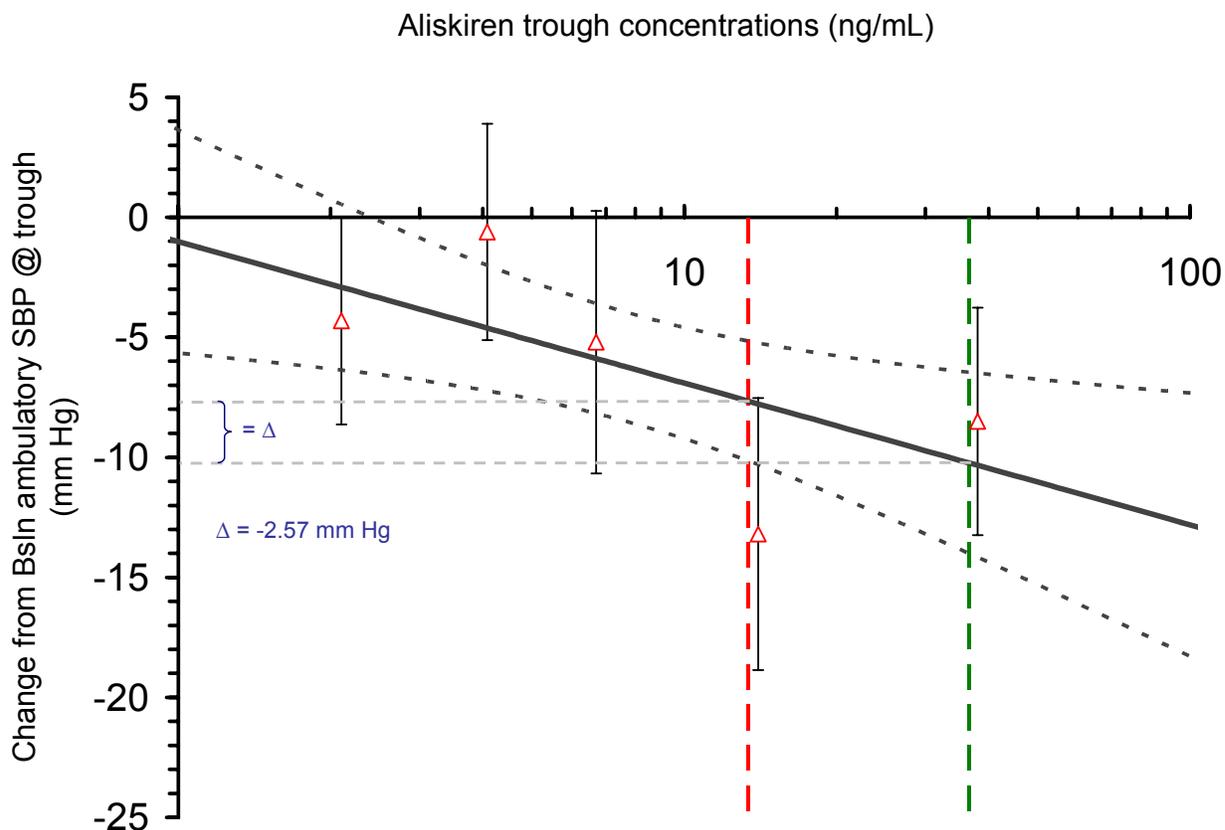


Figure 3: Exposure-change from baseline ambulatory SBP relationship of aliskiren. X-axis represents aliskiren trough plasma concentrations and Y-axis represents corresponding mean change from baseline ambulatory SBP at trough. Red triangles represent the median aliskiren trough plasma concentration in each pentile⁶ plotted against the corresponding mean change from baseline ambulatory SBP at trough. Error bars represent 95% CI around the mean. The solid line represents the log-linear fit modeled through the entire dataset with 95% CI represented by dotted lines. Red and green vertical dashed lines represent the median steady state trough concentration in fed and fasted state following aliskiren 300 mg QD.

2.2.6. What are the drug-drug interactions?

The DDI study was a sub-study of the pivotal efficacy trial (refer Table 1, SAH100A2302). This allowed evaluating the drug interaction due to the addition of the third drug to each of the corresponding dual combination.

The results show an average of 10-20% decrease in the exposure of all three compounds in the triple combination when compared to the three dual combinations (Fig. 4). But, this slight decrease in exposure is not clinically significant, since, this study was done as a part of the pivotal efficacy trial where the triple combination was significantly better than the dual combinations in terms of its blood pressure lowering effect.

⁶ Aliskiren trough plasma concentration was binned into five groups (n ~28) to better represent the data.

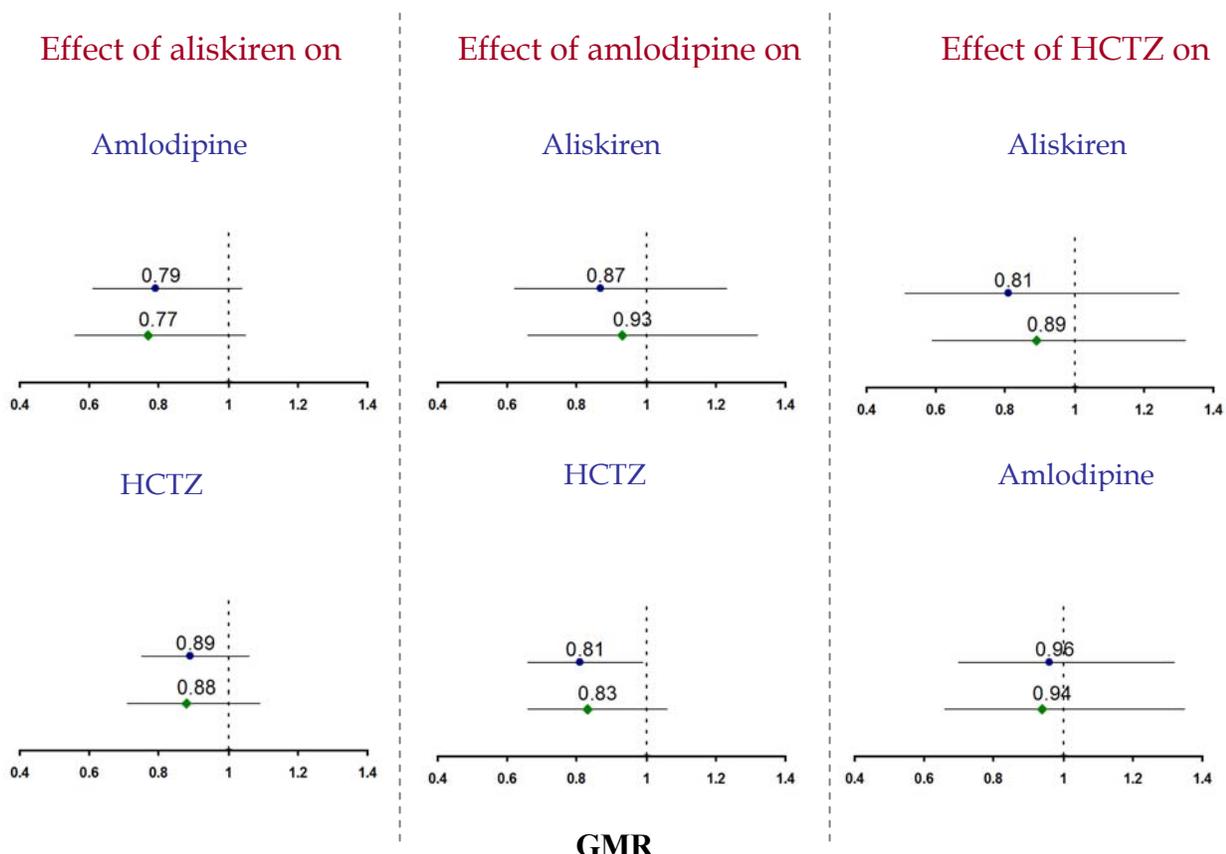


Figure 4: Relative bioavailability of aliskiren, amlodipine and hydrochlorothiazide when administered as a triple combination when compared to each of the corresponding dual combination. X-axis represents the geometric mean ratios. The broken vertical lines represent the pre-determined BE limits. Data is represented as geometric mean ratio of the BE metrics (Blue circles - C_{max} , green diamonds - AUC_{0-24}) with 90% CI around the point estimate.

2.3. General biopharmaceutics

2.3.1. Was an adequate link established between the to-be-marketed formulation and the one used in pivotal efficacy trial?

Yes. The bioequivalence study (CSAH100A2102) and the relative bioavailability study (CSAH100A2104) can be used to bridge the to-be-marketed FDC and the free combination of aliskiren, amlodipine and hydrochlorothiazide used in the pivotal clinical trial. These studies also enable association of the efficacy and safety data of the monotherapies to the FDC.

Based on the results of the bioequivalence study, FDC of Brandname is bioequivalent to the free combination with respect to amlodipine and hydrochlorothiazide, but not aliskiren (Fig. 5). As seen in figure 5, 90% CIs are not contained within 80 to 125 % for C_{max} of aliskiren. However, this is not clinically significant, since approximately 20% decrease in aliskiren's exposure does not have any meaningful change in its blood pressure lowering effect as evidenced by the shallow exposure-response relationship (Fig. 3).

Additionally, bioequivalence for all the three analytes – aliskiren, amlodipine and hydrochlorothiazide (Fig. 6) was demonstrated in the relative bioavailability study. Together, the results from both studies establish an adequate link between the clinical trial formulation and the to-be-marketed FDC. A

biowaiver request for strengths 300/10/12.5, 300/5/12.5 and 150/5/12.5 mg is submitted based on compositional similarity and proportionality.

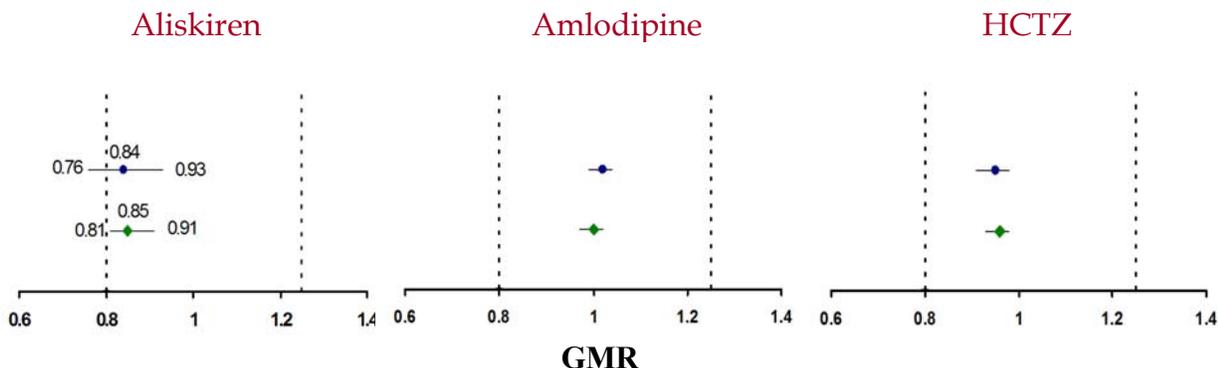


Figure 5: Data is represented as geometric mean ratio of the BE metrics between test: FDC and reference: free combination (blue circles - C_{max} , green diamonds - AUC_{0-inf}) with 90% CI around the point estimate. X-axis represents the geometric mean ratios. The broken vertical lines represent the pre-determined BE limits.

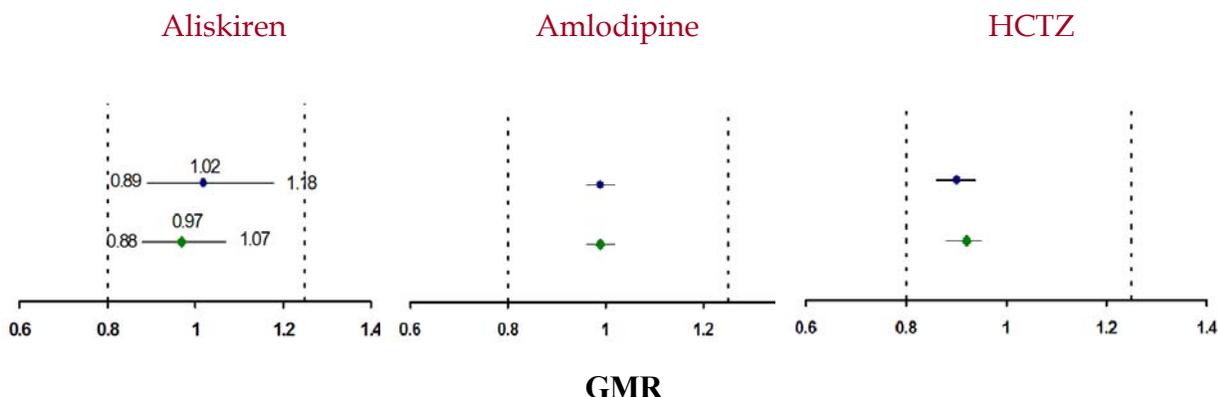


Figure 6: Data is represented as geometric mean ratio of the BE metrics between test: FDC and reference: free combination (blue circles - C_{max} , green diamonds - AUC_{0-inf}) with 90% CI around the point estimate. X-axis represents the geometric mean ratios. The broken vertical lines represent the pre-determined BE limits.

DSI Inspection:

DSI inspection for the bioequivalence study (CSAH100A2102) was not requested. We did not see the need to inspect this study, since it failed to demonstrate bioequivalence for C_{max} of aliskiren. DSI inspection for the relative bioavailability study could not be performed within the time frame of the review cycle, given that the analytical site was in China. But, the following information supports our conclusion to call for bioequivalence, in light of not having a DSI inspection:

- In both studies, bioequivalence of amlodipine and hydrochlorothiazide was unequivocally established. Bioequivalence was not established for aliskiren, which failed on peak concentration in one of the studies. Given that an 80% decrease in systemic exposure of aliskiren with food is not a concern due to the shallow exposure-response relationship, failure to adhere by the strict BE limits of 80-125% will not be a concern.

- In addition, aliskiren's pharmacokinetics observed in this submission, is comparable across aliskiren monotherapy and dual combination submissions.

2.4. Analytical section

2.4.1. How are the active moieties identified and measured in the plasma?

Two validated LC/MS/MS methods (DMPK R0900509 and DMPK R0900509A) were developed to simultaneously determine the plasma concentrations of aliskiren, amlodipine and hydrochlorothiazide. Relative bioavailability and DDI sub-studies used DMPK R0900509. Bioequivalence and food effect studies used DMPK R0900509A.

(b) (4)

2.4.2. For all moieties measured, is free, bound, or total measured?

Total concentrations of aliskiren, amlodipine, and hydrochlorothiazide were measured.

2.4.3. What bioanalytical methods are used to assess concentrations?

Please refer to section 2.5.1. Table 2A and 2B provides the details of both bioanalytical methods used to support the clinical pharmacology studies in this submission. The methods satisfied all criteria for 'method validation' and 'application to routine analysis' set by the '*Guidance for Industry: Bioanalytical Method Development*', and is therefore acceptable.

Table 2A: Assay validation results for aliskiren, amlodipine and hydrochlorothiazide from DMPK R0900509:

	Aliskiren	Amlodipine	Hydrochlorothiazide
Standard curve range	0.5 to 500 ng/mL (weighted $1/x^2$, $r \geq 0.99$)	0.025 to 10 ng/mL (weighted $1/x^2$, $r \geq 0.99$)	1.00 to 200 ng/mL (weighted $1/x^2$, $r \geq 0.99$)
Precision	Intra-day: 2.2 to 6.4% At LLOQ: 4.4 to 8.5% Inter-day: 3.3 to 5.1% At LLOQ: 8.0%	Intra-day: 1.7 to 6.2% At LLOQ: 4.7 to 13.6% Inter-day: 2.1 to 4.9% At LLOQ: 10.2%	Intra-day: 0.9 to 3.0% At LLOQ: 1.9 to 3.3% Inter-day: 1.5 to 3.3% At LLOQ: 3.6%
Accuracy (Bias)	Intra-day: -2.8 to 8.0% At LLOQ: -9.0 to 1.8% Inter-day: -1.3 to 5.2% At LLOQ: -3.0%	Intra-day: -2.0 to 2.9% At LLOQ: -9.2 to 5.6% Inter-day: 0.1 to 1.5% At LLOQ: -2.8%	Intra-day: -7.0 to -2.0% At LLOQ: -11.3 to -6.4% Inter-day: -4.3 to -3.0% At LLOQ: -8.3%
Internal standard	D6 – aliskiren Lot number: WFQ0177 Purity: 99.8%	D4 – amlodipine Lot number: 12-MJC-118-1 Purity: 98%	¹³ C,D2 – HCTZ Lot number: 2-XAL-98-5 Purity: 98%
Reference standard	Aliskiren Lot number: 0724052, C0080.REF Purity: 98.7%, 98.8%	Amlodipine Lot number: G0F133 Purity: 99.7%	HCTZ Lot number: J0F070 Purity: 99.7%
Specificity	No interference	No interference	No interference
Mean recovery	Aliskiren: 102.9% D6 – aliskiren: 113.0 %	Amlodipine: 109.4% D4 – amlodipine: 104.8%	HCTZ: 84.5% ¹³ C,D2 – HCTZ: 83.8%
Matrix	Human plasma	Human plasma	Human plasma
Stability (in human plasma)	Bench-top: 18 hours At 8°C (autosampler): 177 h Freeze-thaw: 5 cycles	Bench-top: 18 hours At 8°C (autosampler): 177 h Freeze-thaw: 5 cycles	Bench-top: 18 hours At 8°C (autosampler): 177 h Freeze-thaw: 5 cycles

Table 2B: Assay validation results for aliskiren, amlodipine and hydrochlorothiazide from DMPK R0900509A:

	Aliskiren	Amlodipine	Hydrochlorothiazide
Standard curve range	0.5 to 500 ng/mL (weighted $1/x^2$, $r \geq 0.99$)	0.025 to 10 ng/mL (weighted $1/x^2$, $r \geq 0.99$)	1.00 to 200 ng/mL (weighted $1/x^2$, $r \geq 0.99$)
Precision	Intra-day: 0.9 to 4.6% At LLOQ: 3.6 to 12.8% Inter-day: 2.2 to 5.7% At LLOQ: 7.9%	Intra-day: 1.0 to 6.1% At LLOQ: 5.2 to 7.0% Inter-day: 2.6 to 6.6% At LLOQ: 7.5%	Intra-day: 0.5 to 4.9% At LLOQ: 1.1 to 4.6% Inter-day: 1.7 to 3.2% At LLOQ: 5.3%
Accuracy (Bias)	Intra-day: -5.5 to 7.3% At LLOQ: -3.2 to 2.8% Inter-day: -4.5 to 1.3% At LLOQ: 0%	Intra-day: -5.2 to 6.3% At LLOQ: -12.0 to -1.2% Inter-day: -1.3 to 4.3% At LLOQ: -6.0%	Intra-day: -9.4 to -0.7% At LLOQ: -11.1 to -1.8% Inter-day: -8.8 to -1.9% At LLOQ: -6.2%
Internal standard	D6 – aliskiren Lot number: WFQ0177 Purity: 99.8%	D4 – amlodipine Lot number: 90A-L03 Purity: 99.3%	¹³ C,D2 – HCTZ Lot number: 5-RUS-25-1 Purity: 98.0%
Reference standard	Aliskiren Lot number: C0001.REF Purity: 99.0%	Amlodipine Lot number: AB/002/5041 Purity: 98.9%	HCTZ Lot number: 064K1361 Purity: 99.9%
Specificity	No interference	No interference	No interference
Mean recovery	Aliskiren: 98.0% D6 – aliskiren: 76.9 %	Amlodipine: 98.4% D4 – amlodipine: 71.7%	HCTZ: 106.6% ¹³ C,D2 – HCTZ: 95.0%
Matrix	Human plasma	Human plasma	Human plasma
Stability (in human plasma)	Bench-top: 25 hours Freeze-thaw: 5 cycles	Bench-top: 25 hours Freeze-thaw: 5 cycles	Bench-top: 25 hours Freeze-thaw: 5 cycles

3. LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the [package insert labeling](#) for NDA 200-045 and finds it acceptable pending the following revisions. ~~Strikethrough text~~ is recommended to be deleted and [underlined text](#) is recommended to be added. Labeling discussions are currently ongoing.

12.3 Pharmacokinetics

Absorption and Distribution

Tradename

Following oral administration of the fixed combination of aliskiren, amlodipine, and hydrochlorothiazide, peak concentrations were achieved within 1-2 hours, ^(b) [6-12 hours](#), and ^{(b) (4)} [1-4](#) hours for aliskiren, amlodipine and hydrochlorothiazide, respectively. The rate and extent of absorption of aliskiren, amlodipine, and hydrochlorothiazide following administration of the fixed combination are similar to when they are administered as individual dosage forms ^{(b) (4)}

[When Tradename is taken with food, mean AUC and C_{max} of aliskiren are decreased by 78% and 89%, respectively. There is no impact of food on the exposures of amlodipine and hydrochlorothiazide.](#)

4. APPENDIX

4.1. Individual study reports

4.1.1. Bioequivalence study – CSAH100A2102

Study Report # CSAH100A2102 - Bioequivalence⁷																			
Title	Bioequivalence between fixed-dose combination and free combination of aliskiren, amlodipine and hydrochlorothiazide (HCTZ) (300/5/25 mg) in healthy volunteers under fasted condition.																		
Objectives	Bioequivalence <input checked="" type="checkbox"/> Bioavailability <input type="checkbox"/>																		
Study Design	Parallel <input type="checkbox"/> Crossover <input checked="" type="checkbox"/> Open-label, randomized, two-period, two-sequence, crossover study with a wash out period of at least 14 days between periods.																		
Formulation	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">Test</th> <th style="text-align: center;">Reference</th> </tr> </thead> <tbody> <tr> <td>Dosage</td> <td>Fixed-dose combination tablet</td> <td>Free combination [Aliskiren</td> </tr> <tr> <td>Form</td> <td>[Aliskiren/Amlodipine/HCTZ]</td> <td>/Amlodipine/HCTZ]</td> </tr> <tr> <td>Dosage</td> <td>300/5/25 mg</td> <td>300/5/25 mg</td> </tr> <tr> <td>Strength</td> <td></td> <td></td> </tr> <tr> <td>Batch #</td> <td>AEUS/2009-0055</td> <td>810089030D/E22221.1/X245IB</td> </tr> </tbody> </table>		Test	Reference	Dosage	Fixed-dose combination tablet	Free combination [Aliskiren	Form	[Aliskiren/Amlodipine/HCTZ]	/Amlodipine/HCTZ]	Dosage	300/5/25 mg	300/5/25 mg	Strength			Batch #	AEUS/2009-0055	810089030D/E22221.1/X245IB
	Test	Reference																	
Dosage	Fixed-dose combination tablet	Free combination [Aliskiren																	
Form	[Aliskiren/Amlodipine/HCTZ]	/Amlodipine/HCTZ]																	
Dosage	300/5/25 mg	300/5/25 mg																	
Strength																			
Batch #	AEUS/2009-0055	810089030D/E22221.1/X245IB																	
PK Sampling	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 12, 24, 48, 72, 96, 144, and 168 hours post-dose. <i>Reviewer's comments: The above sampling scheme is adequate to capture the C_{max} and to get a reasonable estimate of AUC_{0-last/∞} for all three drugs.</i>																		
Statistical Method	A mixed-effect ANOVA model on log transformed parameters. Two-sided 90% CI for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of AUC _{0-last} , AUC _{0-∞} and C _{max} .																		
Population	<p>Healthy subjects</p> <table border="1" style="margin-left: auto; margin-right: auto; border-collapse: collapse;"> <thead> <tr> <th>Total Participants</th> <th>Males</th> <th>Females</th> <th>Completed</th> <th>Withdrawn</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">109</td> <td style="text-align: center;">109</td> <td style="text-align: center;">0</td> <td style="text-align: center;">96</td> <td style="text-align: center;">13</td> </tr> </tbody> </table> <p><i>Reviewer's comment: This study was prospectively powered to establish bioequivalence. Sample size calculation was based on the intra-subject variability of C_{max} of aliskiren.</i></p>	Total Participants	Males	Females	Completed	Withdrawn	109	109	0	96	13								
Total Participants	Males	Females	Completed	Withdrawn															
109	109	0	96	13															

⁷ Link to study report: <\\cdsub1\EVSPROD\NDA200045\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\sah100a2102\sah100a2102p01--legacy-clinical-study-report.pdf>

Results

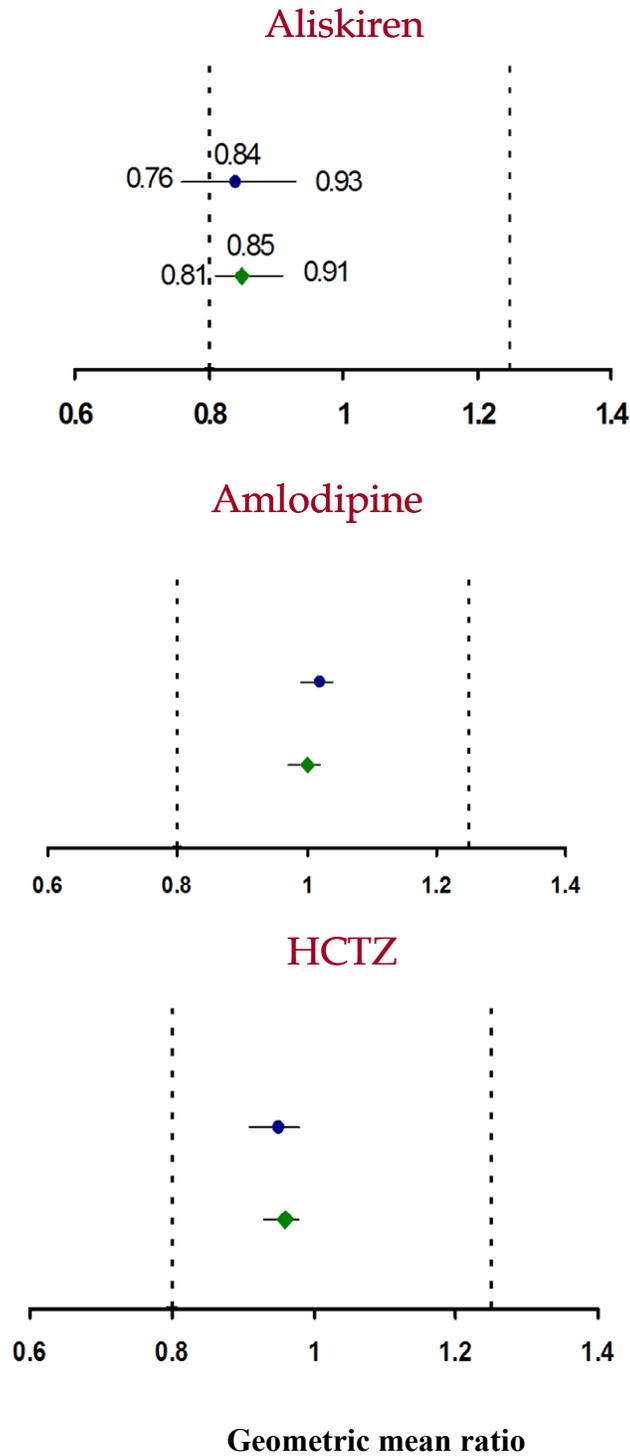


Figure 1: Results of the statistical analysis. X-axis represents the geometric mean ratios. The broken vertical lines represent the pre-determined BE limits. Data is represented as geometric mean ratio of the BE metrics (C_{max} , AUC_{0-last} , $AUC_{0-\infty}$) with 90% CI around the point estimate.

Site Inspection

Performed: Yes No

Assay Method	The performance of the assay method during study sample analysis is summarized in the table below:			
		Aliskiren	Amlodipine	HCTZ
	Method	LC/MS/MS – simultaneous detection of all three analytes		
	LLOQ (ng/mL)	0.500	0.025	1.00
	Range (ng/mL)	0.500 to 500	0.025 to 10.0	1.00 to 200
	QCs (ng/mL)	0.500, 1.50, 16.0, 160, 400	0.025, 0.075, 0.480, 3.00, 8.00	1.00, 3.00, 16.3, 72.0, 160
	Accuracy/Bias	-4.5 to 1.3 %	-6.0 to 4.3 %	-8.8 to -1.9 %
	Precision	2.2 to 7.9 %	2.6 to 7.5 %	1.7 to 5.3 %
	Reviewer's comment: <i>The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'</i>			
	Safety	Death/SAE: None		
Detailed results	Table 1(a): Summary of pharmacokinetic measures and parameters for aliskiren			
	Geometric mean (% CV)			
	PK parameter	Reference (Free, N=102)	Test (Fixed, N=103)	
	C_{max} (ng/mL)	296.7 (62.2)	252.8 (46.7)	
	t_{max} (h)†	2.0 (0.5 – 8.0)	1.0 (0.5 – 6.0)	
	AUC _{0-last} (h*ng/mL)	2154 (39.8)	1855 (39.8)	
	AUC _{0-∞} (h*ng/mL)	2302 (39.2)	1994 (40.1)	
	$t_{1/2}$ (h)‡	63.9 ± 13.3	66.0 ± 14.7	
	Table 1(b): Summary of pharmacokinetic measures and parameters for amlodipine			
	Geometric mean (% CV)			
	PK parameter	Reference (Free, N=100)	Test (Fixed, N=102)	
	C_{max} (ng/mL)	3.05 (21.1)	3.11 (22.2)	
	t_{max} (h)†	8.0 (4.0 – 12.0)	8.0 (6.0 – 12.0)	
	AUC _{0-last} (h*ng/mL)	191.0 (26.2)	191.4 (26.6)	
	AUC _{0-∞} (h*ng/mL)	212.1 (29.6) ¹	210.1 (29.1) ¹	
	$t_{1/2}$ (h)‡	54.6 ± 13.0	53.6 ± 13.5	
	Table 1(c): Summary of pharmacokinetic measures and parameters for HCTZ			
	Geometric mean (% CV)			
PK parameter	Reference (Free, N=102)	Test (Fixed, N=103)		
C_{max} (ng/mL)	138.7 (25.5)	132.2 (24.5)		
t_{max} (h)†	2.0 (1.0 – 4.0)	3.0 (1.5 – 6.0)		
AUC _{0-last} (h*ng/mL)	1065.0 (22.8)	1024.0 (22.8)		
AUC _{0-∞} (h*ng/mL)	1101.0 (21.3)	1056.0 (21.8)		
$t_{1/2}$ (h)‡	9.6 ± 1.1	9.6 ± 1.1		
† Median (range); ‡ Mean ± SD; ¹ N=93				

Conclusion	<ul style="list-style-type: none">• The rate and extent of absorption of amlodipine and HCTZ with fixed combination tablet is similar to free combination of 300 mg aliskiren, 5 mg amlodipine and 25 mg HCTZ.• The rate of absorption of aliskiren form the fixed combination was not similar to that form the free combination. Failure to show bioequivalence by C_{max} of aliskiren is not clinically significant, since ~20% decrease in aliskiren's exposure does not have any meaningful change in its blood pressure lowering effect as seen by the shallow exposure-response relationship⁸. <p><i>Reviewer's comment: Use of a scaled average bioequivalence approach to establish bioequivalence will be reasonable considering a high intra-subject variability of aliskiren. Office of Generic Drugs considers the use of this approach for highly variable drugs defined by intra-individual CV > 30%. But, such an analysis requires a partial replicate study design (for the reference treatment arm) and the current study design does not allow for this approach.</i></p>
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⁸ Please see Appendix for exposure-response report

4.1.2. Relative bioavailability study – CSAH100A2104

Study Report # CSAH100A2104 - Relative bioavailability⁹																
Title	Relative bioavailability of four fixed-dose combination tablet variants relative to the free combination of aliskiren, amlodipine and hydrochlorothiazide (HCTZ) (300/10/25 mg) in healthy volunteers under fasted condition.															
Objectives	Bioequivalence <input type="checkbox"/> Bioavailability <input checked="" type="checkbox"/>															
Study Design	Parallel <input type="checkbox"/> Crossover <input checked="" type="checkbox"/> Open-label, randomized, five-period, five-sequence, single dose crossover study with a wash out period of two weeks between each dosing.															
Formulation	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 20%;"></th> <th style="width: 40%; text-align: center;">Test</th> <th style="width: 40%; text-align: center;">Reference</th> </tr> </thead> <tbody> <tr> <td></td> <td colspan="2" style="text-align: center;">Four variants of fixed-dose combination tablet [Aliskiren/Amlodipine/HCTZ]</td> </tr> <tr> <td>Dosage Form</td> <td> Var1: Target-release monolayer tablet Var2: Fast-release monolayer tablet Var3: Slow-release monolayer tablet Var4: Bilayer tablet </td> <td style="text-align: center;">Free combination [Aliskiren /Amlodipine /HCTZ]¹⁰</td> </tr> <tr> <td>Dosage Strength</td> <td style="text-align: center;">300+10+25 mg</td> <td style="text-align: center;">300/10/25 mg</td> </tr> <tr> <td>Batch #</td> <td> Var1: AEUS/2008-0197 Var2: AEUS/2008-0198 Var3: AEUS/2008-0199 Var4: AEUS/2008-0200 </td> <td style="text-align: center;">810089030D/E22221.1/X245IB</td> </tr> </tbody> </table>		Test	Reference		Four variants of fixed-dose combination tablet [Aliskiren/Amlodipine/HCTZ]		Dosage Form	Var1: Target-release monolayer tablet Var2: Fast-release monolayer tablet Var3: Slow-release monolayer tablet Var4: Bilayer tablet	Free combination [Aliskiren /Amlodipine /HCTZ] ¹⁰	Dosage Strength	300+10+25 mg	300/10/25 mg	Batch #	Var1: AEUS/2008-0197 Var2: AEUS/2008-0198 Var3: AEUS/2008-0199 Var4: AEUS/2008-0200	810089030D/E22221.1/X245IB
	Test	Reference														
	Four variants of fixed-dose combination tablet [Aliskiren/Amlodipine/HCTZ]															
Dosage Form	Var1: Target-release monolayer tablet Var2: Fast-release monolayer tablet Var3: Slow-release monolayer tablet Var4: Bilayer tablet	Free combination [Aliskiren /Amlodipine /HCTZ] ¹⁰														
Dosage Strength	300+10+25 mg	300/10/25 mg														
Batch #	Var1: AEUS/2008-0197 Var2: AEUS/2008-0198 Var3: AEUS/2008-0199 Var4: AEUS/2008-0200	810089030D/E22221.1/X245IB														
PK Sampling	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 144 and 168 hours post-dose. <i>Reviewer's comments: The above sampling scheme is adequate to capture the C_{max} and to get a reasonable estimate of AUC_{0-last/∞} for all three drugs.</i>															
Statistical Method	A mixed-effect ANOVA model on log transformed parameters. Two-sided 90% CI for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of AUC _{0-last} , AUC _{0-∞} and C _{max} .															
Population	Healthy subjects <table border="1" style="margin-left: auto; margin-right: auto; border-collapse: collapse; width: 80%;"> <thead> <tr> <th>Total Participants</th> <th>Males</th> <th>Females</th> <th>Completed</th> <th>Withdrawn</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">80</td> <td style="text-align: center;">63</td> <td style="text-align: center;">17</td> <td style="text-align: center;">63</td> <td style="text-align: center;">17</td> </tr> </tbody> </table>	Total Participants	Males	Females	Completed	Withdrawn	80	63	17	63	17					
Total Participants	Males	Females	Completed	Withdrawn												
80	63	17	63	17												

⁹ [Link to study report: \\cdsesub1\EVSPROD\NDA200045\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\sah100a2104\sah100a2104--legacy-clinical-study-report.pdf](#)

¹⁰ To be consistent with the pivotal efficacy trial, clinical service formulation of amlodipine and HCTZ was used in the free combination (reference treatment arm)

Results:

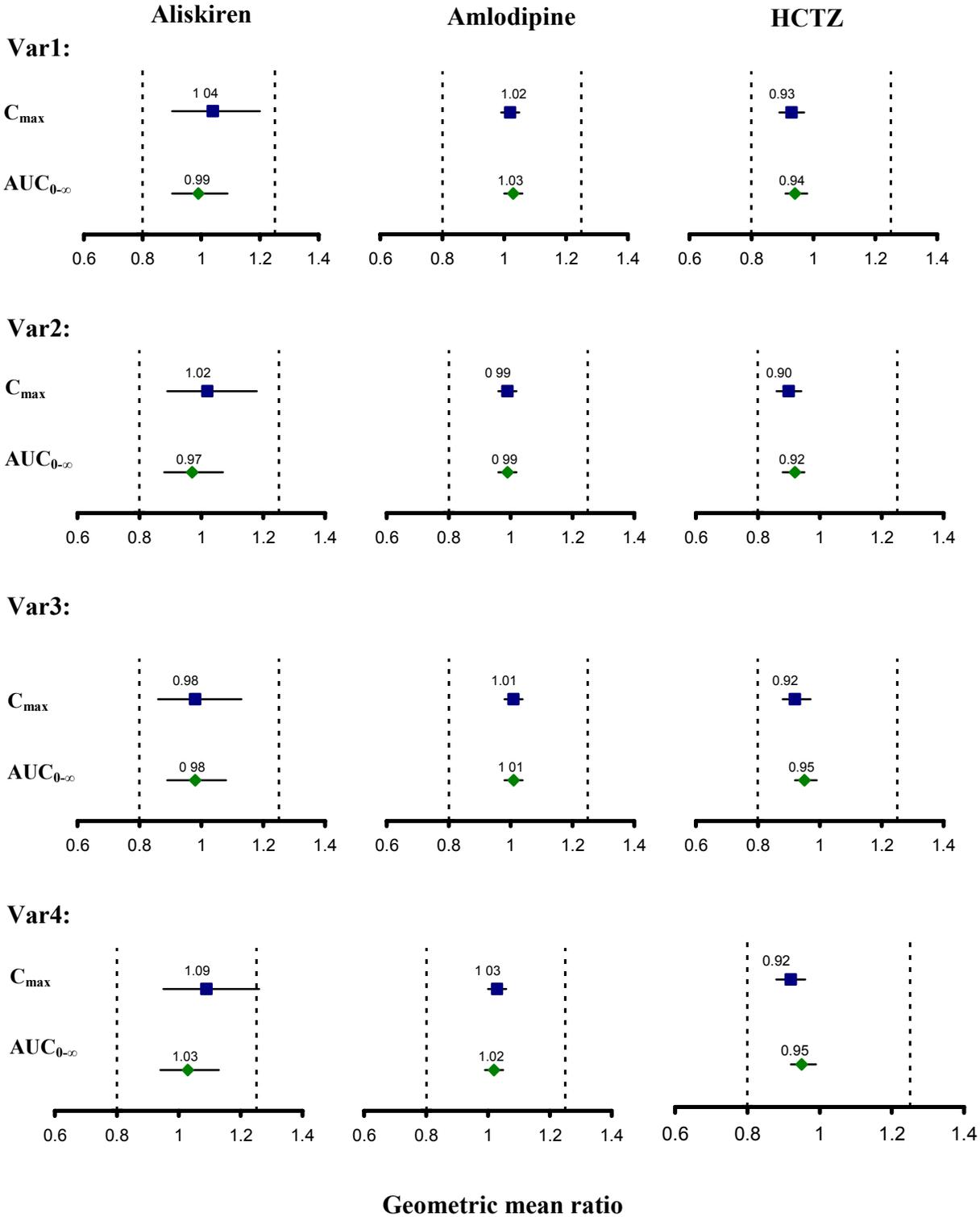


Figure 1: Results of the statistical analysis. X-axis represents the geometric mean ratios. The broken vertical lines represent the pre-determined BE limits. Data is represented as geometric mean ratio of the BE metrics (C_{max} , AUC_{0-last} , $AUC_{0-\infty}$) with 90% CI around the point estimate.

Site Inspection	Performed: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
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Assay Method	The performance of the assay method during study sample analysis is summarized in the table below:					
		Aliskiren	Amlodipine	HCTZ		
	Method	LC/MS/MS – simultaneous detection of all three analytes				
	LLOQ (ng/mL)	0.500	0.025	1.00		
	Range (ng/mL)	0.500 to 500	0.025 to 10.0	1.00 to 200		
	QCs (ng/mL)	0.500, 1.50, 25.0, 400	0.025, 0.075, 0.800, 8.00	1.00, 3.00, 20.0, 160		
	Accuracy/Bias	-3.0 to 5.2 %	-2.8 to 1.5 %	-8.3 to -3.0 %		
	Precision	3.3 to 8.0 %	2.1 to 10.2 %	1.5 to 3.6 %		
	<i>Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'</i>					
	Safety	Death/SAE: None				
Detailed results:						
Table 1(a): Summary of pharmacokinetic measures and parameters for aliskiren						
	C_{max}[§] (ng/mL)	AUC_{0-last}[§] (h*ng/mL)	AUC_{0-∞}[§] (h*ng/mL)	t_{max} (h)[†]	t_{1/2} (h)[‡]	
R (n=68)	148.6 (76.8)	1013 (98.0)	1181 (49.3)	2.50 (0.5 – 6.0)	60.5 ± 21.2	
V1 (n=67)	157.0 (59.4)	1100 (51.4)	1181 (50.8)	1.50 (0.5 – 6.0)	59.3 ± 19.3	
V2 (n=66)	154.4 (56.7)	1077 (56.6)	1158 (55.3)	1.25 (0.5 – 6.0)	60.2 ± 15.1	
V3 (n=68)	148.1 (64.4)	1078 (54.6)	1163 (54.1)	1.50 (0.5 – 6.0)	61.7 ± 18.3	
V4 (n=69)	164.6 (57.6)	1138 (46.3)	1224 (45.7)	1.50 (0.5 – 6.0)	62.7 ± 18.4	
Table 1(b): Summary of pharmacokinetic measures and parameters for amlodipine						
	C_{max}[§] (ng/mL)	AUC_{0-last}[§] (h*ng/mL)	AUC_{0-∞}[§] (h*ng/mL)	t_{max} (h)[†]	t_{1/2} (h)[‡]	
R (n=67)	4.23 (58.0)	214.6 (170.9)	271.5 (29.9)	8.0 (0.5 – 12.0)	50.0 ± 13.8	
V1 (n=67)	4.53 (23.0)	252.8 (25.9)	281.3 (28.2)	8.0 (6.0 – 12.0)	50.5 ± 13.1	
V2 (n=65)	4.39 (24.5)	241.9 (29.1)	268.1 (31.7)	8.0 (4.0 – 12.0)	48.4 ± 11.3	
V3 (n=65)	4.50 (23.9)	244.1 (30.3)	273.0 (27.6)	8.0 (4.0 – 12.0)	50.3 ± 15.1	
V4 (n=66)	4.63 (25.1)	245.7 (28.5)	272.1 (27.6)	8.0 (4.0 – 12.0)	48.2 ± 11.0	
Table 1(b): Summary of pharmacokinetic measures and parameters for HCTZ						
	C_{max}[§] (ng/mL)	AUC_{0-last}[§] (h*ng/mL)	AUC_{0-∞}[§] (h*ng/mL)	t_{max} (h)[†]	t_{1/2} (h)[‡]	
R (n=67)	137.4 (29.5)	1098 (32.0)	1136 (30.7)	3.0 (1.5 – 6.0)	10.7 ± 1.64	
V1 (n=67)	129.3 (25.0)	1044 (29.2)	1082 (28.1)	3.0 (1.0 – 4.0)	10.9 ± 1.80	
V2 (n=66)	123.2 (29.4)	1007 (34.3)	1045 (32.2)	3.0 (1.5 – 6.0)	10.8 ± 2.14	
V3 (n=68)	126.5 (27.7)	1043 (29.0)	1082 (27.8)	3.0 (1.5 – 4.0)	10.9 ± 1.80	
V4 (n=69)	125.9 (30.7)	1046 (27.6)	1085 (26.7)	2.0 (1.0 – 4.0)	10.9 ± 1.90	
[§] Geometric mean (%CV); [†] Median (range); [‡] Mean ± SD						

Conclusion	<ul style="list-style-type: none">• The rate and extent of absorption of aliskiren, amlodipine and HCTZ with fixed-dose combination tablet variants: 1, 2 & 3 is bioequivalent to free combination of 300 mg aliskiren tablet, 5 mg amlodipine capsule and 25 mg HCTZ capsule.• Fixed-dose combination variant 002 (fast-release monolayer tablet) was selected as the final market image (FMI) formulation based on the results of this study and in vitro dissolution test results. <p><i>Reviewer's comment: This study supports biowaiver request for fixed-dose combination strengths 300/10/12.5, 300/5/12.5, 300/5/25 and 150/5/12.5 mg based on compositional similarity and proportionality.</i></p>
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4.1.3. Food effect study – CSAH100A2101

Study Report # CSAH100A2101 - Food effect¹¹													
Title	To determine the effect of food on the pharmacokinetics of a fixed-dose combination of aliskiren/amlodipine/hydrochlorothiazide (HCTZ) (300/10/25 mg) tablet in healthy volunteers												
Objectives	Bioequivalence <input type="checkbox"/> Bioavailability <input checked="" type="checkbox"/>												
Study Design	Parallel <input type="checkbox"/> Crossover <input checked="" type="checkbox"/> Open-label, randomized, two-period, two-sequence, single dose crossover study with a wash out period of at least 14 days between periods.												
Formulation	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">Test</th> <th style="text-align: center;">Reference</th> </tr> </thead> <tbody> <tr> <td>Dosage Form</td> <td>Fixed-dose combination tablet [Aliskiren/Amlodipine/HCTZ] in fed state</td> <td>Fixed-dose combination tablet [Aliskiren /Amlodipine/HCTZ] in fasted state</td> </tr> <tr> <td>Dosage Strength</td> <td style="text-align: center;">300/10/25 mg</td> <td style="text-align: center;">300/10/25 mg</td> </tr> <tr> <td>Batch #</td> <td style="text-align: center;">AEUS/2008-0198</td> <td style="text-align: center;">AEUS/2008-0198</td> </tr> </tbody> </table>		Test	Reference	Dosage Form	Fixed-dose combination tablet [Aliskiren/Amlodipine/HCTZ] in fed state	Fixed-dose combination tablet [Aliskiren /Amlodipine/HCTZ] in fasted state	Dosage Strength	300/10/25 mg	300/10/25 mg	Batch #	AEUS/2008-0198	AEUS/2008-0198
	Test	Reference											
Dosage Form	Fixed-dose combination tablet [Aliskiren/Amlodipine/HCTZ] in fed state	Fixed-dose combination tablet [Aliskiren /Amlodipine/HCTZ] in fasted state											
Dosage Strength	300/10/25 mg	300/10/25 mg											
Batch #	AEUS/2008-0198	AEUS/2008-0198											
PK Sampling	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 144, and 168 hours post-dose. <i>Reviewer's comments: The above sampling scheme is adequate to capture the C_{max} and to get a reasonable estimate of $AUC_{0-last/\infty}$ for all three drugs.</i>												
Statistical Method	A mixed-effect ANOVA model on log transformed parameters. Two-sided 90% CI for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of AUC_{0-last} , $AUC_{0-\infty}$ and C_{max} .												
Population	Healthy subjects <table border="1" style="margin-left: auto; margin-right: auto; border-collapse: collapse;"> <thead> <tr> <th>Total Participants</th> <th>Males</th> <th>Females</th> <th>Completed</th> <th>Withdrawn</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">36</td> <td style="text-align: center;">36</td> <td style="text-align: center;">0</td> <td style="text-align: center;">36</td> <td style="text-align: center;">0</td> </tr> </tbody> </table>	Total Participants	Males	Females	Completed	Withdrawn	36	36	0	36	0		
Total Participants	Males	Females	Completed	Withdrawn									
36	36	0	36	0									
Results	<p style="text-align: center; color: red;">Aliskiren</p> <p style="text-align: right;">● C_{max} ◆ AUC_{0-inf}</p>												

¹¹ Link to study report: <\\cdsesub1\EVSPROD\NDA200045\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\sah100a2101\sah100a2101--legacy-clinical-study-report.pdf>

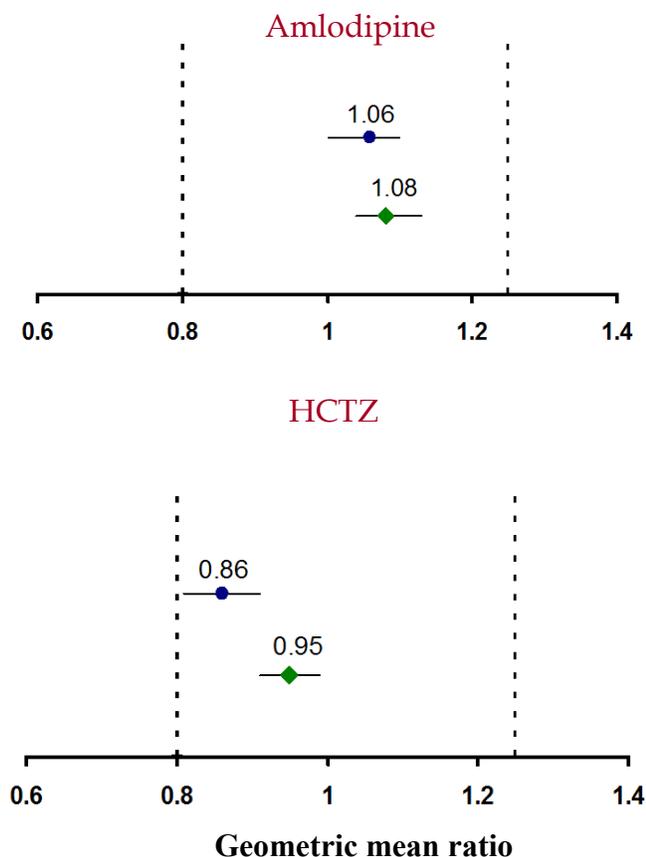


Figure 1: Results of the statistical analysis. X-axis represents the geometric mean ratios. The broken vertical lines represent the pre-determined BE limits. Data is represented as geometric mean ratio of the BE metrics (C_{max} , AUC_{0-last} , $AUC_{0-\infty}$) with 90% CI around the point estimate.

Site Inspection
Performed: Yes No

Assay Method
The performance of the assay method during study sample analysis is summarized in the table below:

	Aliskiren	Amlodipine	HCTZ
Method	LC/MS/MS – simultaneous detection of all three analytes		
LLOQ (ng/mL)	0.500	0.025	1.00
Range (ng/mL)	0.500 to 500	0.025 to 10.0	1.00 to 200
QCs (ng/mL)	0.500, 1.50, 16.0, 160, 400	0.025, 0.075, 0.480, 3.00, 8.00	1.00, 3.00, 16.3, 72.0, 160
Accuracy/Bias	-4.5 to 1.3 %	-6.0 to 4.3 %	-8.8 to -1.9 %
Precision	2.2 to 7.9 %	2.6 to 7.5 %	1.7 to 5.3 %

Reviewer’s comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of $\pm 15\%$ as specified in ‘Guidance for Industry: Bioanalytical Method Validation.’

Safety
Death/SAE: **None**

Detailed results	Table 1(a): Summary of pharmacokinetic measures and parameters for aliskiren		
	Geometric mean (% CV)		
	PK parameter	Reference (Fasted, N=36)	Test (Fed, N=36)
	C _{max} (ng/mL)	289.8 (55.1)	33.8 (56.7)
	t _{max} (h)†	1.5 (0.5 – 6.0)	3.0 (0.5 – 10.0)
	AUC _{0-last} (h*ng/mL)	2488 (47.2)	525.2 (45.0)
	AUC _{0-∞} (h*ng/mL)	2638 (47.4)	580.3 (46.8)
	t _{1/2} (h)‡	64.7 ± 12.1	53.8 ± 30.6
	Table 1(b): Summary of pharmacokinetic measures and parameters for amlodipine		
	Geometric mean (% CV)		
PK parameter	Reference (Fasted, N=36)	Test (Fed, N=36)	
C _{max} (ng/mL)	4.91 (18.4)	5.21 (19.1)	
t _{max} (h)†	8.0 (6.0 – 12.0)	8.0 (4.0 – 12.0)	
AUC _{0-last} (h*ng/mL)	279.8 (23.2)	301.1 (20.8)	
AUC _{0-∞} (h*ng/mL)	309.1 (25.8)	334.8 (22.9)	
t _{1/2} (h)‡	49.2 ± 8.0	51.5 ± 9.4	
Table 1(c): Summary of pharmacokinetic measures and parameters for HCTZ			
Geometric mean (% CV)			
PK parameter	Reference (Fasted, N=36)	Test (Fed, N=36)	
C _{max} (ng/mL)	138.6 (22.7)	119.7 (18.1)	
t _{max} (h)†	3.0 (1.5 – 4.0)	4.0 (2.0 – 6.0)	
AUC _{0-last} (h*ng/mL)	1163 (20.4)	1094 (19.2)	
AUC _{0-∞} (h*ng/mL)	1196 (20.4)	1133 (18.1)	
t _{1/2} (h)‡	9.8 ± 1.3	9.6 ± 1.9	
† Median (range); ‡ Mean ± SD			

**Concentration
– time profile**

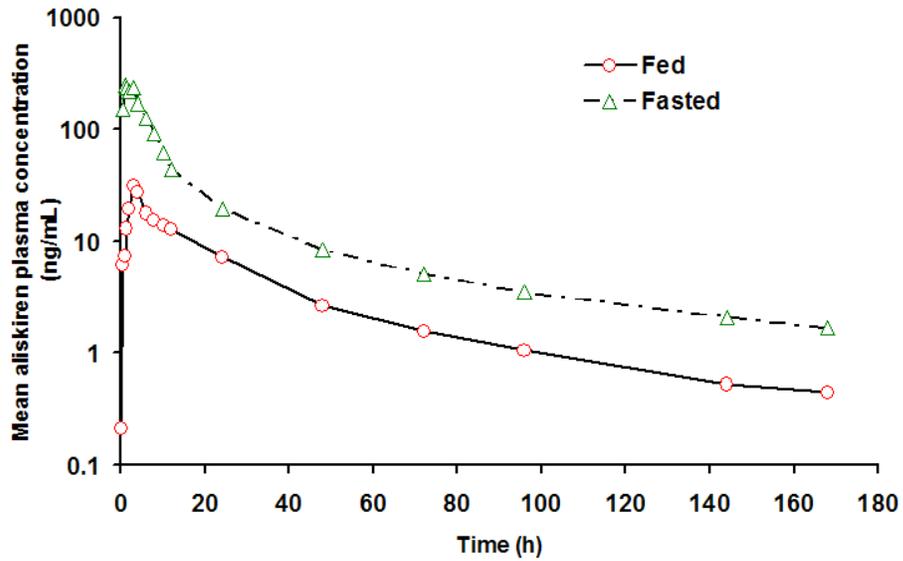


Figure 2: Mean aliskiren plasma concentration-time profile following single oral administration of 300/10/25 mg aliskiren/amlodipine/HCTZ fixed-dose combination tablet in fed vs fasted state

Conclusion

- Systemic exposure to aliskiren was decreased by ~ 80% when administered with a high fat meal. The extent of decrease in aliskiren’s exposure (AUC by 78% and C_{max} by 89%) in the presence of high fat meal is similar to as observed before with aliskiren monotherapy (Tekturna[®]).
- Aliskiren’s decrease in exposure in the presence of a high fat meal is not clinically significant due to a shallow exposure-response relationship¹².
- There is no significant change in the C_{max} and AUC of amlodipine and hydrochlorothiazide due to a high fat meal.

¹² Please see Appendix for exposure-response report

4.1.4. DDI sub-study –SAH100A2302

Study Report # SAH100A2302 - DDI sub-study¹³																			
Title	<p>Drug-drug interaction sub-study in 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</p> <p><i>Reviewer’s comment: This study was implemented as a part of the randomized efficacy and safety trial with a subset of patients selected for assessing steady state pharmacokinetics at week 6.</i></p>																		
Objectives	<ul style="list-style-type: none"> ▪ To characterize the pharmacokinetics of aliskiren, amlodipine and HCTZ at steady state in hypertensive subjects ▪ To assess the drug-drug interaction potential at steady state between aliskiren, amlodipine and HCTZ in the triple combination using population pharmacokinetic approach 																		
Study Design & Treatments	<p>Double-blind, randomized, single-center, multiple-dose, parallel study in moderate to severe hypertensive subjects</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Duration</th> <th style="text-align: center;">1</th> <th style="text-align: center;">2</th> <th style="text-align: center;">3</th> <th style="text-align: center;">4</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Week 1 - 4</td> <td style="text-align: center;">AL 150 mg/ AM 5 mg</td> <td style="text-align: center;">AL 150 mg/ HCTZ 12.5 mg</td> <td style="text-align: center;">AM 5 mg/ HCTZ 12.5 mg</td> <td style="text-align: center;">AL 150 mg/¹⁴ AM 5 mg/ HCTZ 12.5 mg</td> </tr> <tr> <td style="text-align: center;">Week 5 – 8*</td> <td style="text-align: center;">AL 300 mg/ AM 10 mg</td> <td style="text-align: center;">AL 300 mg/ HCTZ 25 mg</td> <td style="text-align: center;">AM 10 mg/ HCTZ 25 mg</td> <td style="text-align: center;">AL 300 mg/ AM 10 mg/ HCTZ 25 mg</td> </tr> </tbody> </table> <p>*Steady state PK was collected at week 6.</p>				Duration	1	2	3	4	Week 1 - 4	AL 150 mg/ AM 5 mg	AL 150 mg/ HCTZ 12.5 mg	AM 5 mg/ HCTZ 12.5 mg	AL 150 mg/ ¹⁴ AM 5 mg/ HCTZ 12.5 mg	Week 5 – 8*	AL 300 mg/ AM 10 mg	AL 300 mg/ HCTZ 25 mg	AM 10 mg/ HCTZ 25 mg	AL 300 mg/ AM 10 mg/ HCTZ 25 mg
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Population	<p>Seventy eight patients enrolled for this sub-study. Number of patients in each cohort were:</p> <table border="1" style="margin-left: auto; margin-right: auto; border-collapse: collapse;"> <tbody> <tr> <td style="text-align: center;">AL 300 mg/ AM 10 mg</td> <td style="text-align: center;">AL 300 mg/ HCTZ 25 mg</td> <td style="text-align: center;">AM 10 mg/ HCTZ 25 mg</td> <td style="text-align: center;">AL 300 mg/ AM 10 mg/ HCTZ 25 mg</td> </tr> <tr> <td style="text-align: center;">18</td> <td style="text-align: center;">23</td> <td style="text-align: center;">19</td> <td style="text-align: center;">17</td> </tr> </tbody> </table>				AL 300 mg/ AM 10 mg	AL 300 mg/ HCTZ 25 mg	AM 10 mg/ HCTZ 25 mg	AL 300 mg/ AM 10 mg/ HCTZ 25 mg	18	23	19	17							
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PK Sampling	<p>0 (pre-dose), 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 3 (±0.5), 4 (±0.5), 6 (±1.0), 10 (±1.0) and 12 (±1.0) h post-dose at week 6 (visit 11).</p> <p>Note: Pre-dose measurement was used to characterize the 24 h post-dose concentration for non-compartmental and population pharmacokinetics</p>																		

¹³ Link to study report: <\\cdsesub1\EVSPROD\NDA200045\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\hypertension\5351-stud-rep-contr\sah100a2302\sah100a2302--legacy-clinical-study-report.pdf> (pages 4220 - 4407)

¹⁴ AL 150 mg/HCTZ 12.5 mg for 3 days and then titrated to AL 150 mg/AM 5 mg/HCTZ 12.5 mg

	<p>analysis. Reviewer's comment: <i>The sampling scheme will allow a reasonably good estimate of pharmacokinetic parameters of all the three drugs by non compartmental analysis.</i></p>																																				
<p>Pharmacokinetic & Statistical Methods</p>	<p>PK parameters were estimated by non-linear mixed-effects using NONMEM. Geometric mean ratios and their 90% CIs were bootstrapped. Reviewer's comment: <i>The population PK model was not reviewed. Instead, ANOVA by treatment on log transformed PK parameters derived from non compartmental analysis was used to calculate geometric mean ratio (Test=triple combination, reference=corresponding dual combination) and its 90% CI for C_{max} and AUC_{0-24}. This gave comparable results to that obtained by the population PK approach. The results are presented as the effect of one component of the triple combination on the exposure of the other two.</i></p>																																				
<p>Results</p>	<p>Interaction of aliskiren with Amlodipine</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric Mean Ratio</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>0.79</td> </tr> <tr> <td>AUC_{0-24}</td> <td>0.77</td> </tr> </tbody> </table> <p>Interaction of aliskiren with HCTZ</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric Mean Ratio</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>0.89</td> </tr> <tr> <td>AUC_{0-24}</td> <td>0.88</td> </tr> </tbody> </table> <p>Interaction of amlodipine with Aliskiren</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric Mean Ratio</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>0.87</td> </tr> <tr> <td>AUC_{0-24}</td> <td>0.93</td> </tr> </tbody> </table> <p>Interaction of amlodipine with HCTZ</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric Mean Ratio</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>0.81</td> </tr> <tr> <td>AUC_{0-24}</td> <td>0.83</td> </tr> </tbody> </table> <p>Interaction of HCTZ with Aliskiren</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric Mean Ratio</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>0.81</td> </tr> <tr> <td>AUC_{0-24}</td> <td>0.89</td> </tr> </tbody> </table> <p>Interaction of HCTZ with Amlodipine</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric Mean Ratio</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>0.96</td> </tr> <tr> <td>AUC_{0-24}</td> <td>0.94</td> </tr> </tbody> </table> <p>Legend: ● C_{max}, ◆ AUC_{0-24}</p>	Parameter	Geometric Mean Ratio	C_{max}	0.79	AUC_{0-24}	0.77	Parameter	Geometric Mean Ratio	C_{max}	0.89	AUC_{0-24}	0.88	Parameter	Geometric Mean Ratio	C_{max}	0.87	AUC_{0-24}	0.93	Parameter	Geometric Mean Ratio	C_{max}	0.81	AUC_{0-24}	0.83	Parameter	Geometric Mean Ratio	C_{max}	0.81	AUC_{0-24}	0.89	Parameter	Geometric Mean Ratio	C_{max}	0.96	AUC_{0-24}	0.94
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	<i>Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of $\pm 15\%$ as specified in 'Guidance for Industry: Bioanalytical Method Validation.'</i>																												
Safety	Death/SAE: None																												
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	Table 1(c): Summary of pharmacokinetic parameters for HCTZ		
	HCTZ in		
	Mean (%CV)		
	PK parameter	AL/HCTZ (N = 23)	AM/HCTZ (N = 19)
$C_{max,ss}$ (ng/mL)	219 (43)	190 (34)	170 (30)
AUC ₀₋₂₄ (h*ng/mL)	1788 (48)	1647 (50)	1454 (45)
Conclusion	<ul style="list-style-type: none"> • An approximate 10-20 % decrease in peak exposure to the components of the FDC was observed when compared to the corresponding duals. However, given that the sub-study was done as a part of the pivotal efficacy trial, where the triple combination beat all high dose dual combinations, this interaction is judged to be not clinically significant. • Moreover, no drug interaction has been reported in the approved dual combination of aliskiren/amlodipine and aliskiren/HCTZ. Also, there is no mechanistic rationale to anticipate a drug interaction between amlodipine and hydrochlorothiazide because of their respective metabolic pathways. 		

4.1.5. Exposure-response analysis for aliskiren

Summary: The purpose of this analysis was to develop an exposure-response relationship of aliskiren, and understand the implications of the same on the observed reduction in aliskiren systemic exposure when administered with food.

Key results:

- The exposure-response relationship for aliskiren is shallow.
- The expected difference in blood pressure reduction resulting from administration of aliskiren in the fed vs fasted state is small.

Recommendations:

- Currently, no dose adjustments are recommended for aliskiren or its fixed dose combinations. Patients are advised to establish a routine for taking aliskiren or its fixed dose combinations with regard to meals. Therefore, based on prior experience and given the fact that aliskiren exposure-response is shallow, no dose adjustments are warranted for Brandname when taken with food. Labeling language should be the same as that in the aliskiren or its fixed dose combination labels.

Background: An approximately 80% decrease in systemic exposure to aliskiren is observed when the fixed-dose combination of aliskiren, amlodipine and hydrochlorothiazide is administered with a high fat meal¹⁵. Similar results have been observed for aliskiren in its monotherapy and dual combination submissions¹⁶. This decrease in exposure has been judged to be not clinically significant based on the fact that the pivotal clinical trial for aliskiren in monotherapy as well as in combination was carried out without requiring a fixed relation to food where aliskiren has been shown to beat the corresponding comparator treatment arm. In addition, the variability in blood pressure reduction observed with aliskiren is lower than the variability in pharmacokinetics, indicating a shallow exposure-response relationship for aliskiren¹⁷. Hence, the current label for aliskiren and its fixed dose combinations does not recommend any dose adjustment when taken with food, but rather recommends maintaining a fixed relationship with meals to avoid fluctuations in exposures, merely from a pharmacokinetic perspective. However, in the absence of a direct comparison of blood pressure reduction between fed and fasted state in the pivotal clinical trial, the question of impact of reduced systemic exposure to aliskiren still remains to be answered.

Objective: To develop an exposure-response relationship for aliskiren, and to understand the clinical significance of approximately 80% decrease in the systemic exposure of aliskiren when Brandname was administered with a high fat meal.

Data: The dataset used to develop the exposure-response relationship of aliskiren was from a Phase II dose-ranging study submitted as a part of aliskiren monotherapy submission (NDA21-985). This study evaluated the effect of aliskiren on blood pressure compared to losartan. Key features of this study pertinent to data analysis are:

¹⁵ Results from food effect study (CSAH100A2101)

¹⁶ Tekturna[®], Tekamlo[®] and Tekturna HCT[®], Package insert

¹⁷ Refer clinical review by Dr. Thomas A. Marciniak. NDA 21-985: DARRTS date: 12/07/2006; pp 47-50.

- **Doses of aliskiren studied:** 37.5, 75, 150 and 300 mg¹⁸
- **Duration of study:** 4 weeks
- **Population:** Mild to moderate hypertensive patients
- **Exposure:** Steady state trough plasma concentration of aliskiren
- **Response:** Change from baseline systolic and diastolic 24 h ambulatory blood pressure monitoring (ABPM) data¹⁹ (week 4 - baseline)

Data from 139 per protocol patients who had baseline ABPM, week 4 ABPM and corresponding aliskiren trough plasma concentration were included in the analysis.

Methodology: Change from baseline ambulatory SBP and DBP values at trough was plotted against corresponding aliskiren trough plasma concentration in all 139 patients. The relationship between change from baseline ambulatory SBP and DBP at trough and corresponding trough plasma aliskiren concentration was investigated using naïve pooled log-linear regression.

Results: Results of the exposure-response relationship are presented in figures 1A and 1B. The log-linear fit as represented by the solid line, describes the relationship between aliskiren plasma concentration and change from baseline in blood pressure. As seen in figures 1A and 1B, a 100-fold increase in aliskiren plasma concentration results in only a 13 mm Hg drop in SBP and 9 mm Hg drop in DBP, indicating a shallow exposure-response relationship. The relationship is presented on a linear scale in figure 2, clearly showing that the relationship reaches a plateau at higher concentrations.

The expected difference in blood pressure reduction between administration of aliskiren in fed and fasted state was estimated using this E-R relationship and aliskiren plasma concentration data observed in the food effect study (CSAH100A2101)²⁰. As seen in figures 1A and 1B, there is a mean difference of -2.57 mm Hg (95% CI: -2.07 to -3.07 mm Hg) in SBP and -1.81 mm Hg (95% CI: -1.45 to -2.16 mm Hg) difference in DBP in fed vs fasted state following once daily 300 mg dose. However, these predictions do not take into account the variability in blood pressure response. Hence, the predicted effect of food on blood pressure response is overly conservative, and can only be used to provide a sense for the food effect on blood pressure for the aliskiren plasma concentrations reported in the food effect study (CSAH100A2101). Further, this is a cross-study comparison.

Finally, the exposure-response relationship of aliskiren as one of the components in the triple combination is generally expected to be shallower because the effect size of aliskiren when added as a third component is usually less than its effect size as monotherapy. Therefore, predicting the effect of food on blood pressure response using the E-R relationship from aliskiren monotherapy data (as performed in the current analysis) is a conservative approach.

¹⁸ Four doses of aliskiren explored in this study gave a wide range of exposures to evaluate its relationship to blood pressure lowering effect.

¹⁹ Having ambulatory blood pressure monitoring allowed to reflect the true drug effect without requiring to have a placebo arm.

²⁰ It should be noted that there are no dedicated studies conducted under the aliskiren monotherapy or dual therapy programs to understand the effect of food on blood pressure reduction

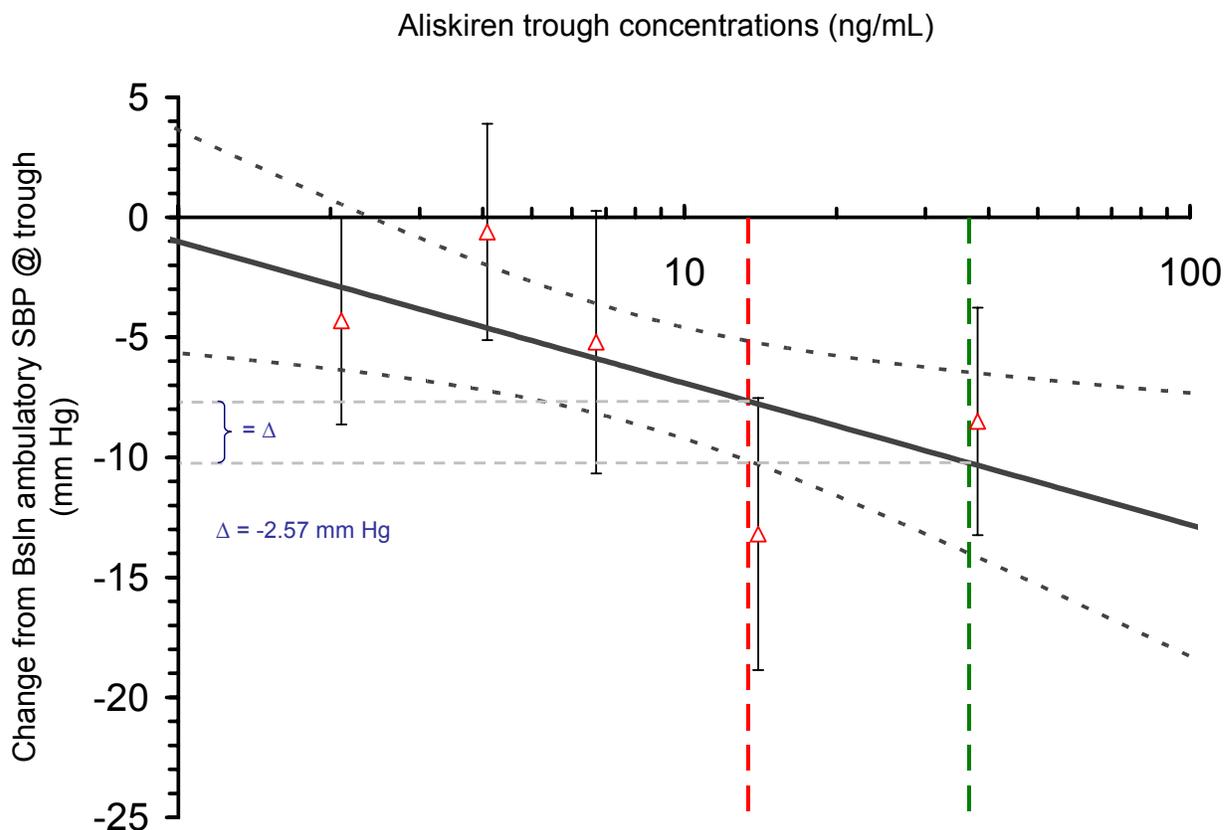


Figure 1A: Exposure-change from baseline ambulatory SBP relationship of aliskiren. X-axis represents aliskiren trough plasma concentrations and Y-axis represents corresponding mean change from baseline ambulatory SBP at trough. Red triangles represent the median aliskiren trough plasma concentration in each pentile²¹ plotted against the corresponding mean change from baseline ambulatory SBP at trough. Error bars represent 95% CI around the mean. The solid line represents the log-linear fit modeled through the entire dataset with 95% CI represented by dotted lines. Red and green vertical dashed lines represent the median steady state trough concentration in fed and fasted state following aliskiren 300 mg QD.

²¹ Aliskiren trough plasma concentration was binned into five groups (n ~28) to better represent the data.

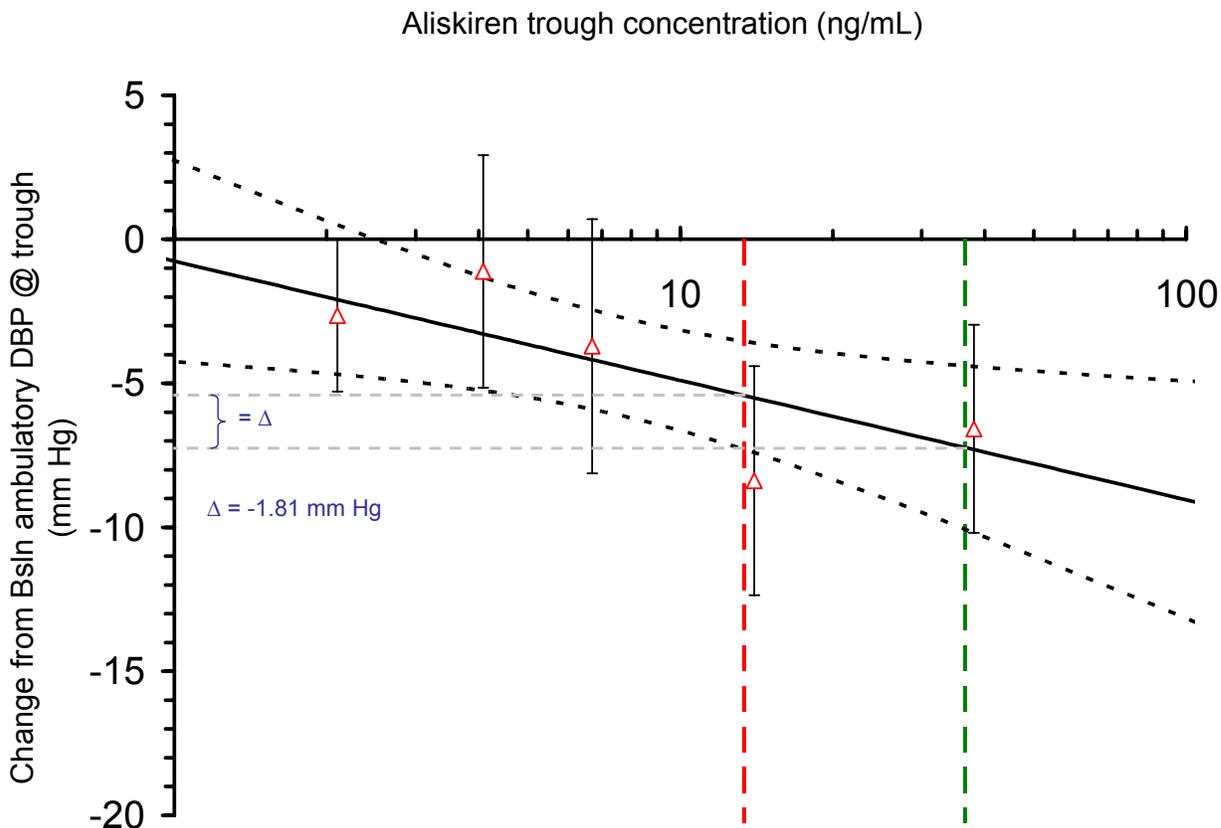


Figure 1B: Exposure-change from baseline ambulatory DBP relationship of aliskiren. X-axis represents aliskiren trough plasma concentrations and Y-axis represents corresponding mean change from baseline ambulatory DBP at trough. Red triangles represent the median aliskiren trough plasma concentration in each pentile plotted against the corresponding mean change from baseline ambulatory DBP at trough. Error bars represent 95% CI around the mean. The solid line represents the log-linear fit modeled through the entire dataset with 95% CI represented by dotted lines. Red and green vertical dashed lines represent the median steady state trough concentration in fed and fasted state following aliskiren 300 mg QD.

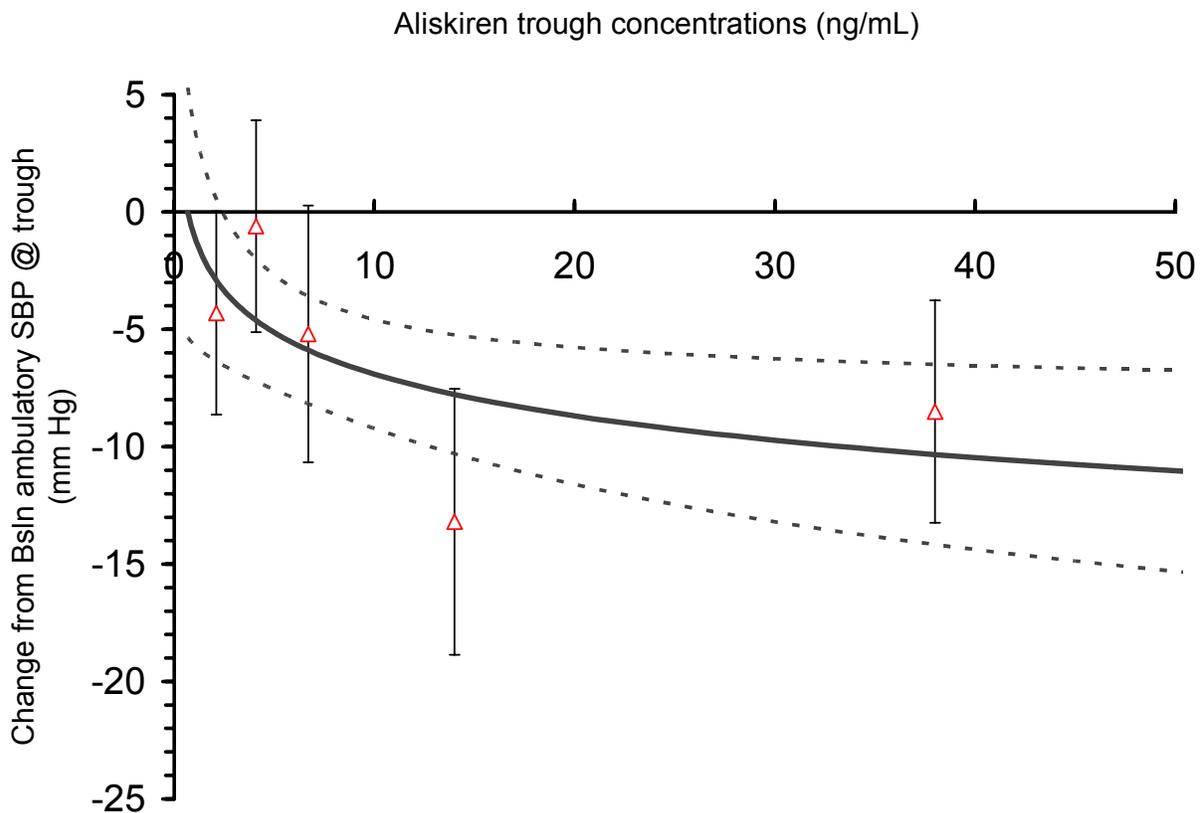


Figure 2: Exposure-change from baseline ambulatory SBP relationship of aliskiren represented in a linear –linear scale. Contents of the plot are same as seen in Fig. 1A.

Conclusion: The exposure – response relationship for aliskiren is shallow. The expected difference in blood pressure reduction resulting from administration of aliskiren in the fed vs fasted state is small. The decrease in systemic exposure with food is not likely to impact the blood pressure reduction of Brandname.

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

/s/

SUDHARSHAN HARIHARAN
11/24/2010

DIVYA MENON ANDERSEN
11/24/2010

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	200-045 (N-000)
Submission Date:	02/25/10
Brand Name:	(b) (4)
Generic Name:	Ariskiren/Amlodipine/Hydrochlorothiazide (HCTZ)
Formulation:	Oral immediate release (IR) fixed dose combination (FDC) tablet
Strength:	5 strengths (300/10/25, 300/10/12.5, 300/5/25, 300/5/12.5, and 150/5/12.5 mg)
Sponsor:	Norvatis
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Novartis' Tekalmo (aliskiren/amlodipine) IR FDC tablets, 300/10, 300/5, 150/10, and 150/5 mg were approved on 08/26/10 for treating hypertension.

On 02/25/10, Novartis submitted NDA 200-045 for (b) (4), another IR FDC oral tablets of aliskiren/amlodipine plus HCTZ. It is also indicated for treating hypertension. Five strengths are proposed, 300/10/25, 300/10/12.5, 300/5/25, 300/5/12.5, and 150/5/12.5 mg. They are compositionally the same in the formulation.

Two strengths (300/10/25 and 300/5/25 mg) of the to-be-marketed (TBM) formulation were clinically tested in Phase 3 trials. They were also compared with 3 individual components in two bioequivalence (BE) studies (CSAH100-A2102 and CSAH100-A2104) which are under reviewed by the Office of Clinical Pharmacology (OCP).

To support the biowaiver for the rest of the three strengths (300/10/12.5, 300/5/12.5, and 150/5/12.5 mg) of the TBM formulation, the sponsor performed comparative dissolution testing on each of the 5 strengths in four dissolution media (0.1N HCl, 0.01N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8) using the proposed dissolution method and submitted the results for review. The comparative dissolution data and the biowaiver are reviewed here.

The medium of 0.01 N HCl was selected which is also the FDA previously approved dissolution methodology for Aliskiren and Amlodipine. The dissolution specifications are proposed as well as shown below.

Apparatus: USP 1 (Basket)
Speed: 100 rpm
Medium: 0.01 N HCl, 900 ml at 37°C
Specification: Q= (b) (4) at 30 min for Aliskiren and amlodipine
Q= (b) (4) at 30 min for HCTZ

The three strengths which were not tested clinically showed similar dissolution profiles with f2 values being between 50-100 (for HCTZ) as compared to the two clinically tested strengths or showed (b) (4) dissolved within 30 min (for Aliskiren and Amlodipine).

RECOMMENDATION

From the Biopharmaceutics perspective, 1). The proposed dissolution method is acceptable, however, the dissolution specifications for aliskiren/amlodipine and for HCTZ need to be tightened and 2). the biowaiver for the three lower strengths (300/10/12.5, 300/5/12.5, and 150/5/12.5 mg) is granted. The following comment needs to be conveyed to the sponsor for implementation.

COMMENT (Needs to be sent to the sponsor).

Your proposed dissolution methodology for aliskiren/amlodipine and for hydrochlorothiazide is acceptable, however, the proposed specifications need to be tightened as follows.

Apparatus: USP 1 (Basket)
Speed: 100 rpm
Medium: 0.01 N HCl , 900 ml at 37°C

Specifications:

From **Q= (b) (4) at 30 min for Aliskiren and Amlodipine**
Q= (b) (4) at 30 min for Hydrochlorothiazide

To: **Q= (b) (4) at 30 min for Aliskiren and Amlodipine**
Q= (b) (4) at 30 min for Hydrochlorothiazide

BACKGROUND

Novartis’ Tekalmo (aliskiren/amlodipine) IR FDC tablets, 300/10, 300/5, 150/10, and 150/5 mg were approved on 08/26/10 for treating hypertension.

CURRENT SUBMISSION

On 02/25/10, Novartis submitted NDA 200-045 for (b) (4), another IR FDC oral tablets of aliskiren/amlodipine plus HCTZ. It is also indicated for treating hypertension. Five strengths are proposed, 300/10/25, 300/5/25, 300/10/12.5, 300/5/12.5, and 150/5/12.5 mg and they are compositionally the same in the formulation.

Two strengths (300/10/25 and 300/5/25 mg) of the TBM formulation were clinically tested in the Phase 3 trials. They were also compared with 3 individual components in two BE studies (CSAH100-A2102 and CSAH100-A2104) which are under reviewed by OCP.

To support the biowaiver for the rest of the three strengths (300/10/12.5, 300/5/12.5, and 150/5/12.5 mg) of the TBM formulation, the sponsor performed dissolution testing on all 5 strengths in four dissolution media (0.1N HCl, 0.01N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8) using the proposed dissolution method and submitted the results for review.

FORMULATION COMPARISONS

The TBM formulation of the 5 strengths is shown below.

Table 1. The TBM Formulation of Five (b) (4) IR FDC Tablet Strengths

Ingredient	Amount (mg) per tablet					Function	Reference to standards
	150/5/12.5 mg	300/5/12.5 mg	300/10/12.5 mg	300/5/25 mg	300/10/25 mg		
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Aliskiren hemifumarate						Active substance	Novartis monograph
Amlodipine besylate						Active substance	Novartis monograph
Hydrochlorothiazide						Active substance	Novartis monograph
Microcrystalline cellulose/ Cellulose microcrystalline							(b) (4) NF / Ph. Eur.
Crospovidone							NF / Ph. Eur.
Povidone							USP / Ph. Eur.
(b) (4)							Novartis monograph
Colloidal silicon dioxide / Silica, colloidal anhydrous							NF / Ph. Eur.
Magnesium stearate ⁶							NF / Ph. Eur.
(b) (4)							

Ingredient	Amount (mg) per tablet					Function	Reference to standards
	150/5/12.5 mg	300/5/12.5 mg	300/10/12.5 mg	300/5/25 mg	300/10/25 mg		
(b) (4)							Novartis monograph Novartis monograph Novartis monograph Novartis monograph USP/ Ph. Eur

¹ Corresponds to e.g. 150 mg aliskiren base

² Corresponds to e.g. 300 mg aliskiren base

³ Corresponds to e.g. 5 mg amlodipine base

⁴ Corresponds to e.g. 10 mg amlodipine base

(b) (4)

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The sponsor tested all 5 strengths in 4 dissolution media (0.1N HCl, 0.01N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8) and selected 0.01 N HCL as the dissolution medium which is also the FDA previously approved dissolution methodology for Aliskiren and Amlodipine. The dissolution specifications are proposed as well as shown below.

Apparatus: USP 1 (Basket)

Speed: 100 rpm

Medium: 0.01 N HCl, 900 ml at 37°C

Specification: Q= (b) (4) at 30 min for Aliskiren and Amlodipine

Q= (b) (4) at 30 min for HCTZ

The following batches were employed in the comparative dissolution testing.

- A. 300/10/25 mg tablet strength: (a biobatch/stability batch No. AEUS2008-0198, pilot; (b) (4))
- B. 300/10/12.5 mg tablet strength: (a representative stability batch No. AEUS2009-0070, pilot; (b) (4))
- C. 300/5/25 mg tablet strength: (a biobatch/stability batch No. AEUS2009-0055, pilot; (b) (4))
- D. 300/5/12.5 mg tablet strength: (a representative stability batch No. AEUS2009-0117, pilot; (b) (4))
- E. 150/5/12.5 mg tablet strength: (a representative stability batch No. AEUS2009-0059, pilot; (b) (4))

Please see individual and mean (n=12) dissolution data of each component of all strengths in the proposed dissolution medium (0.01 N HCl) in Appendix 1 for details.

Reviewer's Comments

1. All of the 5 strengths are compositionally the same (b) (4)

(b) (4)

(b) (4)

Therefore, the changes of inactive ingredients within the 5 strengths are considered acceptable according to the SUPAC guidance.

2. The biowaiver is acceptable since the 3 strengths which were not tested clinically showed similar dissolution profiles with f2 values being between 50-100 (for HCTZ) or showed (b)(4) dissolved within 30 min (for Aliskiren and Amlodipine).
3. The proposed dissolution methodology for aliskiren/amlodipine and for hydrochlorothiazide is acceptable, however, the proposed specifications need to be tightened as follows.

Apparatus: USP 1 (Basket)

Speed: 100 rpm

Medium: 0.01 N HCl, 900 ml at 37°C

Specifications:

From Q= (b)(4) at 30 min for Aliskiren and Amlodipine
Q= (b)(4) at 30 min for Hydrochlorothiazide

To: Q= (b)(4) at 30 min for Aliskiren and Amlodipine
Q= (b)(4) at 30 min for Hydrochlorothiazide

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

11/01/10
Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

11/02/10
Date

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

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

/s/

TIEN MIEN CHEN
11/02/2010

PATRICK J MARROUM
11/02/2010

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	200045	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	I	Generic Name	Aliskiren/amlodipine/HCTZ
Medical Division	DCRP	Drug Class	Renin inhibitor/Calcium channel blocker/Diuretic
OCP Reviewer(s)	Sudharshan Hariharan (Primary) Divya Menon-Andersen (Secondary)	Indication(s)	Treatment of hypertension
OCP Team Leader	Raj Madabushi	Dosage Form	Tablet
Pharmacometrics Reviewer		Dosing Regimen	Once daily
Date of Submission	02/25/2010	Route of Administration	Oral
Estimated Due Date of OCP Review	10/25/2010	Sponsor	Novartis
Medical Division Due Date	12/25/2010	Priority Classification	Standard
PDUFA Due Date	12/25/2010		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2	2	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	pediatrics:				
	geriatrics:				
	renal impairment:				
	hepatic impairment:				
PD -					
	Phase 2:				
	Phase 3:				
PK/PD -					
	Phase 1 and/or 2, proof of concept:				
	Phase 3 clinical trial:				
Population Analyses -					
	Data rich:				
	Data sparse:				
II. Biopharmaceutics					
Absolute bioavailability					
Relative bioavailability -					
	solution as reference:				
	alternate formulation as reference:	X	2	1	
Bioequivalence studies -					
	traditional design; single / multi dose:	X	1	1	
	replicate design; single / multi dose:				
Food-drug interaction studies		X	1	1	
Bio-waiver request based on BCS					
BCS class					
Dissolution study to evaluate alcohol induced dose-dumping					
III. Other CPB Studies					
Genotype/phenotype studies					
Chronopharmacokinetics					
Pediatric development plan					
Literature References					
Total Number of Studies				6	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)				
Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X		
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		X	
Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X	
General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology 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.

Sudharshan Hariharan

Divya Menon-Andersen

04/15/2010

Reviewing Clinical Pharmacologist

Date

Raj Madabushi

Team Leader/Supervisor

04/15/2010

Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200045

ORIG-1

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 (b) (4)

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/s/

SUDHARSHAN HARIHARAN
04/15/2010

DIVYA MENON ANDERSEN
04/15/2010