CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206302Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

ADDENDUM TO STATISTICAL REVIEW

CLINICAL STUDIES

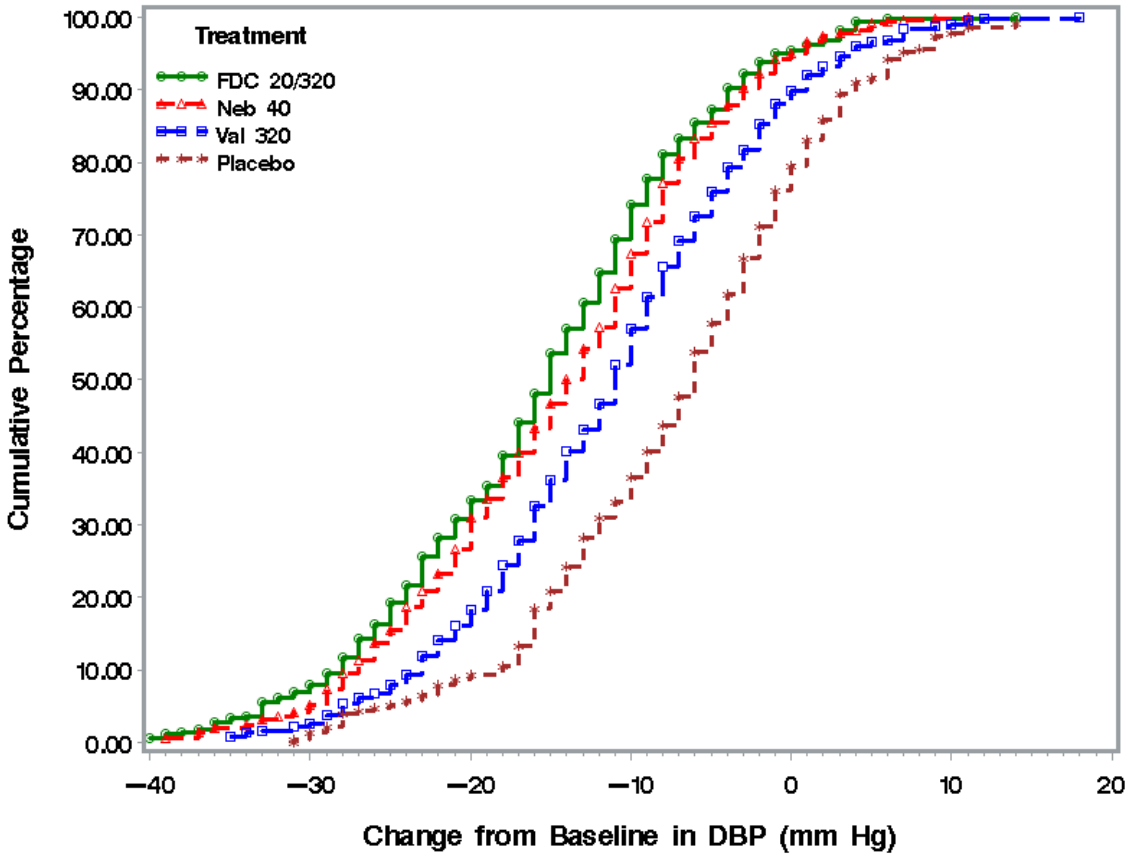
NDA #:	206,302
Drug Name:	Nebivolol/Valsartan Fixed Dose Combination
Indication(s):	Hypertension
Applicant:	Forest Research Institute, Inc.
Dates:	Submission date: February 21, 2014 PDUFA V: December 24, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewers:	George Kordzakhia, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D., H.M. James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Products
Clinical Team:	Shen Xiao, M.D., Reviewer Aliza Thompson, M.D., Team Leader
Project Manager:	Michael Monteleone

Reference ID: 3629518

This addendum to the statistical review (signed off to DARTTS on August 1, 2014) includes the plots of empirical cumulative distribution functions (CDF) of the primary and the key secondary endpoints for four treatment arms: FDC 20/320 mg, nebivolol 40 mg, valsartan 320 mg, and placebo.

Primary Endpoint: Change from Baseline to Week 8 in Diastolic Blood Pressure
Figure 1 displays empirical CDFs of the change from baseline in Diastolic Blood Pressure. The cumulative distribution functions describe the percentage of patients (vertical axis) in each treatment arm with primary endpoint values (horizontal axis) equal to or less than a given number x where x varies from -40 mm Hg to 20 mm Hg. Negative values represent improvement (positive values represent worsening).

Figure 1. Empirical Cumulative Distribution Functions for Change from Baseline in DBP



Source: Reviewer's results

For values of x larger than approximately -30 mm Hg, the CDFs for the FDC 20/320 mg and the nebivolol 40 mg separate from the CDF for the valsartan 320 mg and placebo.

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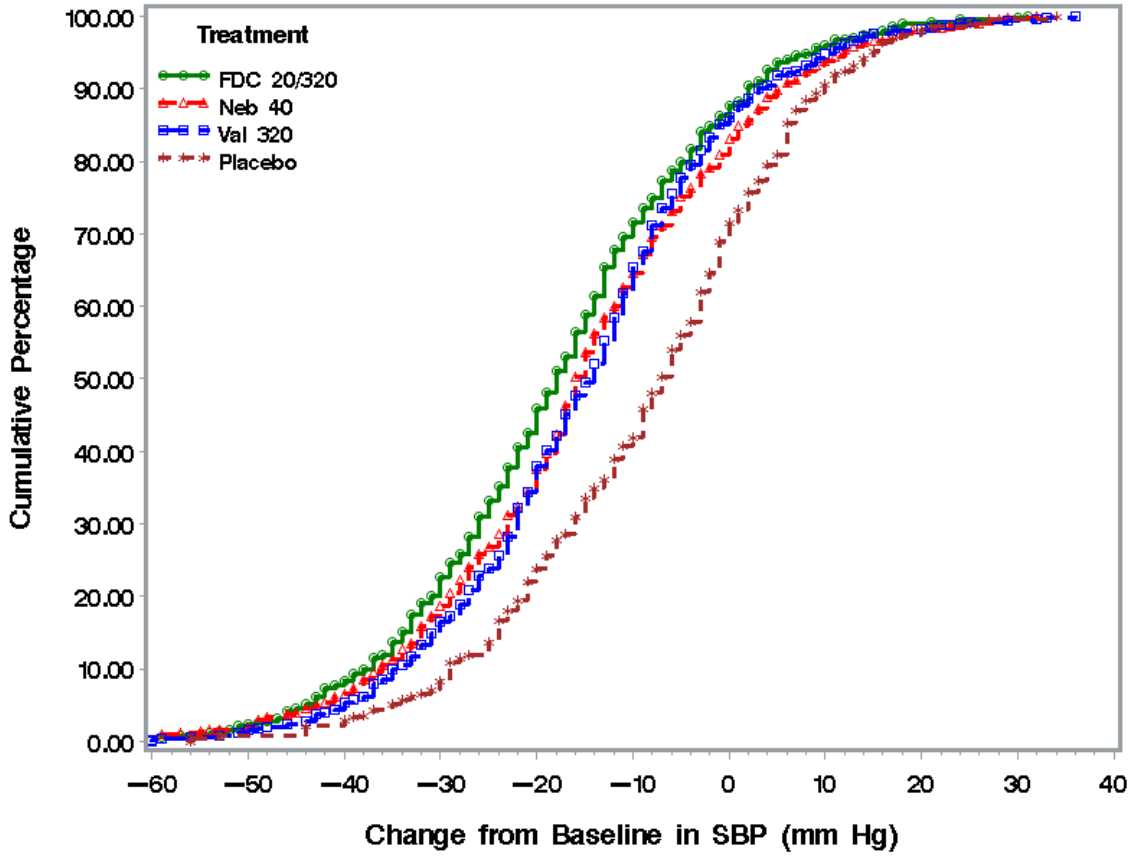
Numerically, in the FDC 20/320 mg and nebivolol 40 mg treatment arms larger proportions of patients had negative value of the primary endpoint compared with the valsartan 320 mg and the placebo arms. There appears to be no discernible difference between the CDF curves corresponding to the FDC and nebivolol 40mg.

Key Secondary Endpoint: Change from Baseline to Week 8 in Systolic Blood Pressure

Figure 2 displays empirical CDFs of the change from baseline in SBP. Negative values represent improvement (positive values represent worsening). The cumulative distribution functions describe the percentage of patients (vertical axis) in each treatment arm with change in SBP (horizontal axis) equal to or less than a given number x where x varies from -60 mm Hg to 40 mm Hg.

Figure 2. Empirical Cumulative Distribution Functions for Change from Baseline in SBP



Source: Reviewer's results

The proportion of patients with negative change in SBP was generally larger in the FDC 20/320 treatment arm than respective proportions in the nebivolol 40 mg, valsartan 320

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mg and placebo arms. For values of x between approximately -40 mm Hg and -5 mm Hg, the cumulative distribution function for the FDC 20/320 mg separate from the CDFs corresponding to the other three arms.

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/s/

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09/17/2014

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09/18/2014

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

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Keywords:

NDA review, ANCOVA, logistic regression.

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1. EXECUTIVE SUMMARY

The sponsor submitted an initial New Drug Application (NDA 206-302) for nebivolol/valsartan fixed dose combinations (FDC) 10/160 mg, 10/320 mg, and 20/320 mg for the treatment of Stage 1 or 2 essential hypertension.

The efficacy of fixed-dose combinations of nebivolol and valsartan has been evaluated in one short-term, 8-arm, multiple-dose, placebo-controlled study conducted in the United States.

Per the Agency's advice, the efficacy of the FDCs had to be demonstrated against the highest approved doses of both component monotherapies: 40 mg of nebivolol and 320 mg of valsartan (i.e., the maximum of two p-values had to be less than 0.05).

Based on the pre-specified primary statistical analysis, the FDC 20/320 mg was statistically superior to both monotherapies (the nebivolol 40 mg and the valsartan 320 mg) as measured by mean reduction in trough seated diastolic blood pressure (DBP) - the primary efficacy endpoint. Whether the observed treatment difference between the FDC 20/320 mg and the nebivolol 40 mg (equal to -1.2 mm Hg) can be considered clinically meaningful is uncertain. In the trough seated systolic blood pressure (SBP) the FDC 20/320 mg also appeared to be more effective than the nebivolol 40 mg and the valsartan 320 mg.

The fixed-dose combinations 10/320 mg and 10/160 mg were not statistically superior to the nebivolol 40 mg monotherapy.

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2. INTRODUCTION

2.1 Overview

The sponsor submitted an initial New Drug Application (NDA 206-302) for nebivolol/valsartan fixed dose combination (FDC) 10/160 mg, 10/320 mg, and 20/320 mg for the treatment of Stage 1 or 2 essential hypertension.

The efficacy of fixed-dose combination of nebivolol and valsartan has been evaluated in one short-term, 8-arm, multiple-dose, placebo-controlled study conducted in the United States.

2.2 Data Sources

The clinical study report and data sets were submitted electronically. The network path for the submission is \\cdsesub1\evsprod\NDA206302\0000. Primary analysis data sets are located at \\cdsesub1\evsprod\NDA206302\0000\m5 . The sponsor's submission to Division's request pertaining to the model diagnostic analyses for the graphs estimating the probability of achieving diastolic and systolic blood pressure goals is located at \\cdsesub1\evsprod\NDA206302\0002 .

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data acceptable for the reviewer's analyses.

3.2 Evaluation of Efficacy

The sponsor submitted the clinical study report of 1 short-term efficacy study, NAC-MD-01, to evaluate the safety and efficacy of nebivolol and valsartan given as a fixed-dose combination in patients with stage 1 or 2 essential hypertension.

3.2.1 Study Design and Endpoints

Study NAC-MD-01 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group fixed-dose combination study of 8-week duration (double-blind phase). The study consisted of 1 week for screening followed by a single-blind, placebo washout/run-in period of up to 6 weeks, an 8-week double-blind treatment period, and a 1-week down-titration period.

At the end of the single-blind placebo washout/run-in period, patients who met the entry criteria for this study were randomized in a 2:2:2:2:2:2:2:1 ratio to 1 of 8 double-blind treatment groups: the starting double-blind doses were FDC of nebivolol 5 mg and valsartan 80 mg, FDC of

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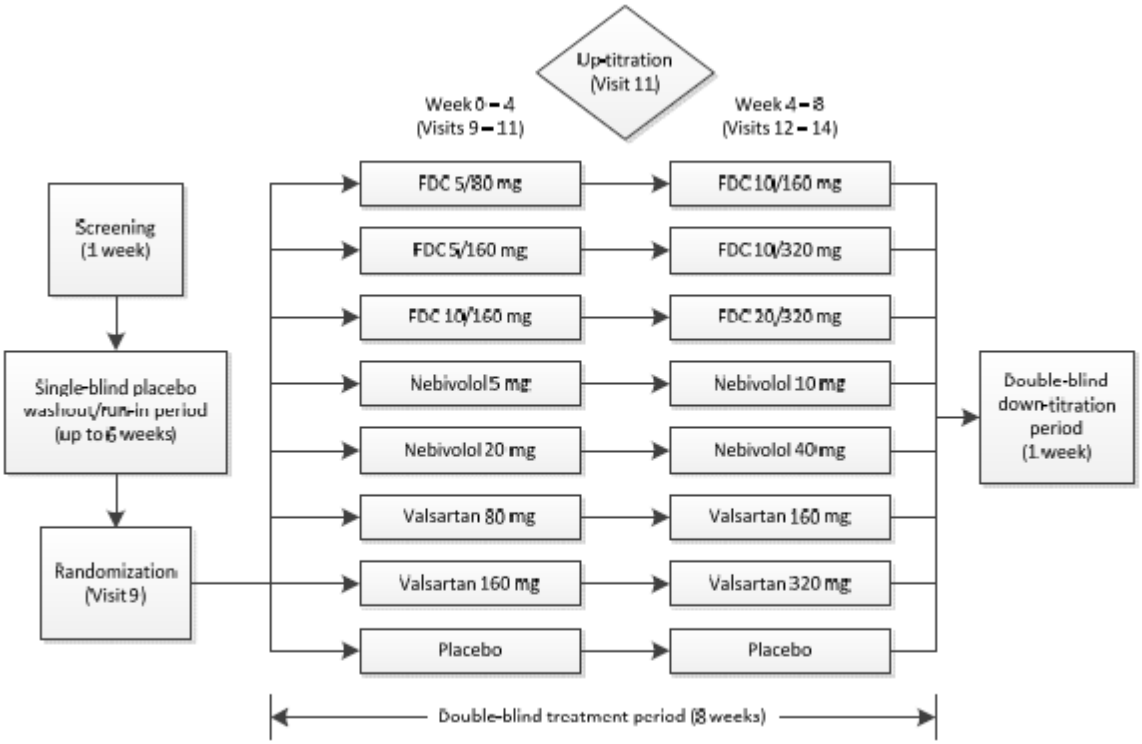
nebivolol 5 mg and valsartan 160 mg, FDC of nebivolol 10 mg and valsartan 160 mg, nebivolol 5 mg monotherapy, nebivolol 20 mg monotherapy, valsartan 80 mg monotherapy, valsartan 160 mg monotherapy, or placebo. All doses were doubled after 4 weeks at Visit 11 to the final assigned treatment groups of FDCs of nebivolol 10 mg and valsartan 160 mg (FDC 10/160 mg), FDC of nebivolol 10 mg and valsartan 320 mg (FDC 10/320 mg), FDC of nebivolol 20 mg and valsartan 320 mg (FDC 20/320 mg), nebivolol 10 mg monotherapy, nebivolol 40 mg monotherapy, valsartan 160 mg monotherapy, valsartan 320 mg monotherapy, or placebo. Figure 1 provides a schematic of the study design.

Figure 1. Overall study design



FDC = fixed dose combination.

Source: Clinical Study Report Figure 9.1-1. (pg. 39)

The *primary efficacy endpoint* was the change from baseline to Week 8 in trough seated DBP, which was measured using an Omron BP monitor in the patient's arm. At each clinic visit, following an initial 5-minute rest period, 4 separate seated BP measurements were taken, with a 2- to 5-minute interval between measurements. The first measurement was disregarded, and the mean of the last 3 values constituted the BP value for that visit.

The sponsor also pre-specified *one key-secondary efficacy endpoint*: the change from baseline in seated trough SBP at Week 8, measured analogously to the primary efficacy endpoint.

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3.2.2 Statistical Methodologies

The efficacy analyses were based on the Intent-To-Treat (ITT) Population. The ITT Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter (seated DBP measurement).

The primary and the key secondary endpoints were analyzed by ANCOVA model, with treatment group and diabetes status as the factors and baseline value as a covariate. The last-observation-carried-forward (LOCF) approach was used to impute missing post-baseline values. *Baseline* for efficacy was defined as the last non-missing efficacy assessment before the date of the first dose of double-blind investigational product.

Primary Efficacy Endpoint Comparisons (as pre-specified)
The FDC 20/320 mg is to be separately compared to nebivolol 40 mg and to valsartan 320 mg. If both comparisons are statistically significant (i.e., the maximum of two p-values is less than 0.05), the study is claimed positive. Then, according to the sponsor's plan, the FDC 10/160 mg and 10/320 mg is be compared with their corresponding monotherapy doses with multiplicity controlled by Hochberg procedure on the adjusted p-values (i.e., the maximum of p-values for the comparisons of the FDC treatment group versus its corresponding monotherapy treatment groups).

Key Secondary Efficacy Endpoint Comparisons (as pre-specified)
For the key secondary endpoint, each FDC compared with its respective monotherapies will be tested only after the same FDC in the primary efficacy parameter is determined to be positive.

Reviewer's Remark 1:
As indicated in the pre-IND teleconference minutes from February 25, 2011, and re-emphasized in the pre-NDA meeting preliminary comments dated September 5, 2013 (meeting was cancelled), the FDC doses should be compared to the highest approved dose of the monotherapy components, not to the corresponding doses of monotherapy components.

Reviewer's Remark 2:
The multiple testing strategy does not control the overall type I error rate. In this setting, hypotheses for the key secondary endpoint should not be formally tested unless the primary efficacy is demonstrated in all three fixed dose combinations. However, as indicated in the pre-IND teleconference minutes from February 25, 2011, since the key secondary endpoint measures a different aspect of blood pressure, the testing approach seems reasonable.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 1 summarizes the subject disposition and analysis sets. A total of 4161 patients were randomized to receive double-blind treatment; 4159 patients received at least 1 dose of double-blind treatment (Safety Population); of those 4118 patients had at least 1 post-baseline trough

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seated DBP assessment (ITT Population), and 3715 (89.3%) patients completed the double-blind treatment period.

Table 1. Patient Populations: Number of Patients by Treatment Group

Patients	Placebo	FDC10/160	FDC10/320	FDC20/320	Neb 10	Neb 40	Val 160	Val 320
Randomized, N (%)	277 (100%)	555 (100%)	555 (100%)	554 (100%)	555 (100%)	555 (100%)	555 (100%)	555 (100%)
Safety, N	277	555	555	554	555	554	555	554
ITT, N	277	549	548	550	552	547	548	547
Completed, N (%)	244 (88.1%)	490 (88.3%)	496 (89.4%)	506 (91.3%)	505 (91.0%)	479 (86.3%)	498 (89.7%)	497 (89.5%)

N=number of patients; percentages are relative to the number of randomized patients; ITT=Intent-To-Treat
Source: Clinical Study Report Figure 10.1-1 (pg. 91) and Table 10.1-1 (pg. 93)

The demographic and baseline characteristics are summarized in Table 2. Approximately 55% of all ITT patients were men, and the overwhelming majority (84.8%) were Caucasian. The mean age was 51.3 years, ranging from 18 to 83 years, and the mean weight was 92 kg, ranging from 44 kg to 195 kg. Approximately 15% of the patients were diabetic. Treatment groups were generally balanced with respect to these demographic and baseline characteristics.

Table 2. Demographic and Baseline Characteristics (ITT Population)

	Placebo	FDC10/160	FDC10/320	FDC20/320	Neb 10	Neb 40	Val 160	Val 320
ITT patients, N (100%)	277 (100%)	549 (100%)	548 (100%)	550 (100%)	552 (100%)	547 (100%)	548 (100%)	547 (100%)
Sex								
Male, N (%)	148 (53.4%)	298 (54.3%)	310 (56.6%)	310 (56.4%)	304 (55.1%)	294 (53.7%)	329 (60.0%)	291 (53.2%)
Female, N (%)	129 (46.6%)	251 (45.7%)	238 (43.4%)	240 (43.6%)	248 (44.9%)	253 (46.3%)	219 (40.0%)	256 (46.8%)
Race								
White, N (%)	231 (83.4%)	459 (83.6%)	470 (85.8%)	470 (85.5%)	450 (81.5%)	466 (85.2%)	476 (86.9%)	469 (85.7%)
Black, N (%)	30 (10.8%)	55 (10.0%)	54 (9.8%)	52 (9.5%)	68 (12.3%)	52 (9.5%)	42 (7.7%)	50 (9.1%)
Asian, N (%)	12 (4.3%)	25 (4.6%)	11 (2.0%)	18 (3.3%)	22 (4.0%)	19 (3.5%)	23 (4.2%)	18 (3.3%)
Other, N (%)	4 (1.4%)	10 (1.8%)	13 (2.4%)	10 (1.8%)	12 (2.2%)	10 (1.8%)	7 (1.3%)	10 (1.8%)
Age (years): Mean (SD**)**	51.1 (10.4)	50.9 (10.1)	51.6 (9.8)	50.8 (9.7)	51.7 (10.2)	51.5 (10.8)	51.8 (9.9)	51.1 (10.7)
Weight (kg)	93.6 (20.7)	91.0 (20.5)	92.2 (20.1)	92.2 (20.8)	92.4 (21.2)	91.5 (21.3)	92.3 (20.9)	92.1 (20.9)
Diabetic								
Yes, N (%)	40 (14.4%)	80 (14.6%)	88 (16.1%)	89 (16.2%)	82 (14.9%)	84 (15.4%)	83 (15.1%)	87 (15.9%)
No, N (%)	237 (85.6%)	469 (85.4%)	460 (83.9%)	461 (83.8%)	470 (85.1%)	463 (84.6%)	465 (84.9%)	460 (84.1%)

N=number of patients; ITT=Intent-To-Treat; percentages are relative to the number of ITT patients; SD=Standard Deviation
Source: Clinical Study Report Table 14.2.1B (pg. 460)

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3.2.4 Efficacy Results and Conclusions

3.2.4.1 Primary Efficacy Measure: Trough Seated DBP

The primary efficacy endpoint, the change from baseline to Week 8 in trough seated DBP, was analyzed by LOCF ANCOVA model with treatment group and diabetes status as the factors and baseline trough seated DBP value as a covariate. The LS Mean reductions in DBP at Week 8 by treatment group are displayed in Table 3 for the ITT population.

Table 3. LS Mean Change from Baseline in Trough Seated Diastolic Blood Pressure at Week 8 (ITT Population, LOCF, ANCOVA)

Treatment Group	*n*	*LSM Change From Baseline (SE)*
Placebo	277	–7.1 (0.6)
Nebivolol 10 mg	552	–12.8 (0.4)
Nebivolol 40 mg	547	–14.5 (0.4)
Valsartan 160 mg	548	–10.9 (0.4)
Valsartan 320 mg	547	–11.4 (0.4)
FDC 10/160 mg	549	–15.0 (0.4)
FDC 10/320 mg	548	–15.1 (0.4)
FDC 20/320 mg	550	–15.7 (0.4)

n=number of patients, SE=Standard Error, LSM=Least Squares Mean
ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Clinical Study Report Table 11.4.1.1-1. (pg. 123)
Results confirmed by the reviewer

The reduction in mean trough seated DBP after 8 weeks of treatment with the FDC 20/320 mg was statistically significantly greater than the reductions observed with the highest approved doses of either the nebivolol (40 mg) or the valsartan (320 mg). The least squares mean difference (LSMD) between the FDC 20/320 mg treatment group and the nebivolol 40 mg monotherapy treatment group was -1.2 mm Hg (p-value = 0.03). The LSMD between the FDC 20/320 mg and the valsartan 320 mg monotherapy treatment groups was -4.4 mm Hg (p-value < 0.0001).

Similarly, the FDC 10/320 mg and the FDC 10/160 mg treatment groups had statistically significantly greater reductions in DBP compared with patients receiving the valsartan 320mg monotherapy (the highest approved dose). However, neither the FDC 10/320 mg nor the FDC 10/160 mg was statistically superior to the nebivolol 40mg (the highest approved dose).

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All the FDC and the monotherapy treatment groups demonstrated statistically significantly greater reductions in DBP compared to the placebo treatment group after 8 weeks of treatment. The least squares (LS) mean treatment differences are summarized in Table 4.

Table 4. LS Mean Differences in Trough Seated Diastolic Blood Pressure at Week 8 (ITT Population, LOCF, ANCOVA)

Pairwise Comparison	LS Mean Difference	95% CI	p-value
FDC 20/320 mg vs Val 320 mg	-4.4	(-5.4, -3.3)	<0.0001
FDC 20/320 mg vs Neb 40 mg	-1.2	(-2.3, -0.1)	0.03
FDC 10/320 mg vs Val 320 mg	-3.7	(-4.8, -2.7)	< 0.0001
FDC 10/320 mg vs Neb 40 mg	-0.6	(-1.7, 0.5)	0.28
FDC 10/160 mg vs Val 320 mg	-3.6	(-4.7, -2.5)	<0.0001
FDC 10/160 mg vs Neb 40 mg	-0.5	(-1.5, 0.6)	0.42
FDC 20/320 mg vs placebo	-8.7	(-10.0, -7.3)	<0.0001
FDC 10/320 mg vs placebo	-8.1	(-9.4, -6.7)	<0.0001
FDC 10/160 mg vs placebo	-7.9	(-9.3, -6.6)	<0.0001
Val 320 mg vs placebo	-4.3	(-5.7, -3.0)	<0.0001
Val 160 mg vs placebo	-3.9	(-5.2, -2.5)	<0.0001
Neb 40 mg vs placebo	-7.5	(-8.8, -6.1)	<0.0001
Neb 10 mg vs placebo	-5.7	(-7.4, -4.4)	<0.0001

LS Mean=Least Squares Mean; CI=Confidence Interval
Source: Clinical Study Report Table 11.4.1.1-1. (pg. 124) and reviewer's results.
Sponsor's results confirmed by the reviewer

Reviewer's Exploratory Analyses of Within-Subject Variability

This reviewer evaluated the variability of trough seated DBP for each patient based on 5 visits including baseline (Baseline, Weeks 2, 4, 6, and 8). Similarly, the variability of change from baseline in trough seated DBP for each patient was estimated based on 4 visits (Weeks 2, 4, 6, and 8). For each patient, the standard deviation was calculated based on the available assessment visits without imputation for the missing visits.

Of the 4118 ITT patients who had at least one post-baseline visit assessment, 3965 (96.3%) patients had at least 2 post-baseline observations; 3751 (91.1%) patients had four post-baseline DBP assessments. Table 5 summarizes the number of ITT patients by the Visit/Week of the last DBP assessment of the double-blind treatment phase.

Table 5. Number of patients by last available DBP assessment visit (ITT Population)

Last DBP Assessment Visit	Week 2	Week 4	Week 6	Week 8	Total
Number of Patients (%)	153 (3.7%)	116 (2.8%)	98 (2.4%)	3751 (91.1%)	4118 (100%)

ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

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[1] Within-Subject Variability of Trough Seated DBP:
The calculation of estimated standard deviation was based on the ITT patients who had at least one post-baseline visit. The results are presented in Table 6. The variability estimation was adjusted for the treatment and visit means; the mean standard deviation is approximately 5.6 mm Hg.

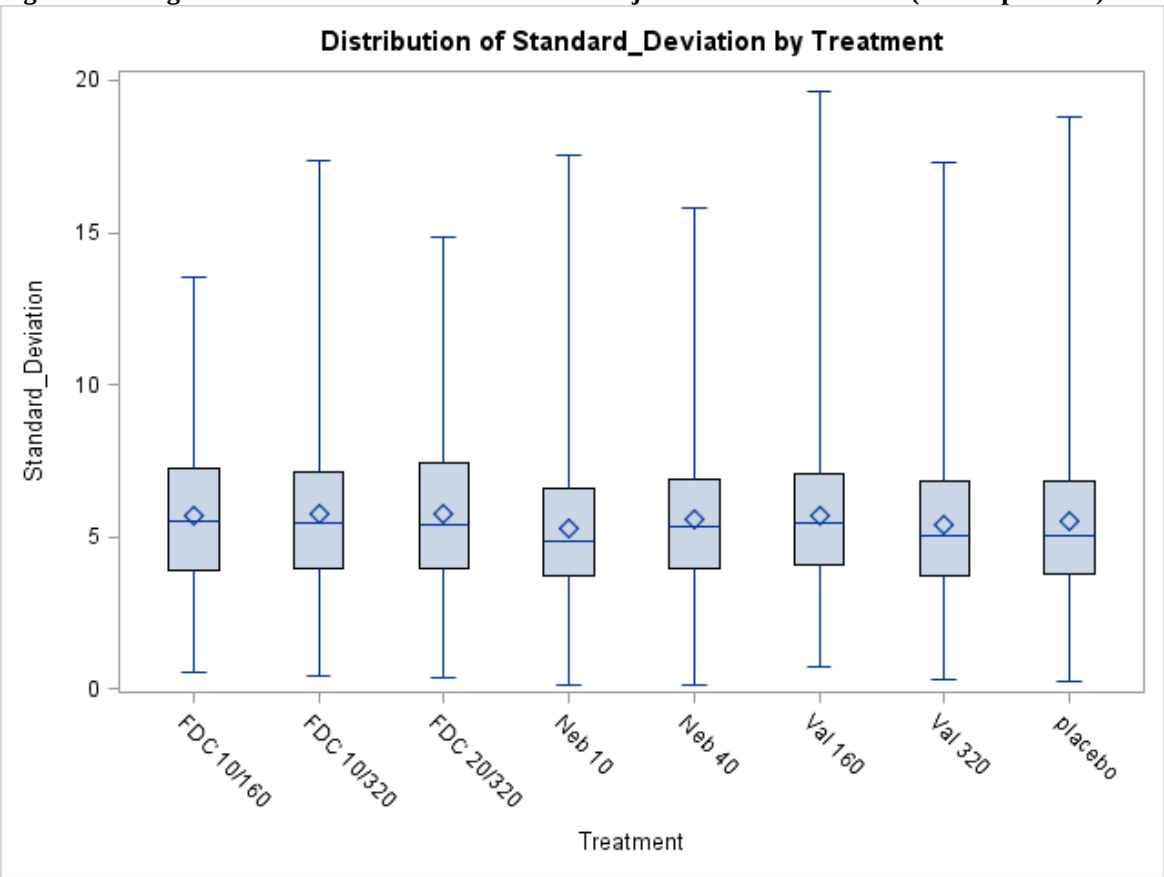
Table 6. Estimated Within-Subject Standard Deviation of Trough Seated DBP (in mm Hg) Adjusted for Treatment & Visit (ITT Population)

ITT Patients	Mean	Minimum	Maximum
N=4118	5.60	0.13	19.64

ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's Results

With DBP being adjusted for Visit*Treatment means, the empirical distribution of the estimated within-subject standard deviations appears to be consistent among the treatment groups, as displayed by the box-plots for the eight treatment arms in Figure 2.

Figure 2. Trough Seated DBP: Box-Plot for Within-Subject Standard Deviation (ITT Population)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's Results

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[2] Within-Subject Variability of Change from Baseline in Trough Seated DBP:
For the change from baseline endpoint, the calculation of standard variation was based on the subset of ITT patients who had at least 2 post-baseline observations (N=3965). Again, the variability is adjusted for treatment and visit means; the mean standard deviation is approximately 5.2 mmHg.

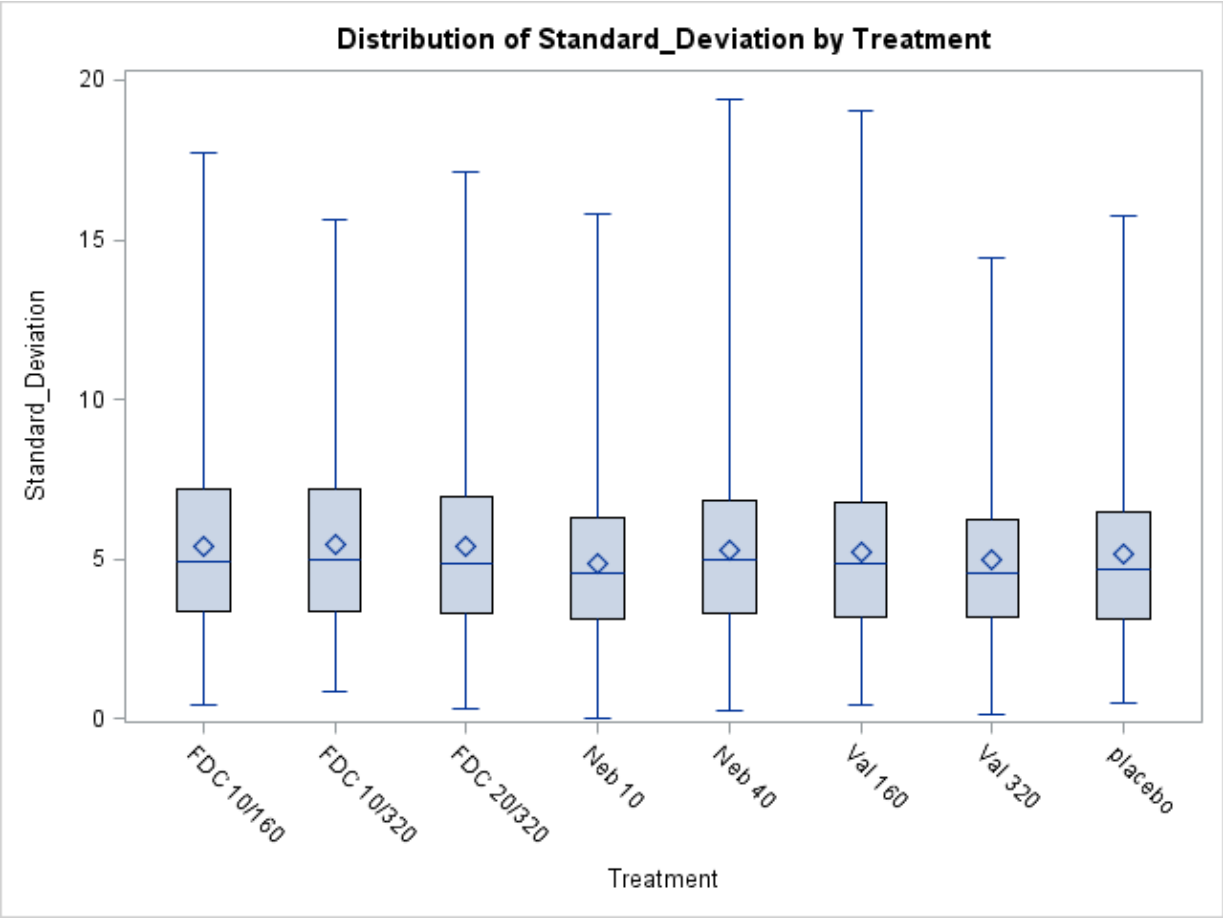
Table 7. Estimated Within-Subject Standard Deviation of Change from Baseline in Trough Seated DBP (in mm Hg) Adjusted for Treatment & Visit

Patients*	Mean	Minimum	Maximum
3965	5.23	0.04	19.39

*All patients who took at least 1 dose of double-blind investigational product and had at least 2 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's Results

The empirical distribution of the within-subject standard deviation of the change from baseline in DBP adjusted for Visit*Treatment means appears to be consistent among the treatment groups, as seen in the boxplots in Figure 3.

Figure 3. Change from Baseline in Trough Seated DBP: Box-Plot for Within-Subject Standard Deviation



All patients who took at least 1 dose of double-blind investigational product and had at least 2 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's Results

Reference ID: 3603072

3.2.4.2 Key Secondary Efficacy Measure: Trough Seated SBP

The sponsor pre-specified one key secondary endpoint: the change from baseline to Week 8 in trough seated SBP. The endpoint was analyzed by the same ANCOVA model as was applied to the primary endpoint (but with trough seated SBP baseline score included as a covariate). The LS mean changes by treatment group at Week 8 are presented in Table 8

Table 8. LS Mean Change from Baseline in Trough Seated Systolic Blood Pressure at Week 8 (ITT Population, LOCF, ANCOVA)

Treatment Group	*n*	*LSM Change From Baseline (SE)*
Placebo	277	−7.2 (0.9)
Nebivolol 10 mg	552	−13.4 (0.7)
Nebivolol 40 mg	547	−14.2 (0.7)
Valsartan 160 mg	548	−13.1 (0.7)
Valsartan 320 mg	547	−14.0 (0.7)
FDC 10/160 mg	549	−17.0 (0.7)
FDC 10/320 mg	548	−17.0 (0.7)
FDC 20/320 mg	550	−17.1 (0.7)

ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
n=number of patients, SE=Standard Error, LSM=Least Squares Mean
Source: Clinical Study Report Table 11.4.1.1-1. (pg. 123)
Sponsor's results confirmed by the reviewer

The nominal p-values shown in Table 9 are very small for the pairwise comparisons on trough seated SBP. The reduction in mean trough seated SBP after 8 weeks of treatment with the FDC 20/320 mg appeared to be greater than the reductions observed with the highest approved doses of either the nebivolol 40 mg or the valsartan 320 mg monotherapy. Similarly, the FDC 10/320 mg and 10/160 mg appeared to have greater reductions in SBP compared with the nebivolol 40 mg and with the valsartan 320 mg monotherapies. All FDC and monotherapy treatment groups were superior to the placebo treatment group after 8 weeks of treatment. The LS Mean treatment differences are summarized in Table 9.

Reference ID: 3603072

Table 9. LS Mean Differences in Trough Seated Systolic Blood Pressure at Week 8 (ITT Population, LOCF, ANCOVA)

Pairwise Comparison	LS Mean Difference	95% CI	p-value
FDC 20/320 mg vs Val 320 mg	-3.1	(-4.9, -1.4)	0.0005
FDC 20/320 mg vs Neb 40 mg	-2.9	(-4.7, -1.1)	0.0013
FDC 10/320 mg vs Val 320 mg	-3.0	(-4.7, -1.2)	0.0011
FDC 10/320 mg vs Neb 40 mg	-2.7	(-4.5, -0.9)	0.0027
FDC 10/160 mg vs Val 320 mg	-3.0	(-4.8, -1.2)	0.0009
FDC 10/160 mg vs Neb 40 mg	-2.7	(-4.5, -1.0)	0.0023
FDC 20/320 mg vs placebo	-9.9	(-12.1, -7.7)	<0.0001
FDC 10/320 mg vs placebo	-9.7	(-11.9, -7.6)	<0.0001
FDC 10/160 mg vs placebo	-9.8	(-11.9, -7.6)	<0.0001
Val 320 mg vs placebo	-6.8	(-8.9, -4.6)	<0.0001
Val 160 mg vs placebo	-5.9	(-8.0, -3.7)	<0.0001
Neb 40 mg vs placebo	-7.0	(-9.2, -4.8)	<0.0001
Neb 10 mg vs placebo	-6.2	(-8.3, -4.0)	<0.0001

ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
LS Mean=Least Squares Mean; CI=Confidence Interval
Source: Clinical Study Report Table 11.4.1.2.1-1. (pg. 126) and reviewer's results.
Sponsor's results confirmed by the reviewer

3.2.4.3 Four Graphs for Probability of Achieving DBP and SBP Goals

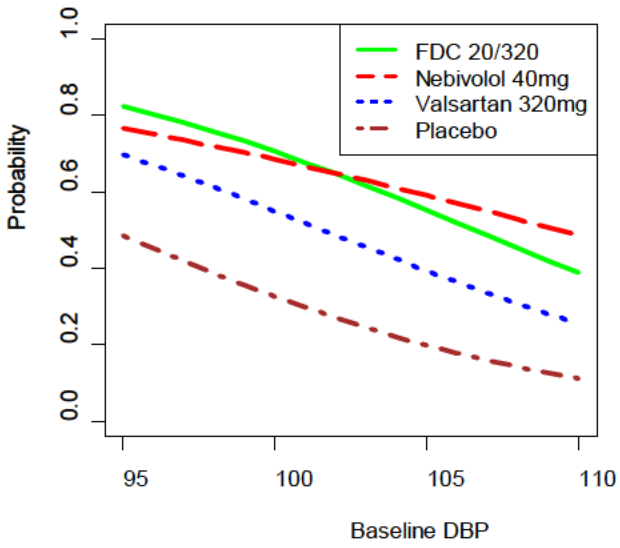
This reviewer generated four graphs of the probability of reaching blood pressure goals of 140 and 130 mm Hg systolic, and 90 and 80 mm Hg diastolic. The probability as a function of baseline blood pressure was estimated using logistic regression (with baseline blood pressure as the only covariate in the model) for the four treatment groups: FDC 20/320 mg, nebivolol 20 mg, valsartan 320 mg, and placebo. Individual logistic regression model was fitted to each treatment arm, respectively. This model is different from the sponsor's model which assumes common slope for the four treatment groups.

Diastolic Blood Pressure (DBP)

Figure 4 and Figure 5 provided below present estimates of the probability of achieving a DBP < 90 mm Hg and < 80 mm Hg, respectively, for the FDC 20/320 mg, placebo and the highest dose monotherapy groups (nebivolol 40 mg and valsartan 320 mg). Based on the figures, in all treatment arms the estimated probability of achieving the diastolic goals decreases as baseline DBP gets higher. For all baseline DBP values, the estimated probability is higher with the FDC 20/320 mg and the nebivolol 40 mg monotherapy than with the valsartan 320 mg monotherapy and placebo. Neither one of the two (FDC 20/320 mg and nebivolol 40 mg) appear to be better than the other.

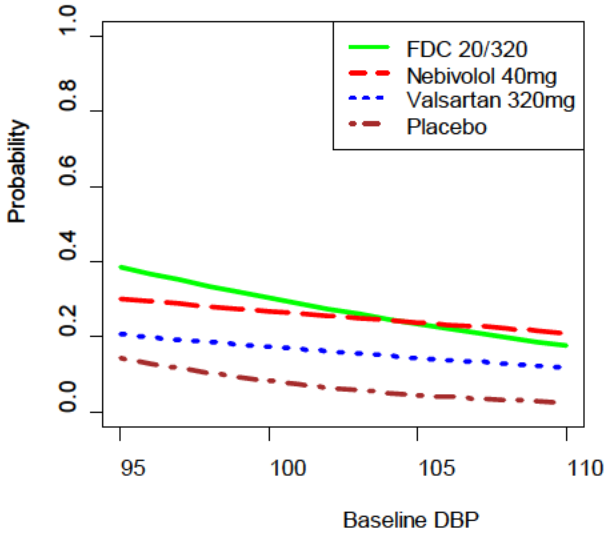
Reference ID: 3603072

Figure 4. Probability of Achieving a Diastolic Blood Pressure Goal <90 mm Hg at Week 8 (ITT Population, LOCF)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

Figure 5. Probability of Achieving a Diastolic Blood Pressure Goal <80 mm Hg at Week 8 (ITT Population, LOCF)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

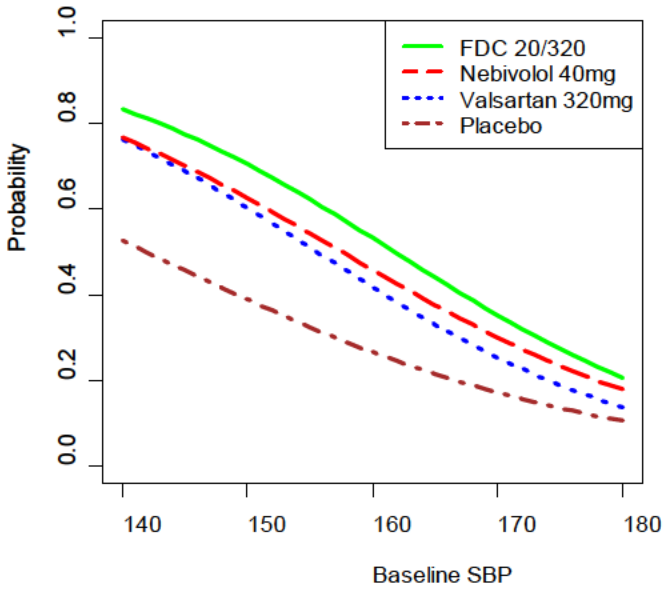
Reference ID: 3603072

Systolic Blood Pressure (SBP)

The probability of patients achieving an SBP goal as a function of the patient's baseline SBP is displayed for the goal of < 140 mm Hg in Figure 6 and for the goal of < 130 mm Hg in

Figure 7. For all baseline SBP values, the estimated probabilities of achieving both goals with the FDC 20/320 mg appear to be higher than with either the nebivolol 40 mg monotherapy or the valsartan 320 mg monotherapy.

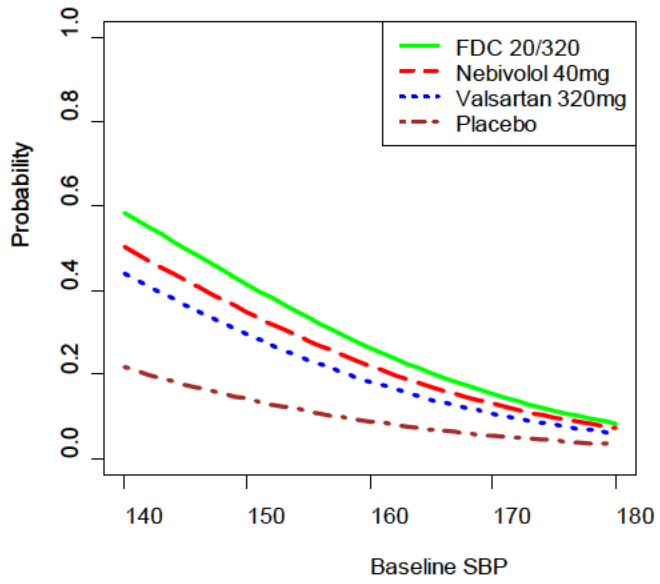
Figure 6. Probability of Achieving a Systolic Blood Pressure Goal <140 mm Hg at Week 8 (ITT Population, LOCF)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

Reference ID: 3603072

Figure 7. Probability of Achieving a Systolic Blood Pressure Goal <130 mm Hg at Week 8 (ITT Population, LOCF)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

The sponsor provided model diagnostics for the logistic regression analyses used in generating the four graphs. The diagnostics which included residual analysis and the comparison of logistic regression with the LOESS model did not reveal any major lack-of-fit problems.

Reviewer's Remark: The model diagnostic analyses provided by the sponsor are applicable to the probability curves this reviewer generated (i.e., model parameter values for each treatment group were estimated only from the data of that treatment group).

Reference ID: 3603072

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age

This section contains reviewer's exploratory subgroup analysis. The primary efficacy analysis model, ANCOVA LOCF, was used to investigate gender (Male, Female), racial (White, Other) and age (<65 years, ≥ 65 years) subgroups. The results are displayed in Table 10. The overwhelming majority of patients were Caucasian and younger than 65 years. Overall, in all subgroups except in the non-Caucasian racial subgroup, all three FDC treatment arms were numerically better than both the nebivolol 40 mg and the valsartan 320 mg arms. In the non-Caucasian subgroup, the nebivolol 40 mg arm had numerically greater LS mean reduction in trough seated SDP compared with the FDC 20/320 and the FDC 10/160.

All monotherapy and FDC arms were numerically better than placebo in all investigated subgroups.

Table 10. Subgroup Analysis: LS mean Change from Baseline in Trough Seated Diastolic Blood Pressure at Week 8 (LOCF, ANCOVA)

	Placebo	**FDC10/160**	**FDC10/320**	**FDC20/320**	**Neb 10**	**Neb 40**	**Val 160**	**Val 320**
ITT patients, N	277	549	548	550	552	547	548	547
Sex								
Male, N	N=148	N=298	N=310	N=310	N=304	N=294	N=329	N=291
LS Mean	**-6.5**	**-14.6**	**-14.5**	**-15.4**	**-12.2**	**-14.4**	**-10.1**	**-10.0**
Female, N	N=129	N=251	N=238	N=240	N=248	N=253	N=219	N=256
LS Mean	**-7.8**	**-15.5**	**-16.0**	**-16.1**	**-13.4**	**-14.7**	**-12.0**	**-13.0**
Race								
White, N	N=231	N=459	N=470	N=470	N=450	N=466	N=476	N=469
LS Mean	**-7.7**	**-15.5**	**-15.4**	**-16.5**	**-13.0**	**-14.9**	**-11.2**	**-12.0**
Other, N	N=46	N=90	N=78	N=80	N=102	N=81	N=72	N=78
LS Mean	**-4.3**	**-12.6**	**-14.1**	**-11.8**	**-12.1**	**-13.0**	**-9.3**	**-8.2**
Age (years)								
<65 years, N	N=250	N=505	N=503	N=509	N=497	N=495	N=498	N=493
LS Mean	**-6.3**	**-14.8**	**-14.8**	**-15.5**	**-12.6**	**-14.5**	**-10.5**	**-11.0**
≥65 years, N	N=27	N=44	N=45	N=41	N=55	N=52	N=50	N=54
LS Mean	**-12.9**	**-15.8**	**-17.2**	**-17.5**	**-13.3**	**-14.2**	**-14.3**	**-13.3**
Diabetic								
Diabetic: Yes, N	N=40	N=80	N=88	N=89	N=82	N=84	N=83	N=87
LS Mean	**-7.1**	**-15.1**	**-13.9**	**-14.1**	**-13.5**	**-15.4**	**-11.9**	**-12.1**
Diabetic: No, N	N=237	N=469	N=460	N=461	N=470	N=463	N=465	N=460
LS Mean	**-6.9**	**-14.8**	**-15.2**	**-15.9**	**-12.5**	**-14.2**	**-10.6**	**-11.1**

N=number of patients; LS Mean- Least Squares Mean
Source: Reviewer's results

Reference ID: 3603072

4.2 Other Special/Subgroup Populations

This reviewer also investigated the subgroups based on diabetic status (Yes, No). The results are presented in Table 11. In diabetic patients, the nebivolol 40 mg arm had numerically greater LS mean reduction in trough seated SDP compared with the three FDC treatment arms.

Table 11. Subgroup Analysis by Diabetic Status: LS mean Change from Baseline in Trough Seated Diastolic Blood Pressure at Week 8 (LOCF, ANCOVA)

	Placebo	**FDC10/160**	**FDC10/320**	**FDC20/320**	**Neb 10**	**Neb 40**	**Val 160**	**Val 320**
ITT patients	277	549	548	550	552	547	548	547
Diabetic								
Yes	N=40	N=80	N=88	N=89	N=82	N=84	N=83	N=87
LS mean	**-7.1**	**-15.1**	**-13.9**	**-14.1**	**-13.5**	**-15.4**	**-11.9**	**-12.1**
No	N=237	N=469	N=460	N=461	N=470	N=463	N=465	N=460
LS mean	**-6.9**	**-14.8**	**-15.2**	**-15.9**	**-12.5**	**-14.2**	**-10.6**	**-11.1**

N=number of patients; LS Mean- Least Squares Mean
Source: Reviewer's results

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

To generate the four graphs estimating the probability of achieving systolic and diastolic blood pressure goals, the sponsor used a logistic regression model with a common slope for the treatment groups. In such a model, the treatment curves are guaranteed to be hierarchically aligned from top to bottom with hierarchy preserved over the baseline blood pressure range. However, the common slope assumption can never be validated; thus, the analysis based on this assumption is not recommended.

In the clinical study report, the efficacy of FDC 10/160 mg and 10/320 mg arms is evaluated against their corresponding monotherapy doses. For example, the FDC 10/160 mg is compared to the nebivolol 10 mg and to the valsartan 160 mg. As indicated in the pre-NDA meeting preliminary comments (dated September 5, 2013), it is required that the FDC be compared to the highest approved dose of the monotherapy.

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5.2 Collective Evidence

The NDA contains only one trial.

Primary efficacy measure: change from baseline in Diastolic Blood Pressure (DBP)

The primary endpoint, change from baseline in DBP, was analyzed by the ANCOVA model with missing data imputed by LOCF method. The key pairwise comparisons are summarized in Table 12. The FDC 20/320 mg treatment group had a statistically significantly greater reduction in DBP relative to the nebivolol 40 mg group (p-value = 0.03) and to the valsartan 320 mg group (p-value < 0.0001), with the estimated treatment differences of -1.2 mm Hg and -4.4 mm Hg, respectively. However, despite the statistical significance, whether the observed treatment effect of -1.2 mm Hg can be considered clinically meaningful is uncertain, since the estimated within-subject deviation is greater than 5 mm Hg.

Based on the graphs of probability of reaching the 90 and 80 mm Hg diastolic blood pressure goals, FDC 20/320 mg did not demonstrate an advantage over the nebivolol 40 mg monotherapy. Neither of the two treatment arms (FDC 20/320 mg or nebivolol 40 mg) appears to be better than the other.

The fixed-dose combinations 10/320 mg and 10/160 mg were not statistically superior to the nebivolol 40 mg monotherapy (respective p-values of 0.28 and 0.42).

Table 12. Pairwise Comparisons in Diastolic Blood Pressure at Week 8 (ITT Population, LOCF, ANCOVA)

Pairwise Comparison	LS Mean Difference	95% CI	p-value
FDC 20/320 mg vs Val 320 mg	-4.4	(-5.4, -3.3)	<0.0001
FDC 20/320 mg vs Neb 40 mg	-1.2	(-2.3, -0.1)	0.03
FDC 10/320 mg vs Val 320 mg	-3.7	(-4.8, -2.7)	< 0.0001
FDC 10/320 mg vs Neb 40 mg	-0.6	(-1.7, 0.5)	0.28
FDC 10/160 mg vs Val 320 mg	-3.6	(-4.7, -2.5)	<0.0001
FDC 10/160 mg vs Neb 40 mg	-0.5	(-1.5, 0.6)	0.42

ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
LS Mean=Least Squares Mean; CI=Confidence Interval
Source: Clinical Study Report Table 11.4.1.1-1. (pg.124) and reviewer's results.
Sponsor's results confirmed by this reviewer

Key-secondary efficacy measure: change from baseline in Systolic Blood Pressure (SBP)

Change from baseline in SBP was analyzed by the same ANCOVA model as was used for the primary efficacy endpoint. Treatment comparisons are summarized in Table 13. The nominal p-values for treatment comparisons on trough seated SBP are very small. The mean reduction in SBP with the FDC 20/320 mg dose appeared greater than the reductions observed with the nebivolol 40 mg and the valsartan 320 mg (nominal p-values 0.0013 and 0.0005 respectively). Similarly, the FDC 10/320 mg and 10/160 mg appeared to have greater reductions in SBP compared with the nebivolol 40 mg and the valsartan 320 mg monotherapies.

Reference ID: 3603072

Table 13. Pairwise Comparisons in Systolic Blood Pressure at Week 8 (ITT Population*, LOCF, ANCOVA)

Pairwise Comparison	LS Mean Difference	95% CI	p-value
FDC 20/320 mg vs Val 320 mg	-3.1	(-4.9, -1.4)	0.0005
FDC 20/320 mg vs Neb 40 mg	-2.9	(-4.7, -1.1)	0.0013
FDC 10/320 mg vs Val 320 mg	-3.0	(-4.7, -1.2)	0.0011
FDC 10/320 mg vs Neb 40 mg	-2.7	(-4.5, -0.9)	0.0027
FDC 10/160 mg vs Val 320 mg	-3.0	(-4.8, -1.2)	0.0009
FDC 10/160 mg vs Neb 40 mg	-2.7	(-4.5, -1.0)	0.0023

*ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
LS Mean=Least Squares Mean; CI=Confidence Interval
Source: Clinical Study Report Table 11.4.1.2.1-1. (pg. 126) and reviewer's results.

5.3 Conclusions and Recommendations

Based on the pre-specified primary statistical analysis, the fixed dose combination (FDC) 20/320 mg was statistically more effective than both the nebivolol 40 mg monotherapy and the valsartan 320 mg monotherapy as measured by mean reduction in diastolic blood pressure. Whether the observed treatment difference between FDC 20/320 mg and nebivolol 40 mg (equal to -1.2 mm Hg) can be considered clinically meaningful is uncertain.

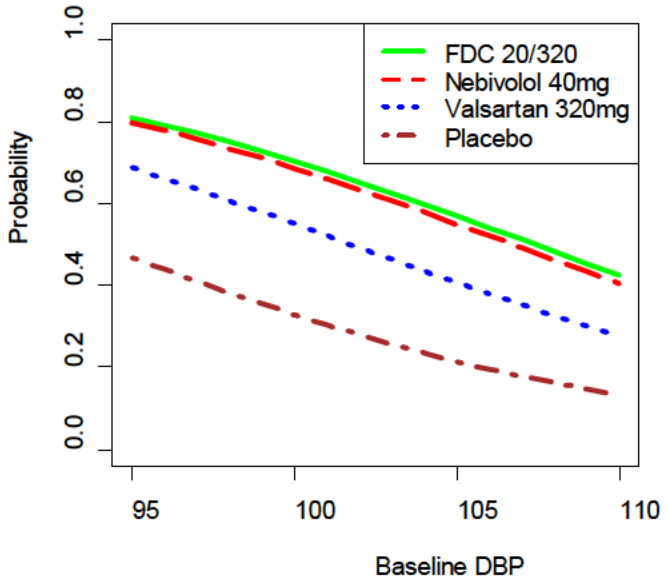
Reference ID: 3603072

APPENDIX A. SPONSOR'S GRAPHS FOR PROBABILITY OF ACHIEVING BLOOD PRESSURE GOALS

The four graphs of probability of reaching blood pressure goals included in the clinical study report are based on the logistic regression model with treatment group as a class variable, baseline blood pressure as a covariate, and the data set consisting of data from the 4 treatment groups (FDC 20/320 mg, nebivolol 40 mg, valsartan 320 mg, and placebo). This reviewer reproduced sponsor's graphs (included below). The logistic model implies the common slope among the treatment groups. The common slope assumption (if used) can never be validated; thus, the analysis based on this assumption is not recommended.

Diastolic Blood Pressure

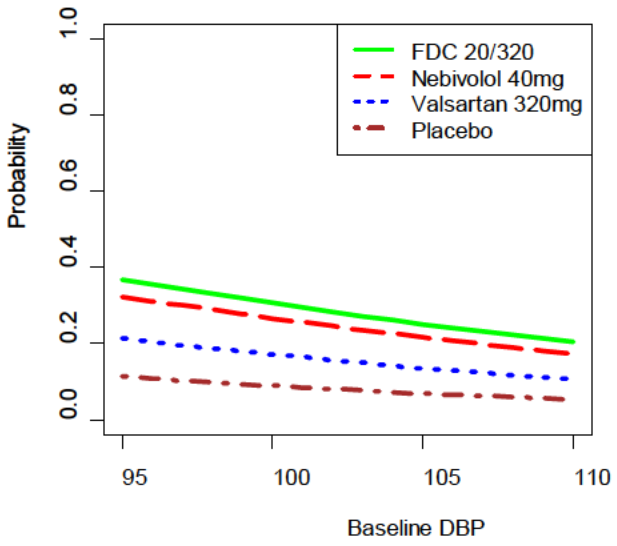
Figure 8. Probability of Achieving a Diastolic Blood Pressure Goal <90 mm Hg based on Logistic Regression with Common Slope (ITT Population, LOCF)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

Reference ID: 3603072

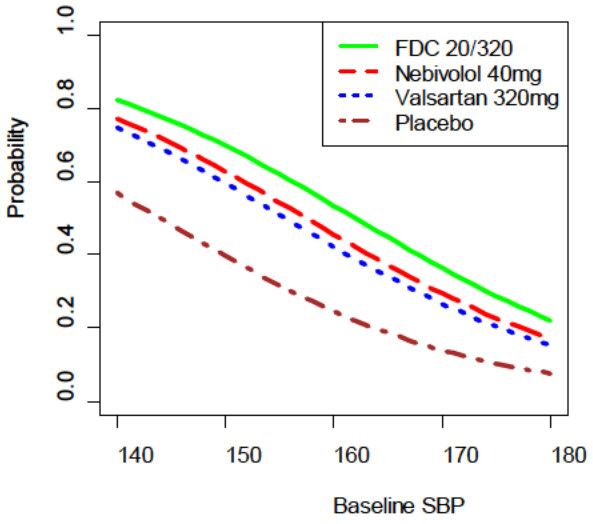
Figure 9. Probability of Achieving a Diastolic Blood Pressure Goal <80 mm Hg based on Logistic Regression with Common Slope (ITT Population, LOCF)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

Systolic Blood Pressure

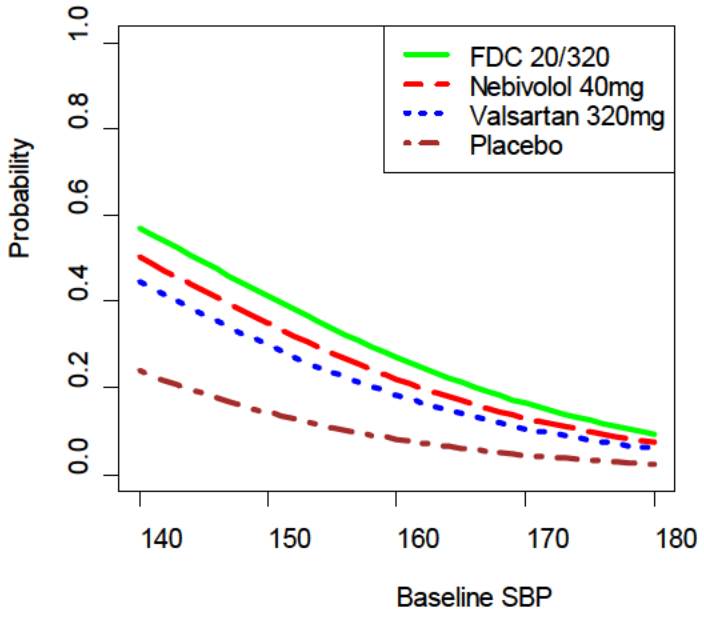
Figure 10. Probability of Achieving a Systolic Blood Pressure Goal <140 mm Hg based on Logistic Regression with Common Slope (ITT Population, LOCF)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

Reference ID: 3603072

Figure 11. Probability of Achieving a Systolic Blood Pressure Goal <130 mm Hg based on Logistic Regression with Common Slope (ITT Population, LOCF)



ITT Population consisted of all patients who took at least 1 dose of double-blind investigational product and had at least 1 post-baseline assessment of the primary efficacy parameter
Source: Reviewer's results

Reference ID: 3603072

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/s/

GEORGE KORDZAKHIA
08/01/2014

PEILING YANG
08/01/2014

HSIEN MING J HUNG
08/01/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206-302/SN000 **Applicant: Forest Research Institute, Inc.** **Stamp Date: 02/24/2014**

Drug Name: Nebivolol/ Valsartan Fixed Dose Combination **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			ISE and ISS were not included, as agreed at pre-NDA meeting
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			x	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

File name: Statistics Filing Checklist for a New NDA 206-302

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

George Kordzakhia	04/07/2014
Reviewing Statistician	Date
Peiling Yang	04/07/2014
Supervisor/Team Leader	Date

File name: Statistics Filing Checklist for a New NDA 206-302

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GEORGE KORDZAKHIA
04/07/2014

PEILING YANG
04/07/2014

HSIEN MING J HUNG
04/10/2014