

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206302Orig1s000

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

CLINICAL PHARMACOLOGY REVIEW

NDA Number	206,302
Submission Type	Resubmission (Complete Response to CRL)
Applicant	Forest Research Institute
Submission Date(s)	9/29/2015 (SDN 28), 2/23/2016 (SDN 33)
Drug Substance(s)	Nebivolol and valsartan
Drug Product	Fixed dose combination of nebivolol/valsartan 5 mg / 80 mg tablets, immediate release
Proposed Indication	Hypertension
OCP Division	DCPI
Primary Reviewer	Martina Sahre, PhD
Secondary Reviewer	Rajanikanth Madabushi, PhD

Background

The Applicant submitted NDA 206302, a fixed dose combination (FDC) of nebivolol and valsartan, for the treatment of hypertension in February of 2014.

The Applicant received a complete response action, because the additional effect of the combination of nebivolol and valsartan 20/320 mg over nebivolol 40 mg alone was 1.2 mmHg, with the lower 95% CI barely excluding 0. That was not considered a meaningful clinical improvement with the combination therapy over the highest dose of monotherapy.¹

The complete response letter suggested that the applicant could try to assess their data in the context of low dose combinations. Under this paradigm, two drugs with distinct mechanism of actions at low dose may provide a significant portion of the effect that is achieved with the highest dose of the monotherapy or the high dose combinations. A byproduct of this approach is avoidance of dose-related adverse reactions of either drug. It should be noted that this is a new paradigm for the Division.

To that end the applicant made a case for the approval of a lower dose combination.

As a result, the applicant provided data in support of the FDC [REDACTED] (b) (4). Further discussion during the review cycle raised the possibility of FDC 5/80 being the more appropriate dose under the paradigm explained in the complete response letter.

This review will focus on presenting information comparing the effect achieved with the two doses FDC 5/80 and [REDACTED] (b) (4).

Recommendation

The Office of Clinical Pharmacology recommends approval of the fixed dose combination of nebivolol and valsartan at a dose of 5/80 mg. The dose-response information for the monotherapies and the FDC provide the supportive evidence of effect for the approval of FDC 5/80 mg.

¹ 21 CFR 300.50(a)

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/s/

MARTINA D SAHRE
03/29/2016

RAJANIKANTH MADABUSHI
03/29/2016

CLINICAL PHARMACOLOGY REVIEW

NDA Number	206302
Submission Type	Standard
Applicant Name	Forest Research Institute
Submission Dates	02/24/2014
Generic Name	Nebivolol/Valsartan
Dosage Form	Oral tablets
Dosage Strengths	5/80, 5/160, 10/160, 10/320, and 20/320 mg
Proposed Indication	Hypertension
OCP Division	DCP1
Primary Reviewers	Martina Sahre, PhD & Bilal AbuAsal, PhD
Secondary Reviewer	Sreedharan Sabarinath, PhD
Team Leaders	Rajanikanth Madabushi, PhD & Jeffry Florian, PhD

The review is unchanged from the previous version except that the proposed “TRADENAME” was replaced by the words “nebiviolol/valsartan” for the purpose of serving as background document for a CRDAC meeting to be held on 9 September 2014.

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1 EXECUTIVE SUMMARY

Forest Research Institute is seeking approval for a fixed dose combination (FDC) tablet of nebivolol and valsartan for the treatment of hypertension. The application was submitted under the 505(b)(2) pathway. Nebivolol/valsartan will be marketed in five strengths for once daily administration.

The applicant conducted six clinical pharmacology studies and two efficacy/safety studies to support this application: A single dose drug-drug interaction study (NAC-PK-01), a multiple dose pharmacokinetic / pharmacodynamic (PK/PD) and tolerability study (NAC-PK-03), a food effect study (NAC-PK-04), a PK bridging study between FDC formulation and the free combination (NAC-PK-05), a strength proportionality study of FDC (NAC-PK-06), and a pivotal bioequivalence (BE) study to compare the clinical trial FDC and the to-be-marketed FDC formulation for the 10/320 mg strength tablet (NAC-PK-07). There was one placebo-controlled pivotal efficacy study comparing the FDC with nebivolol and valsartan monotherapies (NAC-MD-01) and a long term safety and tolerability study (NAC-MD-02). The primary endpoint in the trial NAC-MD-01 was change from baseline in seated diastolic blood pressure (siDBP) after 8 weeks of treatment. The difference in change from baseline between FDC 20/320 and nebivolol 40 mg was -1.2 mmHg ($p=0.03$). The difference in seated systolic blood pressure (siSBP) for the comparison of FDC 20/320 and valsartan 320 mg was -4.4 mmHg ($p<0.0001$).

There was a significant decrease ($\sim 45\%$) in maximum plasma concentrations (C_{max}) of nebivolol but little change in area under the plasma concentration-time curve (AUC), when co-administered with valsartan. This review focused on the drug-drug interaction between nebivolol and valsartan and assessed whether this interaction is likely to have any impact on the tolerability of the FDC compared to nebivolol 40 mg alone. These analyses assessed the event rate for bradycardia and concentration-dependent effect of nebivolol on heart rate as these are considered as the major tolerability issues associated with nebivolol treatment. Based on the available data, it was not possible to determine whether a C_{max} reduction for nebivolol could decrease bradycardia and alter tolerability with the FDC compared to nebivolol administered as a single agent.

1.1 Recommendations

The clinical pharmacology studies submitted by the applicant are sufficient to characterize and bridge the exposure of nebivolol/valsartan free combination with the FDC drug product. The Office of Clinical Pharmacology recommends approval from a clinical pharmacology standpoint.

1.2 Phase 4 Commitments

There are no Phase 4 requirements or commitments.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The components of the FDC (nebivolol/valsartan) are approved for the treatment of hypertension. The approved doses of nebivolol (NDA 021742 Bystolic[®]) range from 5 to 40 mg once daily, while doses for valsartan (NDA 021283 Diovan[®]) range from 80 to 320 mg once daily.

The Clinical Pharmacology studies for nebivolol/valsartan were designed primarily to establish and connect the efficacy and safety data of the monotherapies to the FDC drug product. The key clinical pharmacology findings are listed below:

- The FDC and nebivolol/valsartan free combination were bioequivalent, with the 90% CIs of the geometric LS mean ratios for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ within the 80 - 125% range for both nebivolol and valsartan.
- There is no clinically relevant food effect on nebivolol/valsartan. The pharmacokinetics of both nebivolol and valsartan were proportional over the FDC dose ranges of nebivolol/valsartan 5/80 mg to 20/320 mg.
- Single- and multiple-dose drug interaction studies showed that the coadministration of nebivolol and valsartan resulted in lower maximum plasma drug concentration (C_{max}) for nebivolol (~ 45% decrease) but no significant changes to total systemic exposure (AUC) when compared to nebivolol administered alone.
- Nebivolol 40 mg showed a higher incidence of bradycardia events (counted as bradycardia or sinus bradycardia) compared to other nebivolol containing treatment arms. Valsartan and placebo arms showed the lowest incidence of bradycardia events. The review team used time-matched concentration and heart rate response data to assess whether this could be related to C_{max} .
- Differences in treatment discontinuations and the incidence rate of bradycardia events between FDC 20/320 mg and nebivolol 40 mg arms cannot be explained based on a reduction in C_{max} alone. Data from the ambulatory blood pressure monitoring (ABPM) substudy in trial NAC-MD-01 showed that the relationship between change from baseline in heart rate and C_{max} is shallow for FDC 20/320 and nebivolol 40 mg.

2 QUESTION BASED REVIEW (QBR)

This is an abridged version of the QBR.

2.1 General Attributes of the Drug

This drug product is a fixed-dose combination of nebivolol and valsartan intended for oral administration. Both components of the fixed dose combination have been previously approved in the US for use in the treatment of hypertension¹.

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

The physicochemical properties of nebivolol and valsartan have been summarized under NDA 21-742, NDA 20-665, NDA 21-283, and in the Diovan[®] and Bystolic[®] package inserts. In addition to the active ingredients, nebivolol/valsartan coated tablets contain the following inactive excipients: Lactose monohydrate, NF; Microcrystalline cellulose, NF; Copovidone, NF; Croscarmellose sodium, NF; Colloidal silicon dioxide, NF; Magnesium stearate, NF (vegetable source); Talc, USP; Ferric oxide, NF; Hypromellose 2910, USP; Polysorbate 80, NF; Colloidal silicon dioxide, NF; and Magnesium stearate, NF (vegetable source).

2.1.2 What are the proposed mechanism of action and therapeutic indications?

The proposed FDC is a combination of nebivolol and valsartan. Nebivolol is a β_1 -adrenergic blocker. The antihypertensive mechanism of action of nebivolol has not been definitely established, however it is proposed to be through: decreased heart rate, decreased myocardial contractility, suppression of renin activity and vasodilation effect². Valsartan is an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension.

The proposed indication for nebivolol/valsartan is the treatment of hypertension, alone or in combination with other antihypertensive agents.

2.1.3 What are the proposed dosages and routes of administration?

The FDC is proposed to be marketed in 5 strengths of nebivolol/valsartan for oral administration. These are 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg.

2.2 General Clinical Pharmacology

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

The applicant is relying on FDA's previous findings of safety and effectiveness for Diovan[®] and Bystolic[®] to support the approval of this 505(b)(2) application. The applicant conducted one pivotal efficacy study and one long term safety and tolerability study with supporting efficacy information. These two studies compared the proposed FDC with monotherapies and placebo. In addition, six clinical pharmacology studies were conducted to support this application (Table 1).

¹ NDA 021742 for Bystolic[®] and NDA 020665 & NDA 021283 for Diovan[®].

² Bystolic[®] Package Insert, Approved 12/14/2011:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021742s013lbl.pdf

Table 1. Summary of the clinical development program

Study	Design	Doses
NAC-MD-01 Pivotal efficacy study	Phase 3, placebo controlled, parallel-group, double-blind study, including 1 forced up-titration at Week 4, and a 1-week down-titration phase in patients with stage 1 and 2 essential hypertension (n=4161)	FDC 5/80, 5/160, 10/160, 10/320, 20/320 mg Nebivolol 5, 10, 20, 40 mg Valsartan 80, 160, 320 mg
NAC-MD-02 Long term safety	Phase 3, 52-week, open-label, single arm study, and a 1-week down-titration phase in patient with stage 1 and 2 essential hypertension (n=810)	Nebivolol 5, 10, 20 mg Valsartan 160, 320 mg Hydrochlorothiazide 12.5, 25 mg
Clinical Pharmacology Studies		
NAC-PK-01 Single dose DDI	Open label, single dose, 3-way, crossover in healthy subjects (n=24)	Nebivolol 20 mg Valsartan 320 mg
NAC-PK-03 Multiple dose PK/PD	Open label, multiple dose, 3-way crossover in healthy subjects (n=30)	Nebivolol 20 mg Valsartan 320 mg
NAC-PK-04 Food effect study	Open label, 2-way, crossover, single dose in healthy subjects (n=32)	FDC 20/320 mg
NAC-PK-05 PK bridging study	Open label, 2-way, crossover, single dose study in healthy subjects (n=70)	Nebivolol 20 mg Valsartan 320 mg FDC 20/320 mg
NAC-PK-06 Dose proportionality	Open label, parallel, multiple dose study in healthy subjects (n=30)	FDC 5/80, 10/160, 20/320 mg
NAC-PK-07 FDC pivotal BE	Open label, 2-way, crossover, single dose study in healthy subjects (n=70)	FDC 10/320 mg

[Source: Prepared by FDA from the tabular listing of clinical studies. Section 5.2]

Study NAC-MD-01 was the pivotal efficacy trial conducted for this submission. The study consisted of three phases, a 4 to 6 week single-blind, placebo run-in period, an 8-week double-blind treatment period and a 1-week double-blind down-titration period. Patients who met the criteria for stage 1 and 2 hypertension were randomized into the treatment arms. Pulse rate was

required to be ≥ 55 bpm at randomization. After randomization, patients received one of the following treatments: placebo, nebivolol 5 or 20 mg, valsartan 80 or 160 mg, FDC 5/80, 5/160, and 10/160. After 4 weeks, patients were forced up-titrated to double the doses received in the first four weeks, i.e. placebo, nebivolol 10 or 40 mg, valsartan 160 or 320 mg, FDC 10/160, 10/320, or 20/320, respectively.

A total of 4161 patients were randomized to receive treatment, and 3715 patients completed the double-blind treatment phase (i.e., 89.3%) across all treatments. In the nebivolol 40 mg arm, a total of 76 patients discontinued treatment, which makes the completer rate in this arm (86.3%, or 479 out of 555) slightly lower than the overall rate. Of the 76 patients who discontinued in the 40 mg arm, 48 left the trial during the first 4 weeks of treatment, i.e. prior to the up-titration to 40 mg. Across all treatments, 6.9% of patients discontinued in the first four weeks.

At randomization, 37.7% of patients were in essential hypertension stage 1 and 62.3% were in stage 2. About 19.4% of subjects participated in a substudy, where ambulatory blood pressure monitoring (ABPM), pharmacokinetics (PK) and pharmacodynamic (plasma-renin activity and aldosterone) measures were obtained. The ABPM and PK data from this substudy were used for heart rate analysis.

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

Yes, the plasma levels of *d*-nebivolol, *l*-nebivolol, *d,l*-nebivolol, nebivolol glucuronide, and valsartan were measured. Please see Section 2.4 for the details of the analytical methods.

2.2.2.1 What are the characteristics of the dose-response (D-R) relationships for efficacy and is the dose/dosing regimen selected by the sponsor consistent with the known D-R relationships?

Both nebivolol and valsartan show shallow dose-response at doses above 10 mg and 80 mg, respectively. Figures 1 through 4 show the observed change from baseline response on seated diastolic (siDBP) and systolic blood pressure (siSBP) from the pivotal efficacy study NAC-MD-01 and previously published efficacy studies with nebivolol and valsartan. The shapes of the dose-response curves for nebivolol and valsartan from NAC-MD-01 were similar to the trends observed from previous trials. Saturating responses in the overall change from baseline in blood pressure were observed at nebivolol and valsartan doses higher than 10 mg and 80 mg respectively. Dose response trends for combinations of nebivolol and valsartan from NAC-MD-01 are shown in Table 2. The results from various combinations of the FDC are in agreement with what was observed from the dose-response trends for the individual components. Marginal increases in siDBP and siSBP were observed for doses above FDC 10/160 suggesting limited additional improvement in blood pressure response at higher doses of FDC.

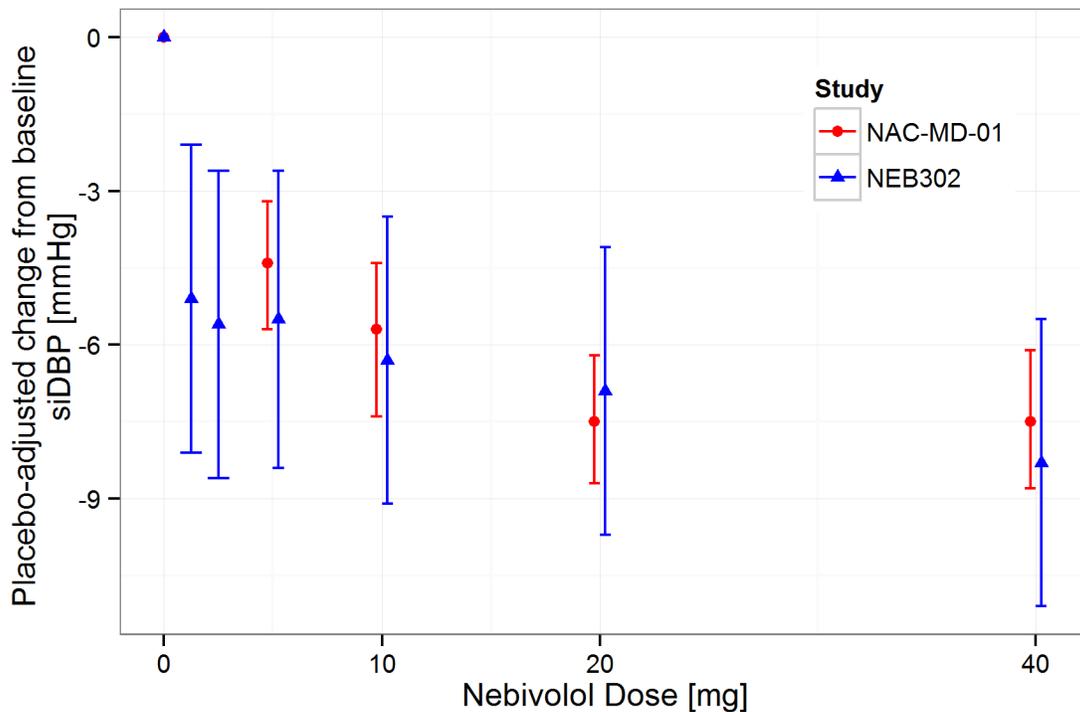


Figure 1. Nebivolol dose-response (siDBP) comparison for monotherapy results from the current submission (NAC-MD-01) and from a previously published efficacy study (NEB302) (The 95% CI for the study under review was obtained from the CSR. The 95% CI for the previously reported study was calculated using propagation of error calculations from reported SD and SEs. A dummy point was also inserted at [0,0] to denote the placebo effect. In study NAC-MD-01, patients in nebivolol-only treatment arms received 5 and 20 mg for the first 4 weeks, and thereafter 10 and 40 mg for the second 4 weeks. Therefore, responses to 5 and 20 mg nebivolol were observed at week 4.)
 [Source: Prepared by FDA using NAC-MD-01 CSR (red circles) and J Clin Hypertens. 2007;9:667–676 (blue triangles)]

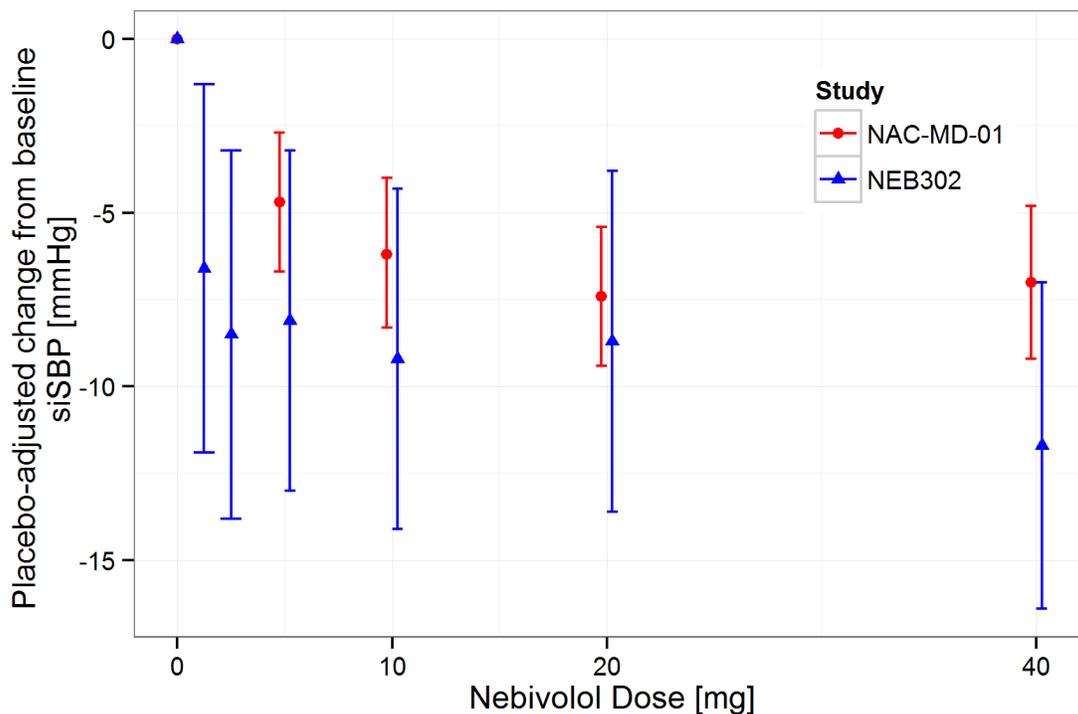


Figure 2. Nebivolol dose-response (siSBP) comparison for monotherapy results from the current submission (NAC-MD-01) and from a previously published efficacy study (NEB302) (The 95% CI for the study under review was obtained from the CSR. The 95% CI for the originator study was calculated using propagation of error calculations from reported SD and SEs. A dummy point was also inserted at [0,0] to denote the placebo effect.

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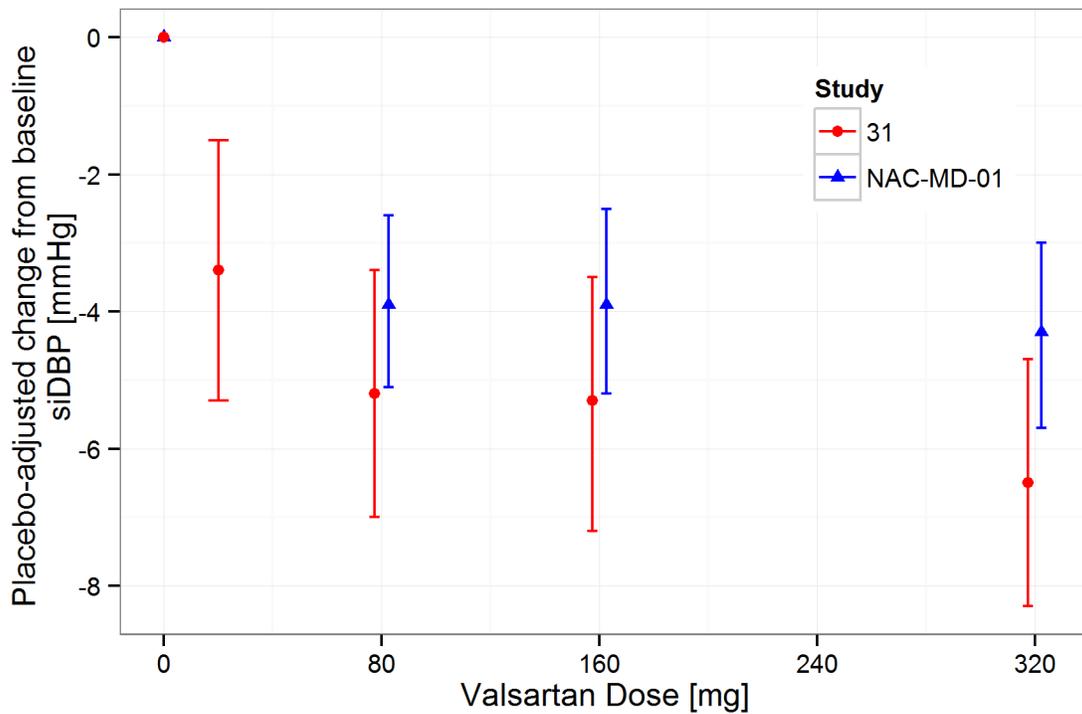


Figure 3. Valsartan dose-response (siDBP) comparison for monotherapy results from the current submission (NAC-MD-01) and from a previously published efficacy study (Study 31) [Source: Prepared by FDA using NAC-MD-01 CSR (triangles, blue) and Diovan NDA 20,665 Medical Review³ (circles, red)]

³ http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020665_s000.pdf, pages 87 and 89 (pdf numbering)

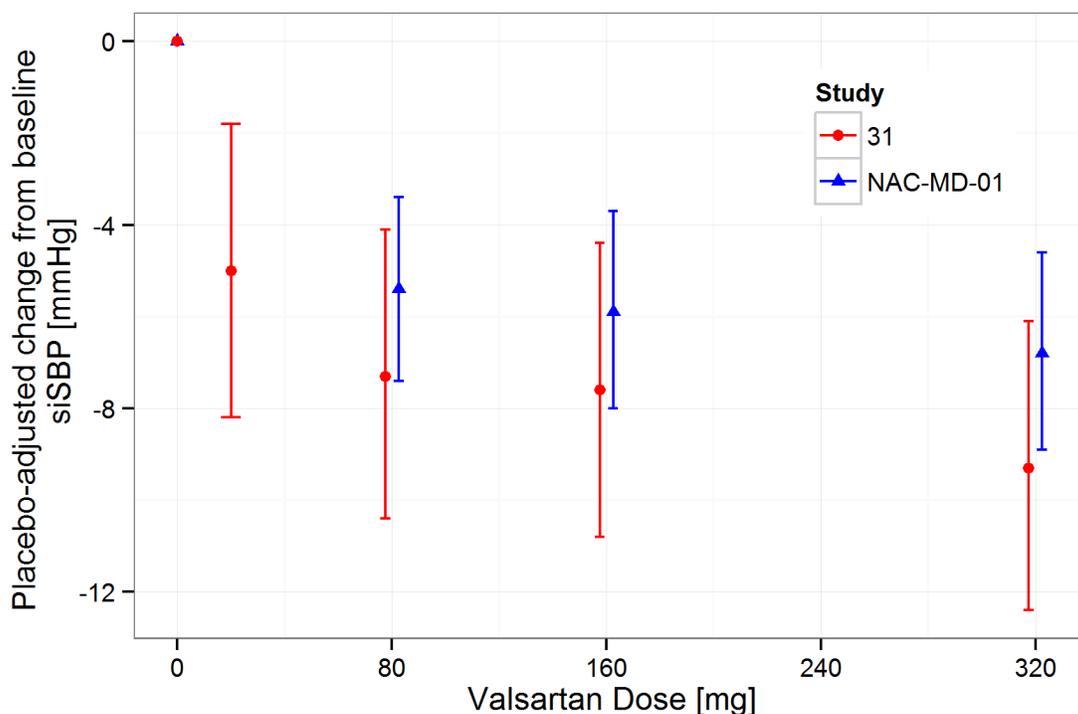


Figure 4. Valsartan dose-response (siSBP) comparison for monotherapy results from the current submission (NAC-MD-01) and from a previously published efficacy study (Study 31) [Source: Prepared by FDA using NAC-MD-01 CSR (triangles, blue) and Diovan NDA 20,665 Medical Review⁴ (circles, red)]

Table 2. Placebo-subtracted least squares mean changes from baseline blood pressure measured at trough for the combination arms at weeks 4 and 8

Time	Arm	siDBP	95% CI	siSBP	95% CI
Week 4	FDC 5/80	-7.2	(-8.4, -5.9)	-8.3	(-10.3, -6.3)
	FDC 5/160	-7.4	(-8.7, -6.1)	-8.8	(-10.9, -6.8)
	FDC 10/160	-7.9	(-9.2, -6.6)	-9.0	(-11.0, -7.0)
Week 8	FDC 10/160	-7.9	(-9.3, -6.6)	-9.8	(-11.9, -7.6)
	FDC 10/320	-8.1	(-9.4, -6.7)	-9.7	(-11.9, -7.6)
	FDC 20/320	-8.7	(-10.0, -7.3)	-9.9	(-12.1, -7.7)

[Source: Reproduction from NAC-MD-01 CSR, Tables 11.4.1.1-1, 11.4.1.2.1-1, 11.4.1.2.2.1-1, and 11.4.1.2.2.1-2]

⁴ http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020665_s000.pdf, pages 87 and 89 (pdf numbering)

2.2.2.2 What are the characteristics of the exposure-response relationships for safety?

The applicant suggested in an Information Efficacy Amendment dated 6/17/2014, that the reduction in nebivolol C_{max} after coadministration of nebivolol with valsartan may improve the tolerability and safety of the FDC compared to nebivolol (40 mg). To support this, the applicant highlighted the higher discontinuation rate and higher number of bradycardia events from the nebivolol 40 mg treatment arm compared to the FDC 20/320 mg arm⁵. The clinical pharmacology review team conducted analyses to assess whether a decrease in nebivolol C_{max} could be related to improved tolerability with FDC 20/320 mg compared to nebivolol 40 mg alone.

This analysis utilized heart rate measurements from the ABPM substudy from week 0 and week 8 as well as concentration assessments at week 8 which were sampled at approximately nebivolol t_{max} (1-4 hours post dose) and t_{trough} (22-24 hours post dose). Changes from baseline heart rate were calculated based on time-matched assessments from week 0 and week 8. The results of this analysis are shown in Tables 3 and 4. There was a significant heart rate lowering effect due to nebivolol, consistent with its mechanism of action, however, this heart rate effect was shallow at concentrations at or above those observed at C_{max} for 10 mg nebivolol. For the highest strength FDC (20/320) the heart rate reduction at C_{max} was similar to that seen with 40 mg nebivolol alone. However, the bradycardia event rate was higher in the 40 mg nebivolol arm (6.1%) compared to the FDC 20/320 arm (2.5%).

Furthermore, assuming a 45% reduction in nebivolol C_{max} when coadministered with valsartan, it is anticipated that nebivolol peak plasma concentrations with the FDC 20/320 would be similar to those from 10 mg nebivolol administered alone. Between 20/320 and 10 mg nebivolol alone, a difference of approximately 3 beats per minute in heart rate was observed. This is a small effect compared to the overall reduction in heart rate observed with nebivolol (~10 beats per minute at C_{min} with 10 mg nebivolol). Occurrences of bradycardia were also not distinguishable between these two groups (10 mg nebivolol and FDC 20/320).

The relationship between nebivolol on heart rate changes was further evaluated in an exposure-response analysis using time-matched nebivolol concentration and change from baseline in heart rate (Figure 5). At concentrations reflecting t_{trough} , an increasing concentration-response relationship was observed, though a majority of the effect on heart rate (~10 bpm) is maintained even at the lowest nebivolol concentrations from this analysis. Concentrations associated with 10 to 40 mg nebivolol C_{max} are on the plateau of the exposure-response relationship. Mean C_{max} for nebivolol 40 mg (all genotypes included) was about 7.1 ng/mL, whereas it was 1.6 ng/mL for FDC 20/320 (annotated with arrows). Comparing these mean concentrations with the expected reduction in heart rate (in Figure 5) shows that these concentrations are in a range where it may be difficult to distinguish differences in the heart rate effect as a saturation of the effect has already been achieved. This is consistent with observations from the overall population in study NAC-MD-01 (Table 12.5.1.2.1.3-1 in the clinical study report). When comparing pulse rates observed at Week 4 and Week 8, one can observe that an 8-fold increase in dose, from 5 mg at week 4 (Nebivolol 10 mg arm), to 40 mg at week 8 leads to a decrease in pulse rate of -9.3 and -14.6 bpm, respectively. In addition, changes from baseline pulse rate showed a 0.5 bpm between 20/320 (-14.0 ± 11.1 bpm) and nebivolol 40 mg alone (-14.6 ± 11.9 bpm). This suggests that

⁵ <\\cdsesub1\evsprod\nda206302\0007\m1\us\efficacy-info-amendment.pdf>, Section 4.0

based on pulse rate data from the overall population and from the ABPM dataset, there would only be small differences in bradycardia events expected. The observed differences in bradycardia events may have been due to pulse rates cut off values used to categorize an event as bradycardia.

Table 3. Mean change from baseline in heart rate at t_{max}

Valsartan Dose [mg]	Nebivolol Dose [mg]			
	0	10	20	40
0	1.08 (2.10)	-14.7 (1.41)		-19.1 (1.48)
160	-1.17 (1.49)	-14.2 (1.46)		
320	-1.56 (1.45)	-15.1 (1.44)	-18.1 (1.42)	

[Source: Prepared by FDA using from NAC-MD-01 vs.xpt, suppvs.xpt, adsl.xpt]

Table 4. Mean change from baseline in heart rate at t_{trough}

Valsartan Dose [mg]	Nebivolol Dose [mg]			
	0	10	20	40
0	1.54 (1.80)	-10.6 (1.22)		-13.1 (1.27)
160	-1.79 (1.28)	-11.2 (1.26)		
320	-0.69 (1.24)	-9.50 (1.23)	-12.9 (1.22)	

[Source: Prepared by FDA using from NAC-MD-01 vs.xpt, suppvs.xpt, adsl.xpt]

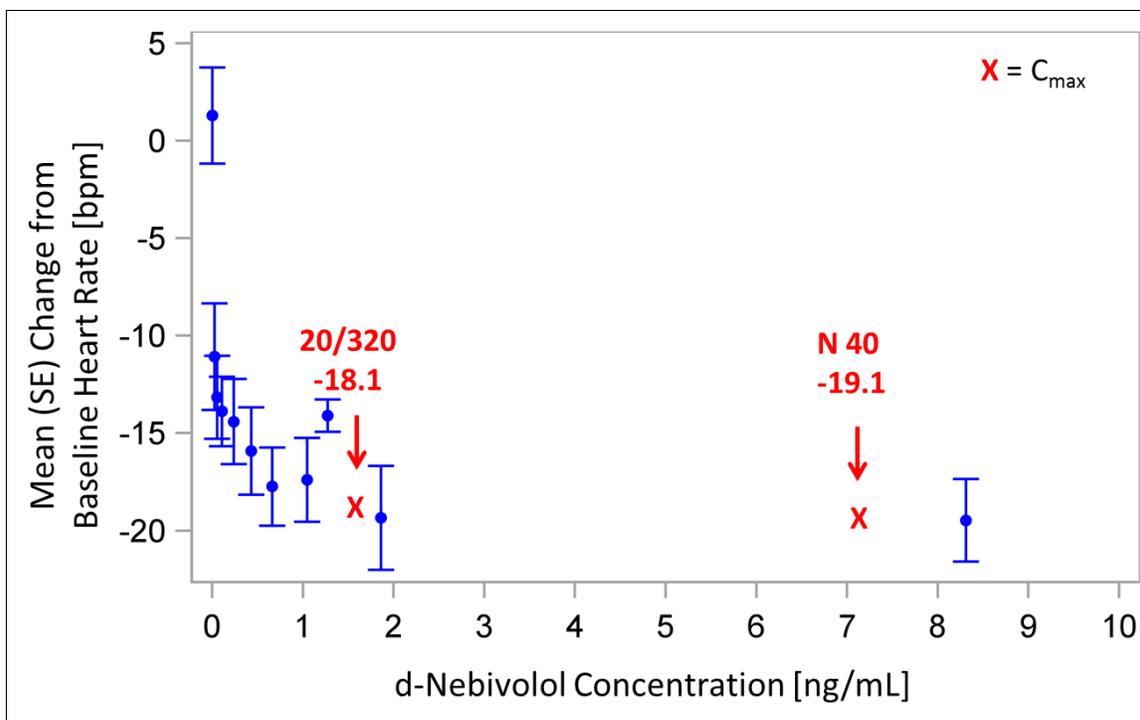


Figure 5. *d*-nebivolol concentrations vs change from baseline heart rate at C_{\max} and C_{\min} [Source: Prepared by FDA using datasets pc.xpt, adsl.xpt, vs.xpt and suppv.s.xpt from study NAC-MD-01]

2.2.2.3 Does this drug prolong QT/QTc Interval?

A thorough QT study for nebivolol/valsartan combination was not conducted.

2.2.3 What are the PK characteristics of the drugs?

2.2.3.1 What are the single and multiple dose PK parameters?

The pharmacokinetic properties of nebivolol and valsartan have been reviewed and reported previously under NDA 21-742, NDA 20-665, NDA 21-283, and in the Bystolic[®] and Diovan[®] package inserts. In brief, the $t_{1/2}$ of valsartan is around 6 hours and reaches t_{\max} after 2-4 hours after oral administration. The absolute bioavailability of valsartan ranges from 10-35% with a mean value of 25%. Valsartan is eliminated unchanged and recovered mainly in the feces.

Nebivolol is mainly cleared by CYP2D6 metabolism and its $t_{1/2}$ ranges from 12 hours in extensive metabolizers (EM) to 19 hours in poor metabolizers (PM) of CYP2D6.

The pharmacokinetics of the FDC was characterized in the dose proportionality study (NAC-PK-06). The pharmacokinetics of nebivolol, its metabolites, and valsartan were proportional over the dose ranges of FDC 5/80 mg, 10/160 and 20/320 mg. There was no significant accumulation for valsartan after once daily multiple dose administration, while the accumulation ratio of nebivolol ranged from 1.3 in EM to 4 in PM. In addition, there was more than 10 fold increase in exposure for poor CYP2D6 metabolizers relative to extensive metabolizers.

2.2.4 Is there a PK interaction after coadministration of nebivolol and valsartan?

Yes, single- and multiple-dose coadministration of nebivolol and valsartan resulted in lower C_{max} and AUC values for both compounds compared to the administration of each drug alone. After single dose administration, the C_{max} and AUC of valsartan were 22 % and 20 % lower when coadministered with nebivolol, respectively. C_{max} and AUC of *d,l*-nebivolol were 53 % and 16 % lower when coadministered with valsartan, respectively (Study NAC-PK-01). Following multiple dose administration, $C_{max,ss}$ (C_{max} at steady state) and $AUC_{0-\tau,ss}$ (AUC over the dosing interval at steady state) of valsartan were both 13% lower with coadministration of nebivolol; $C_{max,ss}$ and $AUC_{0-\tau,ss}$ of *d,l*-nebivolol were 45% and 17% lower with coadministration of valsartan, respectively (Study NAC-PK-03) (Figure 6 & Figure 7).

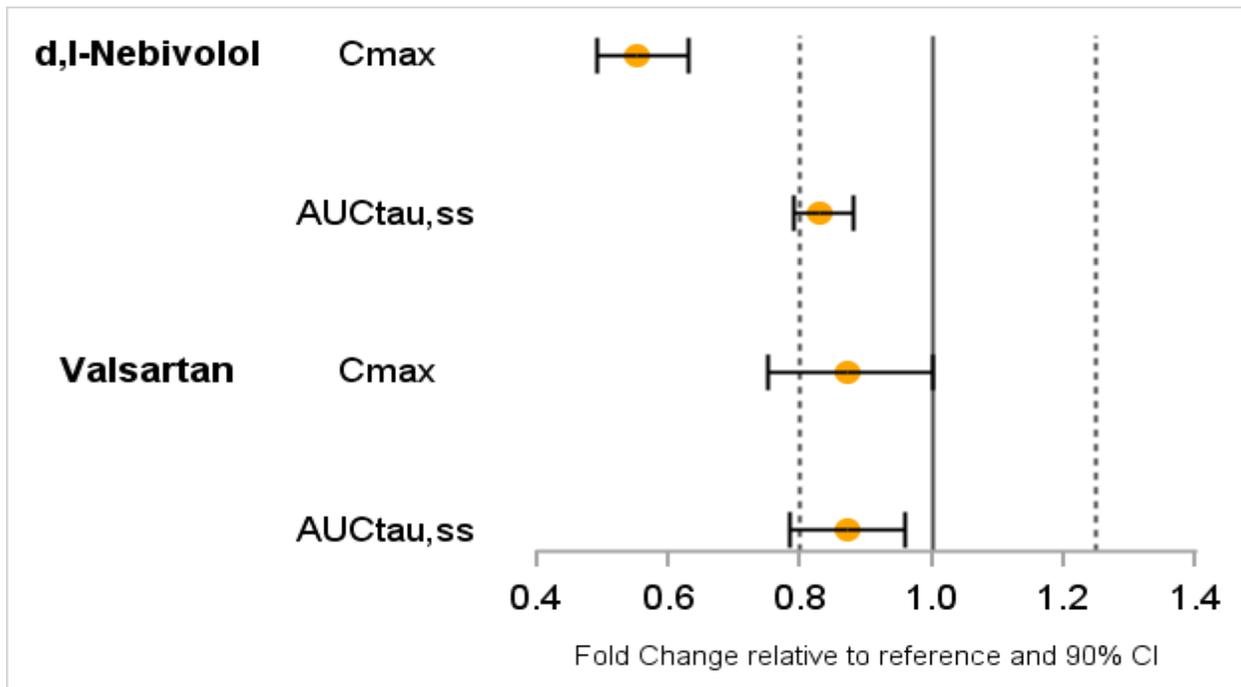


Figure 6. Changes in AUC and C_{max} with a free combination of valsartan and nebivolol relative to their monotherapy.

(The geometric mean ratios are depicted on the X-axis. Closed circles represent the geometric mean of the ratio (drug in combination/individual) and horizontal lines represent the 90% CI associated with the mean fold change in AUC and C_{max})

[Source: Prepared by FDA using data from tables 11.2.3 and 11.2.5 in study report NAC-PK-03]

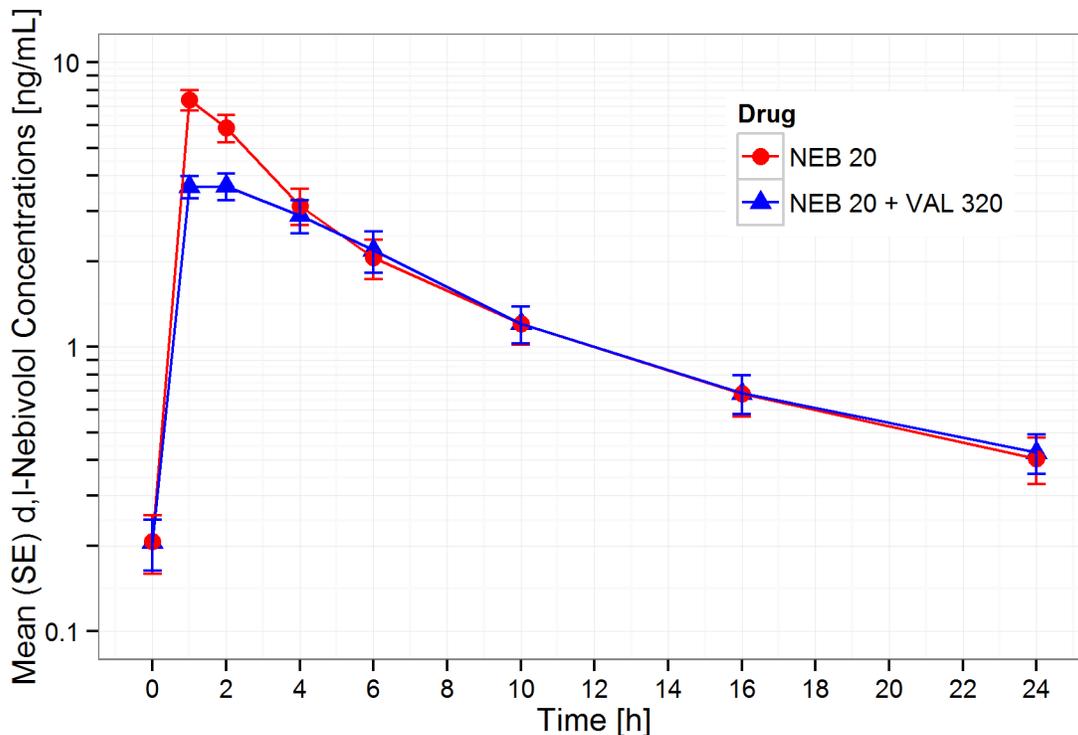


Figure 7. Steady-state plasma concentrations of *d,l*-neбиволol in healthy volunteers after 7 daily doses of 20 mg neбиволol alone (Red), or in combination with 320 mg valsartan (Blue). [Source: Prepared by FDA from data in study report NAC-PK-03]

The reason for this drug interaction is not clear; however the data suggest that the interaction is related to the rate of absorption. This is because only the C_{max} was significantly reduced while the total systemic exposure or extent of absorption (AUC) was not altered significantly. This interaction may be attributed to the inhibition of intestinal influx transporter mediating the uptake of neбиволol; however there are no reports of any transporter involved in the uptake of neбиволol. It is also unlikely that this can be explained by any enzyme induction because enzyme induction would have affected the AUC as well. Moreover, it is unlikely that an interaction mediated by enzyme induction would be observed after a single dose administration as is in single dose PK study NAC-PK-01.

2.3 General Biopharmaceutics

2.3.1 Was an adequate link established between the clinical service formulation and the to-be-marketed formulations?

A PK bridging study (NAC-PK-05) between the FDC formulation and the free combination was conducted (Figure 8). However the formulation used in this trial was not the final 'to-be-marketed' (TBM) formulation that was used in the phase 3 trial. A cross study comparison between NAC-PK-04 which used TBM formulations and NAC-PK-05 suggested that the TBM FDC formulation has 35% and 15% lower exposures in comparison to the formulation used in the PK bridging study for neбиволol and valsartan respectively. These findings suggest that bridging safety data across the FDC formulations and the free combination (Bystolic/Diovan) is reasonable. In addition, safety and efficacy data of the TBM formulations relative to

nebivolol/valsartan individual treatments were also available from the pivotal efficacy study NAC-MD-01. In this study, Diovan[®] and Bystolic[®] at different doses were compared against the TBM FDC formulation which also justifies bridging the safety information.

A pivotal bioequivalence (BE) study (NAC-PK-07) was also conducted to compare the clinical trial FDC and the TBM FDC formulation for the 10/320 mg strength. All other FDC strengths used in phase 3 are same as the TBM formulations. These results establish an adequate link between the clinical trial formulation and the to-be-marketed FDC.

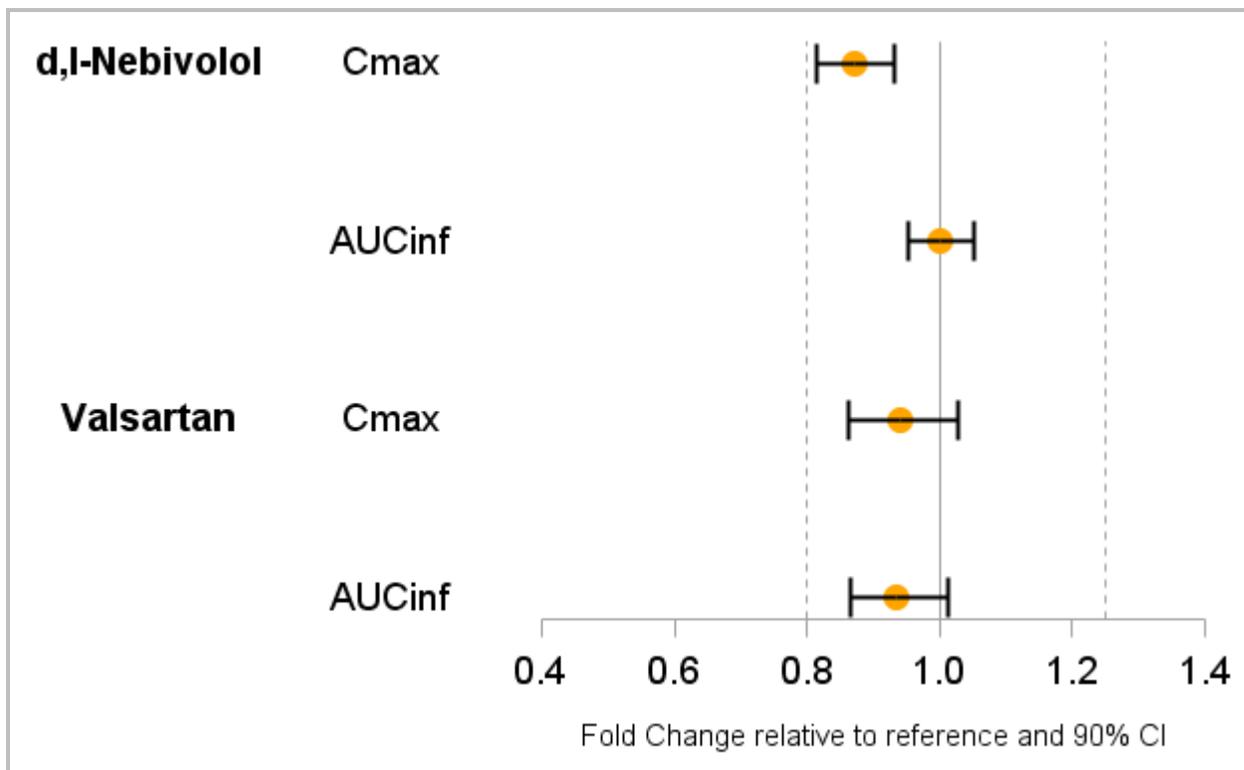


Figure 8. Relative bioavailability of nebivolol 20 mg and valsartan 320 mg when administered as FDC (test) or free combination (reference).

(The X-axis represents the geometric mean ratios of the BE metrics (C_{max} , AUC_{0-inf}) with 90% CI around the point estimate.)

[Source: Prepared by FDA using data from tables 11.2.3-1 and 11.2.4-1 in study report NAC-PK-05]

2.3.2 What is the effect of food on the bioavailability of the drugs from the dosage form?

Differences in the rate and/or extent of exposure (AUC_{0-t} , $AUC_{0-\infty}$ and/or C_{max}) were observed for nebivolol and valsartan but overall these differences were small in magnitude and not expected to be clinically relevant (Figure 9). For valsartan, mean C_{max} and $AUC_{0-\infty}$ under fed conditions were 15% and 5% lower compared to fasted conditions, respectively. For nebivolol, mean C_{max} , and $AUC_{0-\infty}$ of *d,l*-nebivolol under fed conditions were 15% and 5% higher compared to fasted conditions, respectively.

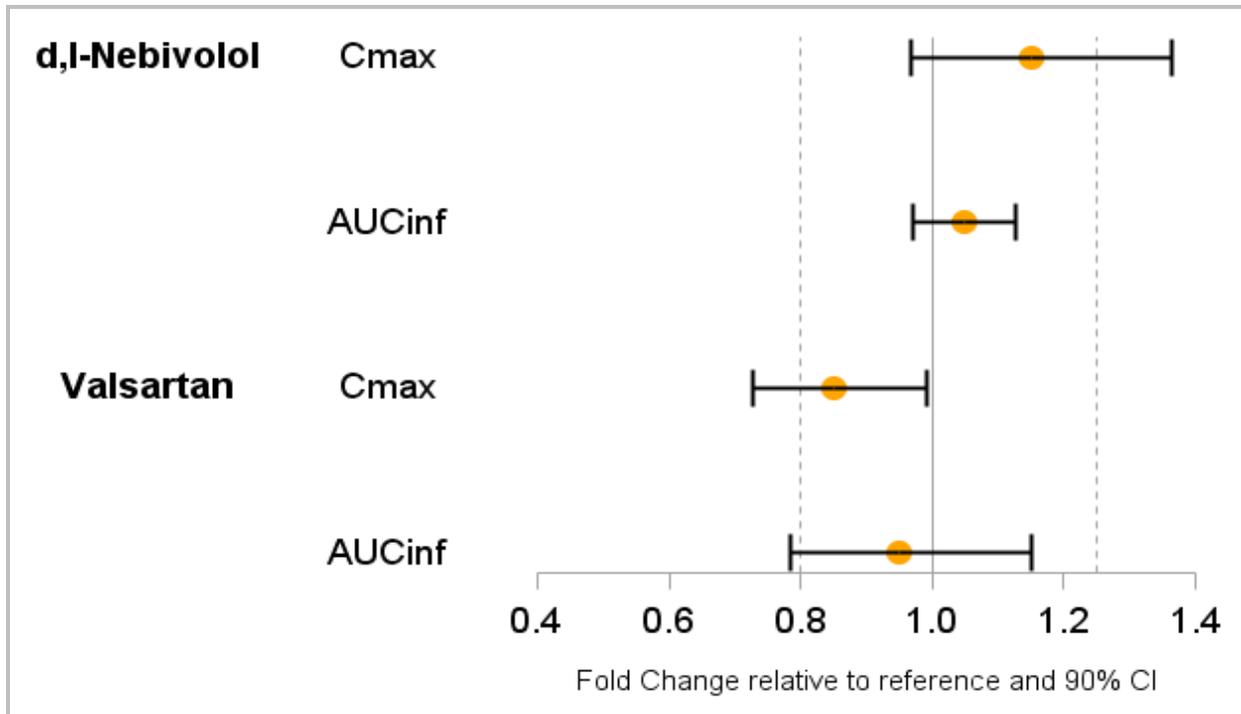


Figure 9. Relative bioavailability of nebivolol and valsartan FDC 20/320 after administration in fed (test) or fasted state (reference).
 (The X-axis represents the geometric mean ratios of the BE metrics (C_{max} , AUC_{0-inf}) with 90% CI around the point estimate.)
 [Source: Prepared by FDA using data from tables 11.2.3-1 and 11.2.5-1 in study report NAC-PK-04]

2.4 Analytical Section

The plasma concentrations of (*d*-, *l*-, *dl*-) nebivolol and valsartan were measured using validated HPLC/MS/MS methods.

The details of the bio-analytical methods used in this NDA are presented in Table 5. The methods satisfied the criteria for method validation and application to routine analysis set by the Guidance for Industry: Bioanalytical Method Validation, and hence were acceptable.

Table 5. Assay validation results for valsartan and nebivolol in human plasma.

<i>Analyte / Parameter</i>	<i>d-nebivolol</i>	<i>l-nebivolol</i>	<i>Total nebivolol</i>	<i>valsartan</i>
Range (ng/ml)	0.05 to 20	0.05 to 20	0.5 to 200	50.0 to 10,000
Inter day Precision (%CV)	0.0 to 2.8	2.0 to 6.7	2.0 to 3.4	0.0 to 1.8
Inter day Accuracy (%Dev)	0.1 to 6.7	-1.1 to 7	-1.8 to -0.4	-3.6 to -2
Internal standard	[² H ₈] nebivolol Lot # FMD- NEB-034,	[² H ₈] nebivolol Lot #FMD- NEB-034	[² H ₈] nebivolol Lot #FMD- NEB-034	Valsartan-D9 Lot# S-1160- 034C6
Reference standard	nebivolol Lot #FMD- NEB-017	nebivolol Lot #FMD- NEB-017	nebivolol Lot# FMD- EB017	valsartan Lot#G0F065
Specificity	No interference	No interference	No interference	No interference
Recovery (%)	90.3 to 91.5	87.5 to 88.2	60 to 64	73.1 to 73.9
<u>Stability</u>				
Freeze/Thaw Stability	6 cycles	6 cycles	4 cycles	7 cycles
Human plasma (RT)	24 hrs	24 hrs	24 hrs	6 hrs
Stock solution (-70C)	70 days	70 days	46 days	484 days
Auto sampler stability	7 days	7 days	43 hrs	142 hrs

[Sources: Prepared by FDA using Report Number PRD-RPT-BDM-00369, PRD-RPT-BDM-00365) and Report Number TSLR07-115, PRD-RPT-BDM-00494)]

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CLINICAL PHARMACOLOGY REVIEW

NDA Number	206302
Submission Type	Standard
Applicant Name	Forest Research Institute
Submission Dates	02/21/2014
Brand Name	Byvalson™
Generic Name	Nebivolol/Valsartan
Dosage Form	Oral tablets
Dosage Strengths	5/80, 5/160, 10/160, 10/320, and 20/320 mg
Proposed Indication	Hypertension
OCP Division	DCP1
Primary Reviewers	Martina Sahre, PhD & Bilal AbuAsal, PhD
Secondary Reviewer	Sreedharan Sabarinath, PhD
Team Leaders	Rajanikanth Madabushi, PhD & Jeffry Florian, PhD

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1 EXECUTIVE SUMMARY

Forest Research Institute is seeking approval for Byvalson™, a fixed dose combination (FDC) tablet of nebivolol and valsartan for the treatment of hypertension. The application was submitted under the 505(b)(2) pathway. Byvalson™ will be marketed in five strengths for once daily administration.

The applicant conducted six clinical pharmacology studies and two efficacy/safety studies to support this application: A single dose drug-drug interaction study (NAC-PK-01), a multiple dose pharmacokinetic / pharmacodynamic (PK/PD) and tolerability study (NAC-PK-03), a food effect study (NAC-PK-04), a PK bridging study between FDC formulation and the free combination (NAC-PK-05), a strength proportionality study of FDC (NAC-PK-06), and a pivotal bioequivalence (BE) study to compare the clinical trial FDC and the to-be-marketed FDC formulation for the 10/320 mg strength tablet (NAC-PK-07). There was one placebo-controlled pivotal efficacy study comparing the FDC with nebivolol and valsartan monotherapies (NAC-MD-01) and a long term safety and tolerability study (NAC-MD-02). The primary endpoint in the trial NAC-MD-01 was change from baseline in seated diastolic blood pressure (siDBP) after 8 weeks of treatment. The difference in change from baseline between FDC 20/320 and nebivolol 40 mg was -1.2 mmHg (p=0.03). The difference in siDBP for the comparison of FDC 20/320 and valsartan 320 mg was -4.4 mmHg (p<0.0001).

There was a significant decrease (~ 45%) in maximum plasma concentrations (C_{max}) of nebivolol but little change in area under the plasma concentration-time curve (AUC), when co-administered with valsartan. This review focused on the drug-drug interaction between nebivolol and valsartan and assessed whether this interaction is likely to have any impact on the tolerability of the FDC compared to nebivolol 40 mg alone. These analyses assessed the event rate for bradycardia and concentration-dependent effect of nebivolol on heart rate as these are considered as the major tolerability issues associated with nebivolol treatment. Based on the available data, it was not possible to determine whether a C_{max} reduction for nebivolol could decrease bradycardia and alter tolerability with the FDC compared to nebivolol administered as a single agent.

1.1 Recommendations

The clinical pharmacology studies submitted by the applicant are sufficient to characterize and bridge the exposure of nebivolol/valsartan free combination with the FDC drug product. The Office of Clinical Pharmacology recommends approval from a clinical pharmacology standpoint.

1.2 Phase 4 Commitments

There are no Phase 4 requirements or commitments.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The components of Byvalson™ are approved for the treatment of hypertension. The approved doses of nebivolol (NDA 021742 Bystolic®) range from 5 to 40 mg once daily, while doses for valsartan (NDA 021283 Diovan®) range from 80 to 320 mg once daily.

The Clinical Pharmacology studies for Byvalson™ were designed primarily to establish and connect the efficacy and safety data of the monotherapies to the FDC drug product. The key clinical pharmacology findings are listed below:

- The FDC and nebivolol/valsartan free combination were bioequivalent, with the 90% CIs of the geometric LS mean ratios for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ within the 80 - 125% range for both nebivolol and valsartan.
- There is no clinically relevant food effect on Byvalson™. The pharmacokinetics of both nebivolol and valsartan were proportional over the FDC dose ranges of nebivolol/valsartan 5/80 mg to 20/320 mg.
- Single- and multiple-dose drug interaction studies showed that the coadministration of nebivolol and valsartan resulted in lower maximum plasma drug concentration (C_{max}) for nebivolol (~ 45% decrease) but no significant changes to total systemic exposure (AUC) when compared to nebivolol administered alone.
- Nebivolol 40 mg showed a higher incidence of bradycardia events (counted as bradycardia or sinus bradycardia) compared to other nebivolol containing treatment arms. Valsartan and placebo arms showed the lowest incidence of bradycardia events. The review team used time-matched concentration and heart rate response data to assess whether this could be related to C_{max} .
- Differences in treatment discontinuations and the incidence rate of bradycardia events between FDC 20/320 mg and nebivolol 40 mg arms cannot be explained based on a reduction in C_{max} alone. Data from the ambulatory blood pressure monitoring (ABPM) substudy in trial NAC-MD-01 showed that the relationship between change from baseline in heart rate and C_{max} is shallow for FDC 20/320 and nebivolol 40 mg.

2 QUESTION BASED REVIEW (QBR)

This is an abridged version of the QBR.

2.1 General Attributes of the Drug

Byvalson™ tablet is a fixed-dose combination of nebivolol and valsartan intended for oral administration. Both components of Byvalson™ have been previously approved in the US for use in the treatment of hypertension¹.

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

The physicochemical properties of nebivolol and valsartan have been summarized under NDA 21-742, NDA 20-665, NDA 21-283, and in the Diovan® and Bystolic® package inserts.

In addition to the active ingredients, Byvalson™ coated tablets contain the following inactive excipients: Lactose monohydrate, NF; Microcrystalline cellulose, NF; Copovidone, NF; Croscarmellose sodium, NF; Colloidal silicon dioxide, NF; Magnesium stearate, NF (vegetable source); Talc, USP; Ferric oxide, NF; Hypromellose 2910, USP; Polysorbate 80, NF; Colloidal silicon dioxide, NF; and Magnesium stearate, NF (vegetable source).

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Byvalson™ is a combination of nebivolol and valsartan. Nebivolol is a β_1 -adrenergic blocker. The antihypertensive mechanism of action of nebivolol has not been definitely established, however it is proposed to be through: decreased heart rate, decreased myocardial contractility, suppression of renin activity and vasodilation effect². Valsartan is an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension.

The proposed indication for Byvalson™ is the treatment of hypertension, alone or in combination with other antihypertensive agents.

2.1.3 What are the proposed dosages and routes of administration?

Byvalson™ is proposed to be marketed in 5 strengths of nebivolol/valsartan for oral administration. These are 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg.

2.2 General Clinical Pharmacology

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

The applicant is relying on FDA's previous findings of safety and effectiveness for Diovan® and Bystolic® to support the approval of this 505(b)(2) application. The applicant conducted one pivotal efficacy study and one long term safety and tolerability study with supporting efficacy information. These two studies compared the proposed FDC with monotherapies and placebo. In addition, six clinical pharmacology studies were conducted to support this application (Table 1).

¹ NDA 021742 for Bystolic® and NDA 020665 & NDA 021283 for Diovan®.

² Bystolic® Package Insert, Approved 12/14/2011:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021742s013lbl.pdf

Table 1. Summary of the clinical development program

Study	Design	Doses
NAC-MD-01 Pivotal efficacy study	Phase 3, placebo controlled, parallel-group, double-blind study, including 1 forced up-titration at Week 4, and a 1-week down-titration phase in patients with stage 1 and 2 essential hypertension (n=4161)	FDC 5/80, 5/160, 10/160, 10/320, 20/320 mg Nebivolol 5, 10, 20, 40 mg Valsartan 80, 160, 320 mg
NAC-MD-02 Long term safety	Phase 3, 52-week, open-label, single arm study, and a 1-week down-titration phase in patient with stage 1 and 2 essential hypertension (n=810)	Nebivolol 5, 10, 20 mg Valsartan 160, 320 mg Hydrochlorothiazide 12.5, 25 mg
Clinical Pharmacology Studies		
NAC-PK-01 Single dose DDI	Open label, single dose, 3-way, crossover in healthy subjects (n=24)	Nebivolol 20 mg Valsartan 320 mg
NAC-PK-03 Multiple dose PK/PD	Open label, multiple dose, 3-way crossover in healthy subjects (n=30)	Nebivolol 20 mg Valsartan 320 mg
NAC-PK-04 Food effect study	Open label, 2-way, crossover, single dose in healthy subjects (n=32)	FDC 20/320 mg
NAC-PK-05 PK bridging study	Open label, 2-way, crossover, single dose study in healthy subjects (n=70)	Nebivolol 20 mg Valsartan 320 mg FDC 20/320 mg
NAC-PK-06 Dose proportionality	Open label, parallel, multiple dose study in healthy subjects (n=30)	FDC 5/80, 10/160, 20/320 mg
NAC-PK-07 FDC pivotal BE	Open label, 2-way, crossover, single dose study in healthy subjects (n=70)	FDC 10/320 mg

[Source: Prepared by FDA from the tabular listing of clinical studies. Section 5.2]

Study NAC-MD-01 was the pivotal efficacy trial conducted for this submission. The study consisted of three phases, a 4 to 6 week single-blind, placebo run-in period, an 8-week double-blind treatment period and a 1-week double-blind down-titration period. Patients who met the criteria for stage 1 and 2 hypertension were randomized into the treatment arms. Pulse rate was

required to be ≥ 55 bpm at randomization. After randomization, patients received one of the following treatments: placebo, nebivolol 5 or 20 mg, valsartan 80 or 160 mg, FDC 5/80, 5/160, and 10/160. After 4 weeks, patients were forced up-titrated to double the doses received in the first four weeks, i.e. placebo, nebivolol 10 or 40 mg, valsartan 160 or 320 mg, FDC 10/160, 10/320, or 20/320, respectively.

A total of 4161 patients were randomized to receive treatment, and 3715 patients completed the double-blind treatment phase (i.e., 89.3%) across all treatments. In the nebivolol 40 mg arm, a total of 76 patients discontinued treatment, which makes the completer rate in this arm (86.3%, or 479 out of 555) slightly lower than the overall rate. Of the 76 patients who discontinued in the 40 mg arm, 48 left the trial during the first 4 weeks of treatment, i.e. prior to the up-titration to 40 mg. Across all treatments, 6.9% of patients discontinued in the first four weeks.

At randomization, 37.7% of patients were in essential hypertension stage 1 and 62.3% were in stage 2. About 19.4% of subjects participated in a substudy, where ambulatory blood pressure monitoring (ABPM), pharmacokinetics (PK) and pharmacodynamic (plasma-renin activity and aldosterone) measures were obtained. The ABPM and PK data from this substudy were used for heart rate analysis.

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

Yes, the plasma levels of *d*-nebivolol, *l*-nebivolol, *d,l*-nebivolol, nebivolol glucuronide, and valsartan were measured. Please see Section 2.4 for the details of the analytical methods.

2.2.2.1 What are the characteristics of the dose-response (D-R) relationships for efficacy and is the dose/dosing regimen selected by the sponsor consistent with the known D-R relationships?

Both nebivolol and valsartan show shallow dose-response at doses above 10 mg and 80 mg, respectively. Figures 1 through 4 show the observed change from baseline response on seated diastolic (siDBP) and systolic blood pressure (siSBP) from the pivotal efficacy study NAC-MD-01 and previously published efficacy studies with nebivolol and valsartan. The shapes of the dose-response curves for nebivolol and valsartan from NAC-MD-01 were similar to the trends observed from previous trials. Saturating responses in the overall change from baseline in blood pressure were observed at nebivolol and valsartan doses higher than 10 mg and 80 mg respectively. Dose response trends for combinations of nebivolol and valsartan from NAC-MD-01 are shown in Table 2. The results from various combinations of the FDC are in agreement with what was observed from the dose-response trends for the individual components. Marginal increases in siDBP and siSBP were observed for doses above FDC 10/160 suggesting limited additional improvement in blood pressure response at higher doses of FDC.

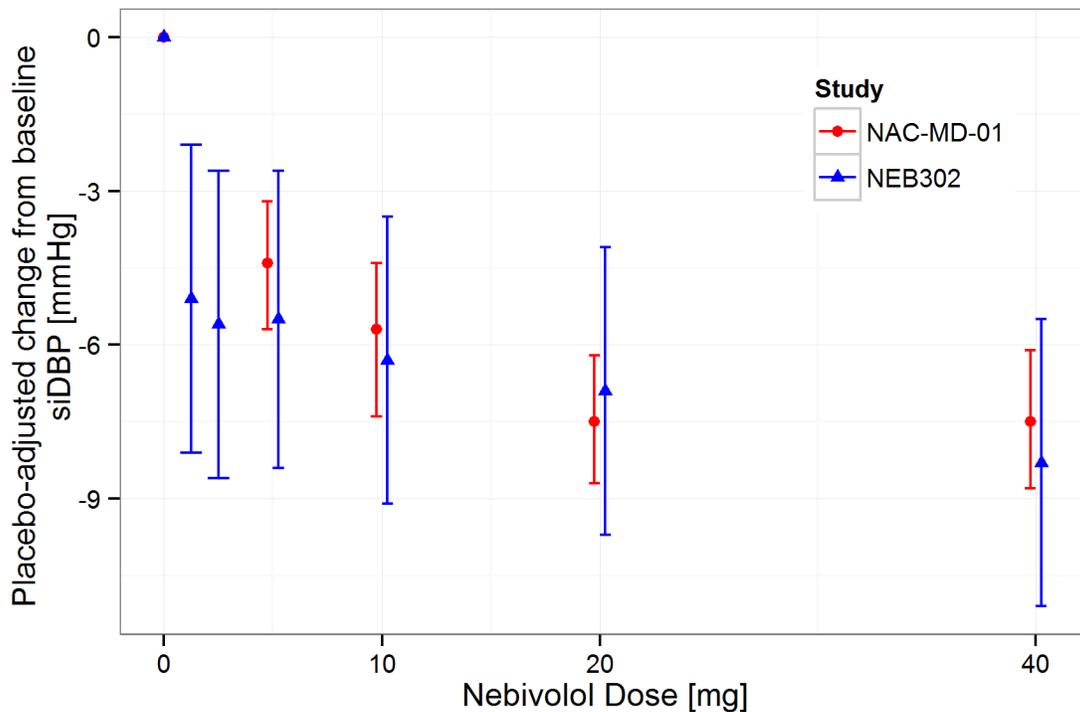


Figure 1. Nebivolol dose-response (siDBP) comparison for monotherapy results from the current submission (NAC-MD-01) and from a previously published efficacy study (NEB302) (The 95% CI for the study under review was obtained from the CSR. The 95% CI for the previously reported study was calculated using propagation of error calculations from reported SD and SEs. A dummy point was also inserted at [0,0] to denote the placebo effect. In study NAC-MD-01, patients in nebivolol-only treatment arms received 5 and 20 mg for the first 4 weeks, and thereafter 10 and 40 mg for the second 4 weeks. Therefore, responses to 5 and 20 mg nebivolol were observed at week 4.)
 [Source: Prepared by FDA using NAC-MD-01 CSR (red circles) and J Clin Hypertens. 2007;9:667–676 (blue triangles)]

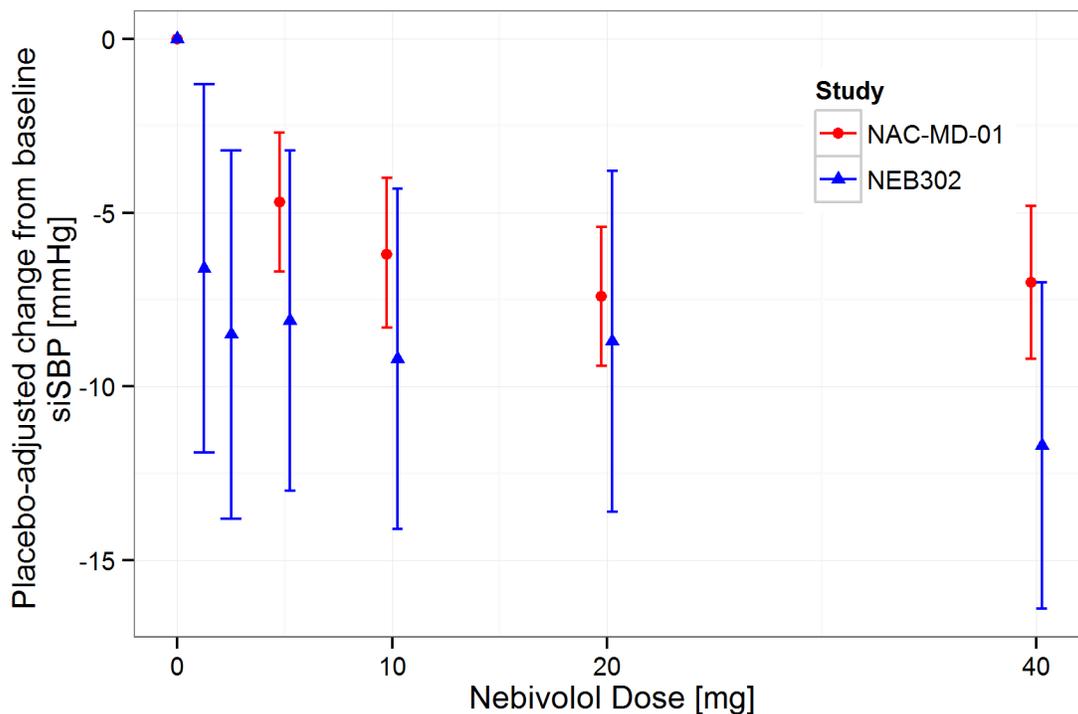


Figure 2. Nebivolol dose-response (siSBP) comparison for monotherapy results from the current submission (NAC-MD-01) and from a previously published efficacy study (NEB302) (The 95% CI for the study under review was obtained from the CSR. The 95% CI for the originator study was calculated using propagation of error calculations from reported SD and SEs. A dummy point was also inserted at [0,0] to denote the placebo effect.

In study NAC-MD-01, patients in nebivolol-only treatment arms received 5 and 20 mg for the first 4 weeks, and thereafter 10 and 40 mg for the second 4 weeks. Therefore, responses to 5 and 20 mg nebivolol were observed at week 4.)

[Source: Prepared by FDA using NAC-MD-01 CSR (red circles) and J Clin Hypertens. 2007;9:667–676 (blue triangles)]

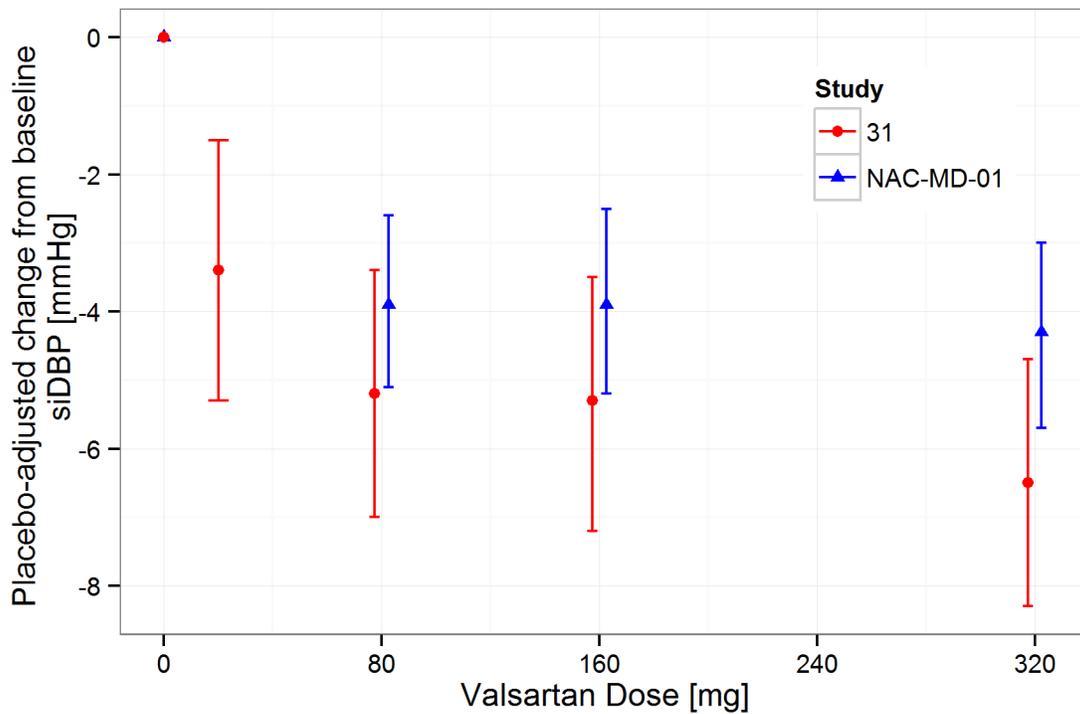


Figure 3. Valsartan dose-response (siDBP) comparison for monotherapy results from the current submission (NAC-MD-01) and from a previously published efficacy study (Study 31) [Source: Prepared by FDA using NAC-MD-01 CSR (triangles, blue) and Diovan NDA 20,665 Medical Review³ (circles, red)]

³ http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020665_s000.pdf, pages 87 and 89 (pdf numbering)

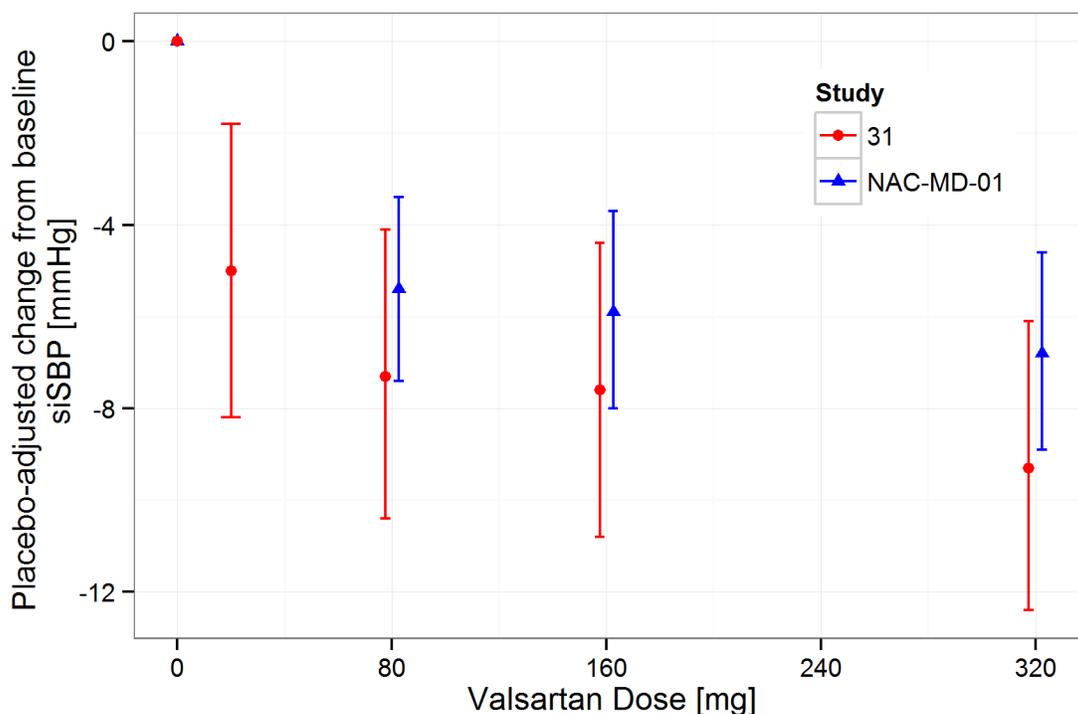


Figure 4. Valsartan dose-response (siSBP) comparison for monotherapy results from the current submission (NAC-MD-01) and from a previously published efficacy study (Study 31) [Source: Prepared by FDA using NAC-MD-01 CSR (triangles, blue) and Diovan NDA 20,665 Medical Review⁴ (circles, red)]

Table 2. Placebo-subtracted least squares mean changes from baseline blood pressure measured at trough for the combination arms at weeks 4 and 8

Time	Arm	siDBP	95% CI	siSBP	95% CI
Week 4	FDC 5/80	-7.2	(-8.4, -5.9)	-8.3	(-10.3, -6.3)
	FDC 5/160	-7.4	(-8.7, -6.1)	-8.8	(-10.9, -6.8)
	FDC 10/160	-7.9	(-9.2, -6.6)	-9.0	(-11.0, -7.0)
Week 8	FDC 10/160	-7.9	(-9.3, -6.6)	-9.8	(-11.9, -7.6)
	FDC 10/320	-8.1	(-9.4, -6.7)	-9.7	(-11.9, -7.6)
	FDC 20/320	-8.7	(-10.0, -7.3)	-9.9	(-12.1, -7.7)

[Source: Reproduction from NAC-MD-01 CSR, Tables 11.4.1.1-1, 11.4.1.2.1-1, 11.4.1.2.2.1-1, and 11.4.1.2.2.1-2]

⁴ http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020665_s000.pdf, pages 87 and 89 (pdf numbering)

2.2.2.2 What are the characteristics of the exposure-response relationships for safety?

The applicant suggested in an Information Efficacy Amendment dated 6/17/2014, that the reduction in nebivolol C_{max} after coadministration of nebivolol with valsartan may improve the tolerability and safety of the FDC compared to nebivolol (40 mg). To support this, the applicant highlighted the higher discontinuation rate and higher number of bradycardia events from the nebivolol 40 mg treatment arm compared to the FDC 20/320 mg arm⁵. The clinical pharmacology review team conducted analyses to assess whether a decrease in nebivolol C_{max} could be related to improved tolerability with FDC 20/320 mg compared to nebivolol 40 mg alone.

This analysis utilized heart rate measurements from the ABPM substudy from week 0 and week 8 as well as concentration assessments at week 8 which were sampled at approximately nebivolol t_{max} (1-4 hours post dose) and t_{trough} (22-24 hours post dose). Changes from baseline heart rate were calculated based on time-matched assessments from week 0 and week 8. The results of this analysis are shown in Tables 3 and 4. There was a significant heart rate lowering effect due to nebivolol, consistent with its mechanism of action, however, this heart rate effect was shallow at concentrations at or above those observed at C_{max} for 10 mg nebivolol. For the highest strength FDC (20/320) the heart rate reduction at C_{max} was similar to that seen with 40 mg nebivolol alone. However, the bradycardia event rate was higher in the 40 mg nebivolol arm (6.1%) compared to the FDC 20/320 arm (2.5%).

Furthermore, assuming a 45% reduction in nebivolol C_{max} when coadministered with valsartan, it is anticipated that nebivolol peak plasma concentrations with the FDC 20/320 would be similar to those from 10 mg nebivolol administered alone. Between 20/320 and 10 mg nebivolol alone, a difference of approximately 3 beats per minute in heart rate was observed. This is a small effect compared to the overall reduction in heart rate observed with nebivolol (~10 beats per minute at C_{min} with 10 mg nebivolol). Occurrences of bradycardia were also not distinguishable between these two groups (10 mg nebivolol and FDC 20/320).

The relationship between nebivolol on heart rate changes was further evaluated in an exposure-response analysis using time-matched nebivolol concentration and change from baseline in heart rate (Figure 5). At concentrations reflecting t_{trough} , an increasing concentration-response relationship was observed, though a majority of the effect on heart rate (~10 bpm) is maintained even at the lowest nebivolol concentrations from this analysis. Concentrations associated with 10 to 40 mg nebivolol C_{max} are on the plateau of the exposure-response relationship. Mean C_{max} for nebivolol 40 mg (all genotypes included) was about 7.1 ng/mL, whereas it was 1.6 ng/mL for FDC 20/320 (annotated with arrows). Comparing these mean concentrations with the expected reduction in heart rate (in Figure 5) shows that these concentrations are in a range where it may be difficult to distinguish differences in the heart rate effect as a saturation of the effect has already been achieved. This is consistent with observations from the overall population in study NAC-MD-01 (Table 12.5.1.2.1.3-1 in the clinical study report). When comparing pulse rates observed at Week 4 and Week 8, one can observe that an 8-fold increase in dose, from 5 mg at week 4 (Nebivolol 10 mg arm), to 40 mg at week 8 leads to a decrease in pulse rate of -9.3 and -14.6 bpm, respectively. In addition, changes from baseline pulse rate showed a 0.5 bpm between 20/320 (-14.0 ± 11.1 bpm) and nebivolol 40 mg alone (-14.6 ± 11.9 bpm). This suggests that

⁵ <\\cdsesub1\evsprod\nda206302\0007\m1\us\efficacy-info-amendment.pdf>, Section 4.0

based on pulse rate data from the overall population and from the ABPM dataset, there would only be small differences in bradycardia events expected. The observed differences in bradycardia events may have been due to pulse rates cut off values used to categorize an event as bradycardia.

Table 3. Mean change from baseline in heart rate at t_{max}

Valsartan Dose [mg]	Nebivolol Dose [mg]			
	0	10	20	40
0	1.08 (2.10)	-14.7 (1.41)		-19.1 (1.48)
160	-1.17 (1.49)	-14.2 (1.46)		
320	-1.56 (1.45)	-15.1 (1.44)	-18.1 (1.42)	

[Source: Prepared by FDA using from NAC-MD-01 vs.xpt, suppvs.xpt, adsl.xpt]

Table 4. Mean change from baseline in heart rate at t_{trough}

Valsartan Dose [mg]	Nebivolol Dose [mg]			
	0	10	20	40
0	1.54 (1.80)	-10.6 (1.22)		-13.1 (1.27)
160	-1.79 (1.28)	-11.2 (1.26)		
320	-0.69 (1.24)	-9.50 (1.23)	-12.9 (1.22)	

[Source: Prepared by FDA using from NAC-MD-01 vs.xpt, suppvs.xpt, adsl.xpt]

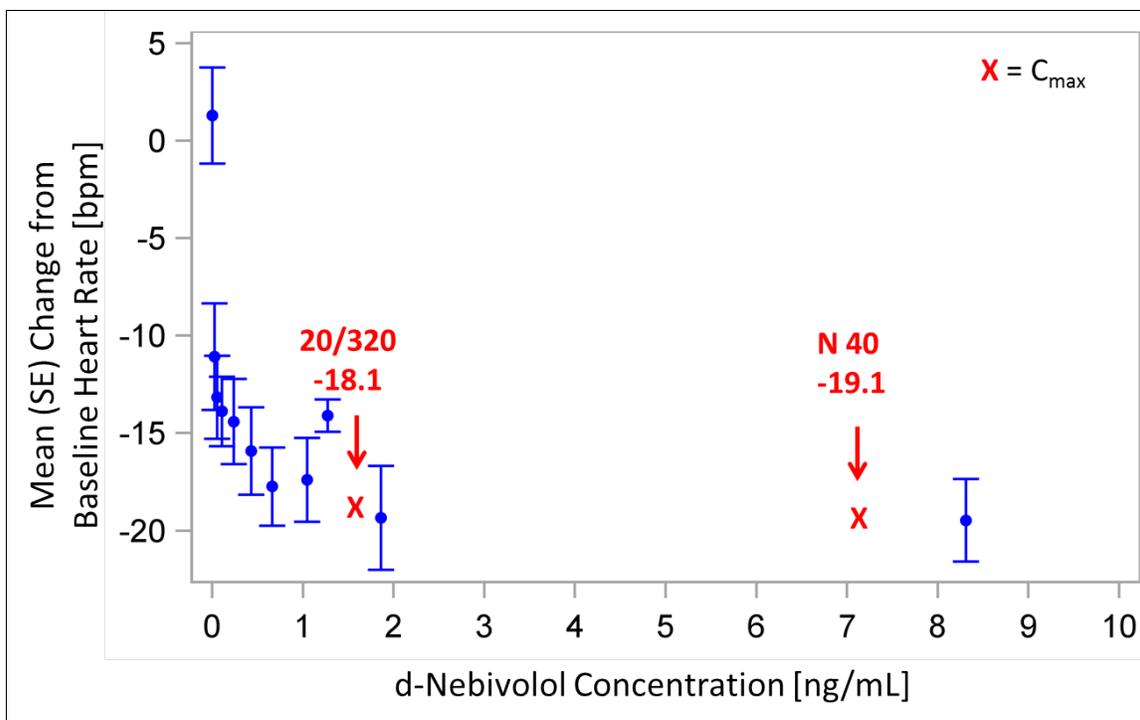


Figure 5. *d*-nebivolol concentrations vs change from baseline heart rate at C_{max} and C_{min} [Source: Prepared by FDA using datasets pc.xpt, adsl.xpt, vs.xpt and suppv.s.xpt from study NAC-MD-01]

2.2.2.3 Does this drug prolong QT/QTc Interval?

A thorough QT study for nebivolol/valsartan combination was not conducted.

2.2.3 What are the PK characteristics of the drugs?

2.2.3.1 What are the single and multiple dose PK parameters?

The pharmacokinetic properties of nebivolol and valsartan have been reviewed and reported previously under NDA 21-742, NDA 20-665, NDA 21-283, and in the Bystolic[®] and Diovan[®] package inserts. In brief, the $t_{1/2}$ of valsartan is around 6 hours and reaches t_{max} after 2-4 hours after oral administration. The absolute bioavailability of valsartan ranges from 10-35% with a mean value of 25%. Valsartan is eliminated unchanged and recovered mainly in the feces.

Nebivolol is mainly cleared by CYP2D6 metabolism and its $t_{1/2}$ ranges from 12 hours in extensive metabolizers (EM) to 19 hours in poor metabolizers (PM) of CYP2D6.

The pharmacokinetics of the FDC was characterized in the dose proportionality study (NAC-PK-06). The pharmacokinetics of nebivolol, its metabolites, and valsartan were proportional over the dose ranges of nebivolol/valsartan 5/80 mg, 10/160 and 20/320 mg. There was no significant accumulation for valsartan after once daily multiple dose administration, while the accumulation ratio of nebivolol ranged from 1.3 in EM to 4 in PM. In addition, there was more than 10 fold increase in exposure for poor CYP2D6 metabolizers relative to extensive metabolizers.

2.2.4 Is there a PK interaction after coadministration of nebivolol and valsartan?

Yes, single- and multiple-dose coadministration of nebivolol and valsartan resulted in lower C_{max} and AUC values for both compounds compared to the administration of each drug alone. After single dose administration, the C_{max} and AUC of valsartan were 22 % and 20 % lower when coadministered with nebivolol, respectively. C_{max} and AUC of *d,l*-nebivolol were 53 % and 16 % lower when coadministered with valsartan, respectively (Study NAC-PK-01). Following multiple dose administration, $C_{max,ss}$ (C_{max} at steady state) and $AUC_{0-\tau,ss}$ (AUC over the dosing interval at steady state) of valsartan were both 13% lower with coadministration of nebivolol; $C_{max,ss}$ and $AUC_{0-\tau,ss}$ of *d,l*-nebivolol were 45% and 17% lower with coadministration of valsartan, respectively (Study NAC-PK-03)(Figure 6 and Figure 7).

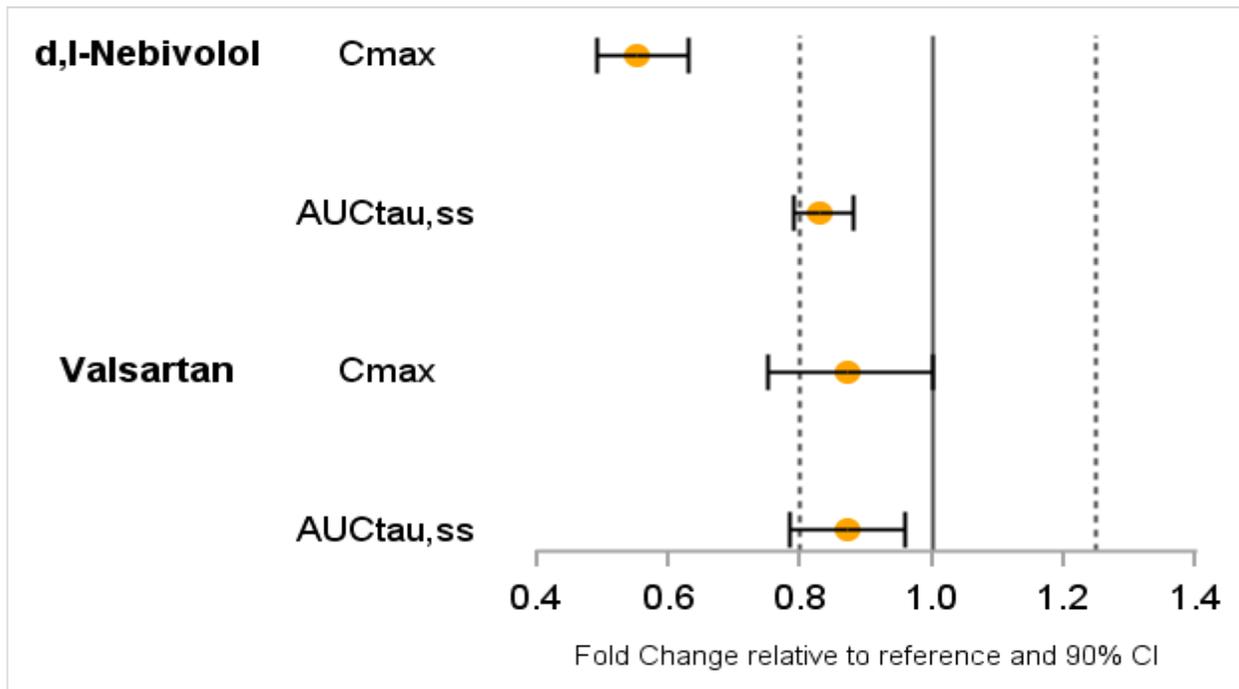


Figure 6. Changes in AUC and C_{max} with a free combination of valsartan and nebivolol relative to their monotherapy.

(The geometric mean ratios are depicted on the X-axis. Closed circles represent the geometric mean of the ratio (drug in combination/individual) and horizontal lines represent the 90% CI associated with the mean fold change in AUC and C_{max})

[Source: Prepared by FDA using data from tables 11.2.3 and 11.2.5 in study report NAC-PK-03]

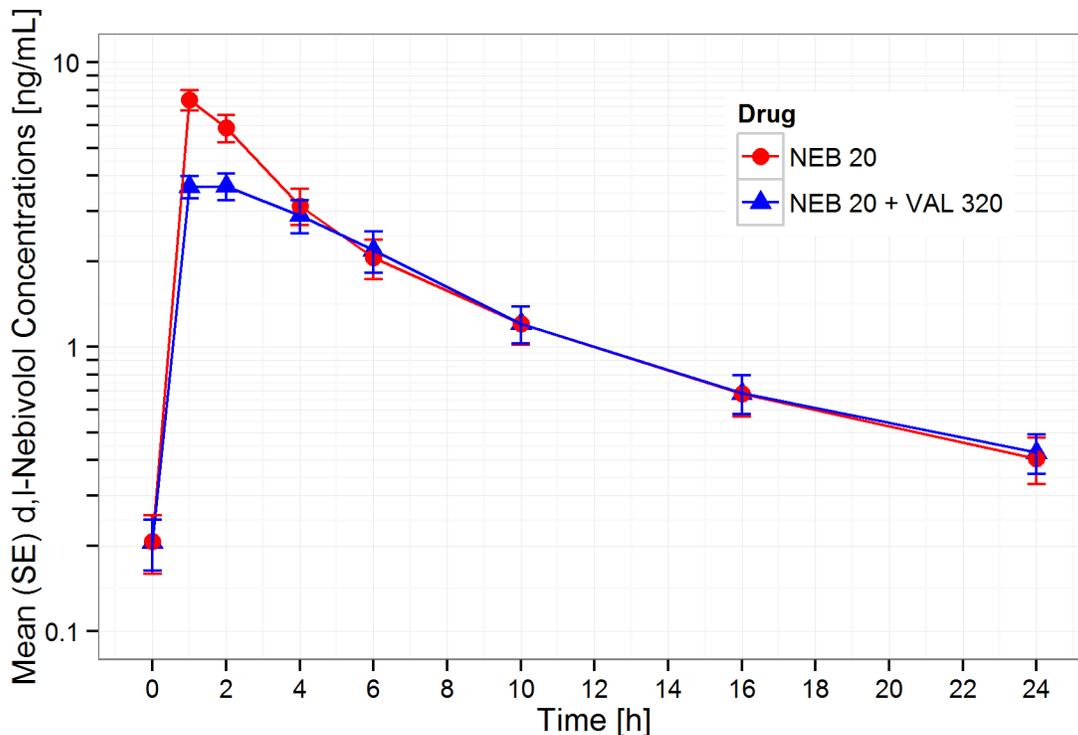


Figure 7. Steady-state plasma concentrations of *d,l*-neбиволol in healthy volunteers after 7 daily doses of 20 mg neбиволol alone (Red), or in combination with 320 mg valsartan (Blue). [Source: Prepared by FDA from data in study report NAC-PK-03]

The reason for this drug interaction is not clear; however the data suggest that the interaction is related to the rate of absorption. This is because only the C_{max} was significantly reduced while the total systemic exposure or extent of absorption (AUC) was not altered significantly. This interaction may be attributed to the inhibition of intestinal influx transporter mediating the uptake of neбиволol; however there are no reports of any transporter involved in the uptake of neбиволol. It is also unlikely that this can be explained by any enzyme induction because enzyme induction would have affected the AUC as well. Moreover, it is unlikely that an interaction mediated by enzyme induction would be observed after a single dose administration as is in single dose PK study NAC-PK-01.

2.3 General Biopharmaceutics

2.3.1 Was an adequate link established between the clinical service formulation and the to-be-marketed formulations?

A PK bridging study (NAC-PK-05) between the FDC formulation and the free combination was conducted (

Figure 8). However the formulation used in this trial was not the final ‘to-be-marketed’ (TBM) formulation that was used in the phase 3 trial. A cross study comparison between NAC-PK-04 which used TBM formulations and NAC-PK-05 suggested that the TBM FDC formulation has 35% and 15% lower exposures in comparison to the formulation used in the PK bridging study for neбиволol and valsartan respectively. These findings suggest that bridging safety data across the FDC formulations and the free combination (Byvalson/Diovan) is reasonable. In addition,

safety and efficacy data of the TBM formulations relative to nebivolol/valsartan individual treatments were also available from the pivotal efficacy study NAC-MD-01. In this study, Diovan[®] and Bystolic[®] at different doses were compared against the TBM FDC formulation which also justifies bridging the safety information.

A pivotal bioequivalence (BE) study (NAC-PK-07) was also conducted to compare the clinical trial FDC and the TBM FDC formulation for the 10/320 mg strength. All other FDC strengths used in phase 3 are same as the TBM formulations. These results establish an adequate link between the clinical trial formulation and the to-be-marketed FDC.

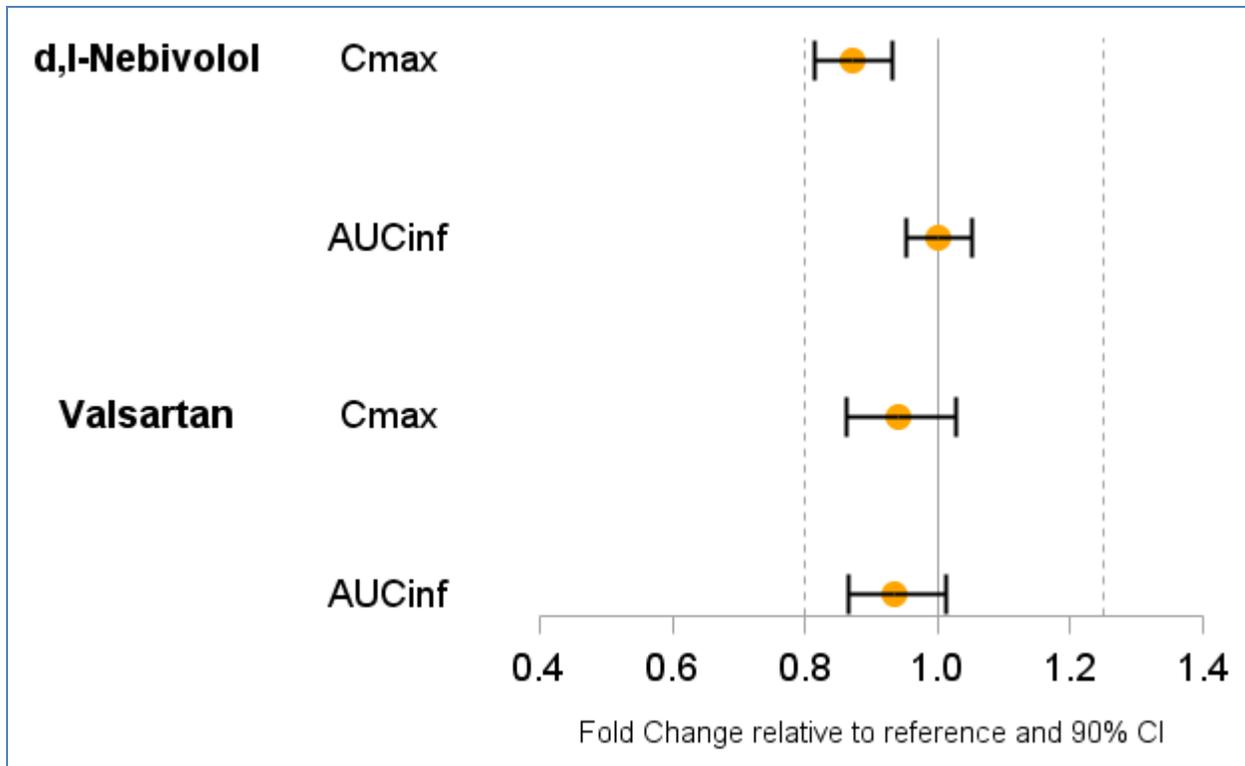


Figure 8. Relative bioavailability of nebivolol 20 mg and valsartan 320 mg when administered as FDC (test) or free combination (reference).

(The X-axis represents the geometric mean ratios of the BE metrics (C_{max} , AUC_{0-inf}) with 90% CI around the point estimate.)

[Source: Prepared by FDA using data from tables' 11.2.3-1 and 11.2.4-1 in study report NAC-PK-05]

2.3.2 What is the effect of food on the bioavailability of the drugs from the dosage form?

Differences in the rate and/or extent of exposure (AUC_{0-t} , $AUC_{0-\infty}$ and/or C_{max}) were observed for nebivolol and valsartan but overall these differences were small in magnitude and not expected to be clinically relevant (Figure 9). For valsartan, mean C_{max} and $AUC_{0-\infty}$ under fed conditions were 15% and 5% lower compared to fasted conditions, respectively. For nebivolol, mean C_{max} , and $AUC_{0-\infty}$ of *d,l*-nebivolol under fed conditions were 15% and 5% higher compared to fasted conditions, respectively.

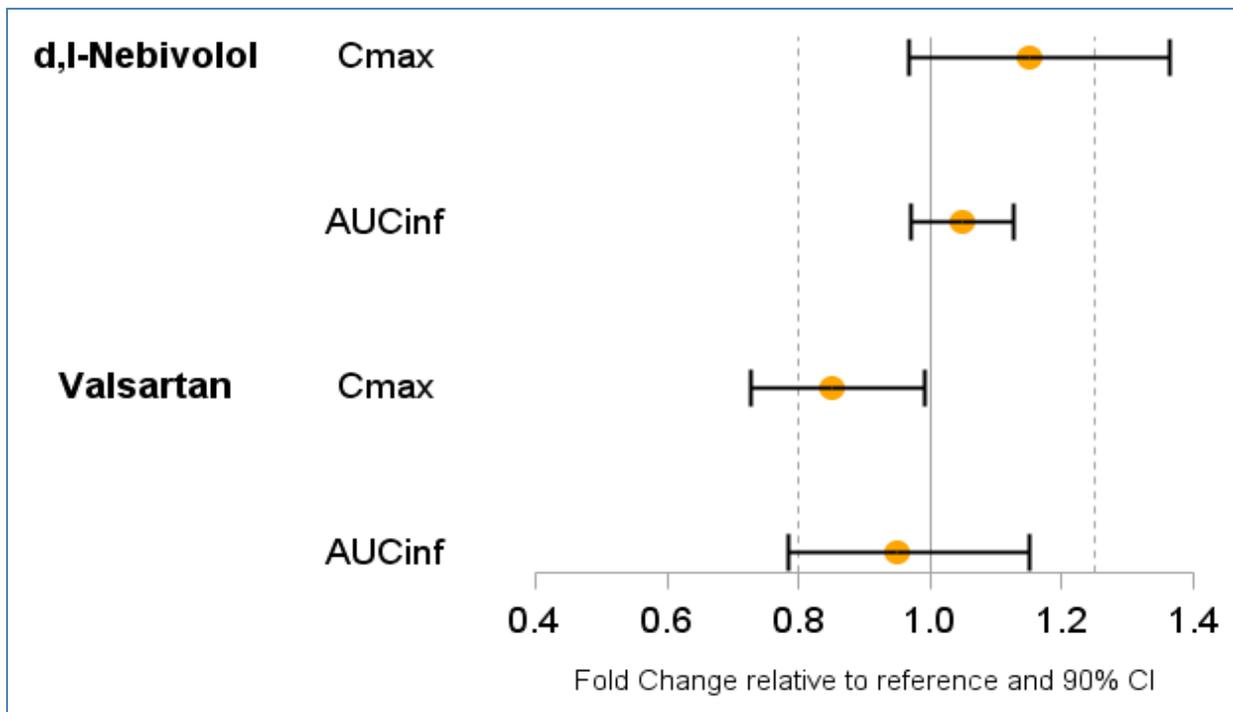


Figure 9. Relative bioavailability of nebivolol and valsartan FDC 20/320 after administration in fed (test) or fasted state (reference).

(The X-axis represents the geometric mean ratios of the BE metrics (C_{max} , AUC_{0-inf}) with 90% CI around the point estimate.)

[Source: Prepared by FDA using data from tables' 11.2.3-1 and 11.2.5-1 in study report NAC-PK-04]

2.4 Analytical Section

The plasma concentrations of (*d*-, *l*-, *dl*-) nebivolol and valsartan were measured using validated HPLC/MS/MS methods.

The details of the bio-analytical methods used in this NDA are presented in Table 5. The methods satisfied the criteria for method validation and application to routine analysis set by the Guidance for Industry: Bioanalytical Method Validation, and hence were acceptable.

Table 5. Assay validation results for valsartan and nebivolol in human plasma.

<i>Analyte / Parameter</i>	<i>d-nebivolol</i>	<i>l-nebivolol</i>	<i>Total nebivolol</i>	<i>valsartan</i>
Range (ng/ml)	0.05 to 20	0.05 to 20	0.5 to 200	50.0 to 10,000
Inter day Precision (%CV)	0.0 to 2.8	2.0 to 6.7	2.0 to 3.4	0.0 to 1.8
Inter day Accuracy (%Dev)	0.1 to 6.7	-1.1 to 7	-1.8 to -0.4	-3.6 to -2
Internal standard	[² H ₈] nebivolol Lot # FMD- NEB-034,	[² H ₈] nebivolol Lot #FMD- NEB-034	[² H ₈] nebivolol Lot #FMD- NEB-034	Valsartan-D9 Lot# S-1160- 034C6
Reference standard	nebivolol Lot #FMD- NEB-017	nebivolol Lot #FMD- NEB-017	nebivolol Lot# FMD- EB017	valsartan Lot#G0F065
Specificity	No interference	No interference	No interference	No interference
Recovery (%)	90.3 to 91.5	87.5 to 88.2	60 to 64	73.1 to 73.9
<u>Stability</u>				
Freeze/Thaw Stability	6 cycles	6 cycles	4 cycles	7 cycles
Human plasma (RT)	24 hrs	24 hrs	24 hrs	6 hrs
Stock solution (-70C)	70 days	70 days	46 days	484 days
Auto sampler stability	7 days	7 days	43 hrs	142 hrs

[Sources: Prepared by FDA using Report Number PRD-RPT-BDM-00369, PRD-RPT-BDM-00365) and Report Number TSLR07-115, PRD-RPT-BDM-00494)]

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/s/

BILAL S ABU ASAL
08/04/2014

MARTINA D SAHRE
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JEFFRY FLORIAN
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SREEDHARAN N SABARINATH
08/04/2014

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

The applicant, Forest laboratories Inc, is seeking approval for a fixed dose combination of nebivolol and valsartan for the treatment of hypertension. Both nebivolol (Bystolic[®]) and valsartan (Diovan[®]) are highly utilized antihypertensive drugs approved to be used alone or in combination with other classes of antihypertensive drugs. The applicant is relying on FDA's previous findings of safety and effectiveness for Diovan[®] and Bystolic[®] to support the approval of this 505(b)(2) application. The applicant conducted one pivotal efficacy study and one long term safety and tolerability study with supporting efficacy information. These two studies compared the proposed Fixed Dose Combination (FDC) with monotherapies. In addition, the following clinical pharmacology studies were conducted to support this application: A single dose drug interaction study, multiple dose Pharmacokinetic / pharmacodynamic (PK/PD) and tolerability study, food effect study, PK bridging study between FDC used in the clinical trial and the free combination, strength proportionality study of FDC, and finally a bioequivalence (BE) study to compare the clinical trial FDC and the to-be-marketed FDC formulation.

	Information		Information
NDA/BLA Number	206302	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	I	Generic Name	(nebivolol/valsartan), tablets
Medical Division	DCRP	Drug Class	Anti-hypertensive
OCP Reviewer(s)	Bilal AbuAsal	Indication(s)	Hypertension
OCP Team Leader	Raj Madabushi	Dosage Form/Strength	Tablets/ Nebivolol / valsartan FDC is available as 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg tablets for oral administration.
Pharmacometrics Reviewer	Martina Sahre	Dosing Regimen	Once daily
Date of Submission	24 February 2014	Route of Administration	Oral
Estimated Due Date of OCP Review	24 October 2014	Sponsor	Forest Laboratories, Inc.
AC Meeting	08 September 2014	Priority Classification	Standard
PDUFA Due Date	24 December 2014		

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			

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Reference Bioanalytical and Analytical Methods	x	3		3 analytical methods were used. There are 24 bio-analytical reports
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x	6		NAC-PK-01, NAC-PK-03, NAC-PK-04, NAC-PK-05, NAC-PK-06, NAC-PK-07.
Healthy Volunteers-				
single dose:				
multiple dose:	x			NAC-PK-03 (Evaluate the PK and PD interaction between nebivolol and valsartan at steady state and to determine the safety and tolerability of concomitantly administered multiple doses of nebivolol and valsartan in healthy subjects)
Patients-				
single dose:				
multiple dose:	x			NAC-MD-01 (PK samples were collected from this study)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x			NAC-PK-06 (Characterize the Pharmacokinetics and assess dose proportionality of nebivolol and valsartan following once daily administration of the FDC of Nebivolol and valsartan)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x			NAC-PK-01(Evaluate the PK interaction between nebivolol and valsartan and to determine the safety and tolerability of concomitantly administered single doses of Nebivolol and valsartan in healthy subjects)
In-vivo effects of primary drug:	x			NAC-PK-01
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				

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

Phase 3:	x	2		NAC-MD-01 (Evaluate the efficacy and safety of an FDC of nebivolol and valsartan compared to the monotherapy components and placebo in patients with stage 1 or stage 2 essential hypertension) NAC-MD-02 (Evaluate the long-term safety of nebivolol and valsartan given as a free tablet combination in patients 18 years and older with stage 1 or 2 essential hypertension)
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	2		NAC-MD-01 (Evaluate the efficacy and safety of an FDC of nebivolol and valsartan compared to the monotherapy components and placebo in patients with stage 1 or stage 2 essential hypertension) NAC-MD-02 (Evaluate the long-term safety of nebivolol and valsartan given as a free tablet combination in patients 18 years and older with stage 1 or 2 essential hypertension)
Population Analyses -				
Pop PK	x			Population pharmacokinetic (PK) models were developed for valsartan, <i>d</i> -nebivolol, <i>l</i> -nebivolol and nebivolol glucuronide based on data from studies NAC-PK-01, NAC-PK-03, NAC-PK-04, NACPK- 05, NAC-PK-06, NAC-PK-07 and NAC-MD-01. Population PKPD models were developed from study NACMD-01 data. BP were described by inhibitory maximum effect (Emax) models with a parameter (α) to account for the interaction between the compounds
Pop PK/PD	x			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	x			
solution as reference:				
alternate formulation as reference:	x			NAC-PK-07 (Evaluate the BE of the current FDC formulation of nebivolol and valsartan and the new FDC formulation of nebivolol and valsartan)
Bioequivalence studies -				
traditional design; single / multi dose:	x			NAC-PK-07, NAC-PK-05(Compare the systemic exposures following administration of a FDC tablet of nebivolol and valsartan versus the coadministration of separate nebivolol and valsartan tablets)
replicate design; single / multi dose:	x			
Food-drug interaction studies	x			
Bio-waiver request based on BCS				
BCS class				

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Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				The sponsor asked for a waiver
Literature References	x			
Total Number of Studies	8	5		

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			NAC-PK-07. ONDQA will review this study
2	Has the applicant provided metabolism and drug-drug interaction information?	x			This is a 505(b)(2) submission. The applicant conducted PK interaction study between valsartan and neбиволол (NAC-PK-01).
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	Factorial Design
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			
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?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		x		Descriptive analysis assessed CYP2D6 metabolizer status for neбиволол exposure
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-	x			

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

	response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		Waiver requested
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		x		Waiver requested
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

Bilal AbuAsal

04/11/2014

Reviewing Clinical Pharmacologist

Date

Raj Madabushi

04/11/2014

Team Leader/Supervisor

Date

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

/s/

BILAL S ABU ASAL
04/11/2014

RAJANIKANTH MADABUSHI
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