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Forest Laboratories, Inc., a subsidiary of Actavis plc
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

Advisory Committee Briefing Book

Nebivolol/Valsartan Fixed-Dose Combination

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3.0 LIST OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
AE	adverse event
AERS	adverse event reporting system
ARB	angiotensin II receptor blocker
AUC	area under the plasma concentration versus time curve
BP	blood pressure
C_{max}	maximum plasma drug concentration
CV	cardiovascular
DBP	diastolic blood pressure
ECG	electrocardiogram
FDA	US Food and Drug Administration
FDC	fixed-dose combination
FRI	Forest Research Institute, Inc.
HCTZ	hydrochlorothiazide
HF	heart failure
HR	hazard ratio
ITT	intent to treat
LSM	least squares mean
MI	myocardial infarction
MMRM	mixed model for repeated measurement
msDBP	mean seated diastolic blood pressure
msSBP	mean seated systolic blood pressure
NDA	New Drug Application

OR	odds ratio
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRA	plasma renin activity
QTc	QT interval correct for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RAAS	renin-angiotensin-aldosterone system
SAE	serious adverse event
SBP	systolic blood pressure
TEAE	treatment-emergent adverse event

4.0 EXECUTIVE SUMMARY

The nebivolol/valsartan fixed-dose combination (FDC), studied in a development program of almost 5000 hypertensive patients, demonstrates a favorable benefit-risk profile for all doses of nebivolol and valsartan administered in combination. For patients with hypertension, this provides the first and only FDC of a β-blocker and an angiotensin II receptor blocker (ARB), and does so in a range of combinations that will allow prescribers to tailor therapy to an individual patient's needs. Nebivolol and valsartan are both FDA-approved, alone and in combination, for the treatment of hypertension, and their safety and efficacy profiles have been well defined by their extensive use in clinical practice. Building on that basis, this development program demonstrated the efficacy, safety, and tolerability of the nebivolol/valsartan FDC.

Hypertension is the most frequently diagnosed cardiovascular (CV) disease in the United States and its prevalence continues to rise. Despite the plethora of effective treatment options available, most patients continue to have uncontrolled hypertension. Noncompliance with prescribed treatments has been frequently cited as a major factor associated with the high prevalence of uncontrolled hypertension. As most patients with hypertension remain largely asymptomatic until major health consequences occur, tolerability of antihypertensive medications is critical to long-term treatment compliance.

Most patients with hypertension require more than 1 medication to achieve blood pressure (BP) control, and the combination of 2 medications with different mechanisms of action is likely to result in a greater reduction in BP. Furthermore, this approach of combining low to moderate doses of 2 medications may allow for better tolerability in comparison to the use of higher doses of a single agent. Thus, for those patients who need more than 1 drug to achieve BP control (eg, those with stage 2 hypertension), a valuable treatment approach is with an FDC of 2 drugs.

Moreover, the utility of antihypertensive FDCs in improving overall compliance to the prescribed treatment regimen has been well established. Treatment with FDCs of 2 medications has been associated with better BP control, improved tolerability (via fewer adverse events [AEs]), and better compliance compared with the use of higher doses of 1 of the components alone. Hence the addition of an FDC of 2 widely used, well-tolerated individual therapies would be of significant value in the armamentarium of the prescribing physician. Finally and importantly, FDCs represent combinations of antihypertensive medications that have been systematically well examined, resulting in more predictable treatment results compared with free-tablet combinations.

Free-tablet combinations of a β-blocker and an ARB are highly prescribed and this combination is used by approximately 2.4 million hypertensive patients in the United States. Despite this frequent coadministration of a β-blocker and an ARB, there is currently no FDC approved which is comprised of these 2 drug classes. The valsartan/nebivolol combination represents the first FDC of a β-blocker and an ARB, containing 2 well-established, safe, well-tolerated, and effective drugs, and is intended to be used as initial, add-on, or replacement therapy for the treatment of hypertension.

The clinical development program for the nebivolol/valsartan FDC comprised 2 Phase 3 clinical studies that included approximately 5000 patients: NAC-MD-01, an 8-week, double-blinded, placebo-controlled, factorial study; and NAC-MD-02, a 52-week, open-label, titrate-to-goal, long-term, safety study. Study NAC-MD-01 fulfilled the regulatory "combination rule" and demonstrated statistically significantly greater reductions in BP for patients treated with FDC 20/320 mg as compared with patients treated with maximum-dose monotherapies (nebivolol 40 mg, valsartan 320 mg), thereby showing that each component contributed to the effect of the FDC. This efficacy comparison was particularly stringent, as nebivolol 40 mg (which is rarely used in clinical practice [< 1%]) is double the dose of the nebivolol component of this FDC (20/320 mg).

Study NAC-MD-01 was also prospectively designed to examine the clinical efficacy of 4 other FDC doses of nebivolol and valsartan (5/80 mg, 5/160 mg, 10/160 mg, and 10/320 mg) in stepwise analyses. The totality of the data from the assessments of diastolic blood pressure (DBP) and systolic blood pressure (SBP) responses for each of the 5 FDCs compared to the individual nebivolol and valsartan components provides ample evidence of the clinically meaningful treatment improvements across the most frequently clinically utilized doses of these agents in the United States. Moreover, greater percentages of patients achieved BP control with FDC treatment than with the corresponding monotherapies, with statistical significance. These positive findings are supported by the maintenance of ambulatory BP reductions over the 24-hour dosing period and BP reductions observed in the long-term study, NAC-MD-02, that are comparable to those observed in the double-blind, controlled study, NAC-MD-01.

Data from both studies show the nebivolol/valsartan combination to be safe and well tolerated. The Safety Population of Study NAC-MD-01 consisted of 4159 patients. There was a low incidence of serious adverse events (SAEs), AEs, premature discontinuations due to any reason, or discontinuations due to AEs in this study, as was expected based on the well-known safety profiles of the individual monotherapies. Rates of AEs in FDC groups in Study NAC-MD-01 were not dose-dependent and were similar to rates observed in monotherapy and even placebo groups. These findings are supported by the long-term safety study, NAC-MD-02, which demonstrated the safety of nebivolol and valsartan when used in combination over 52 weeks of treatment. In this long-term study, 807 patients were administered nebivolol and valsartan, and there was a low incidence of SAEs, AEs, or discontinuations due to AEs. There was also a low incidence of β-blocker-typical AEs (eg, bradycardia, erectile dysfunction, fatigue, weight gain), which is in line with prior monotherapy trials of nebivolol. The overall safety profile was as favorable, or even more favorable with respect to some events, than the safety profile of each of the individual therapies. No new AEs were reported that were not already described in the nebivolol or valsartan package inserts.

In summary, this Phase 3 program, which studied almost 5000 hypertensive patients, demonstrates a favorable benefit-risk profile of all doses of nebivolol and valsartan administered in combination. This treatment is the first and only FDC of a β-blocker and an ARB, both widely used drug classes for hypertension, in a number of combinations that will allow for flexible dosing to tailor therapy to the needs of the individual patient.

5.0 INTRODUCTION

Hypertension is the most frequently diagnosed CV disease in the United States. Hypertensive disease continues to demonstrate an increasing prevalence and, as such, remains one of the most important preventable contributors to morbidities and mortality (Go et al, 2014; James et al, 2014). A multiplicity of therapies exist for the treatment of hypertension, however, despite the array of options, many patients still do not achieve adequate BP control (Gu et al, 2012). This lack of control is in part driven by a lack of treatment compliance, of which tolerability and pill burden are considered to be major factors. Adherence and persistence, or the degree to which a patient correctly and persistently follows a treatment regimen is herein used as "compliance." An FDC of 2 well tolerated individual therapies that are commonly coadministered should increase compliance and thus be of high value for both patients and physicians. Nebivolol and valsartan are 2 commonly coadministered safe, well tolerated, and effective treatments; however currently there is no FDC comprising these drug classes. The nebivolol/valsartan FDC will be the first FDC of a β-blocker and an ARB.

5.1 RATIONALE FOR FIXED-DOSE COMBINATION OF NEBIVOLOL AND VALSARTAN

Both nebivolol and valsartan are approved for the treatment of hypertension and are highly utilized in many countries including the United States. The drugs have well-established safety and efficacy profiles, both as monotherapy and in combination with other agents as free-tablet combinations. Thus, combining these 2 approved agents into a single tablet results in an FDC that is safe, effective, and provides the compliance advantages observed with FDCs in the treatment of hypertension.

5.1.1 Value for Fixed-Dose Combination Antihypertensive Therapy

The value of combination antihypertensive treatment has been highlighted in multiple sets of guidelines (Gradman et al, 2010; Mancia et al, 2013; Weber et al, 2014), including a recommendation to consider 2 drugs as initial therapy in patients with stage 2 hypertension (Chobanian et al, 2003). More than 75% of hypertensive individuals cannot have their BP controlled by 1 drug and require 2 or more antihypertensive agents (National Institutes of Health, 2004). The combination of 2 antihypertensive drugs is likely to cause a greater reduction in BP than would an increase in the dose of a single agent (Wald et al, 2009).

Providing combination therapy as an FDC is known to lead to greater treatment compliance than to free-tablet combinations of the same medications. Lack of compliance, known to lead to poor BP control, is driven, in part, by pill burden and poor tolerability (Fung et al, 2007; Gradman et al, 2010; Pimenta and Oparil, 2008). Database analyses have found that patients on single-tablet FDCs have a 24% higher rate of compliance compared with patients on the same medications as 2 separate tablets (Bangalore et al, 2007; Dezii, 2000). Thus, an FDC of antihypertensive agents represents a therapeutic alternative to free-tablet combinations and, importantly, simplifies treatment (Burnier, 2006).

Treatment compliance is also driven by the medication's tolerability. Since hypertension is an asymptomatic disease, any drug-associated side effect will have a magnified impact on a patient's willingness to comply with therapy (Osterberg and Blaschke, 2005). For example, up to 37% of patients are noncompliant with antihypertensive therapy due to AEs (Dusing et al, 1998; Lip and Beevers, 1997; Vawter et al, 2008; Wilinski and Dabrowski, 2013), and patients who report AEs are twice as likely to discontinue therapy (Elliot, 2009). An FDC that combines 2 agents from different pharmacological classes is likely to have fewer AEs compared to full-dose monotherapy (Mancia, 2007), and therefore is more likely to improve compliance through better tolerability.

Overall, the use of antihypertensive FDCs compared with higher doses of the monotherapy components has been associated with improved BP control, lower rates of AEs, lower healthcare costs, and improved drug compliance (Bangalore et al, 2007; Sherrill et al, 2011). Moreover, FDCs, representing drugs which have been studied extensively in combination, result in more predictable treatment effects.

5.1.2 Utilization of β-Blockers and Angiotensin II Receptor Blockers in the United States

Currently, in the United States, β-blockers and ARBs are frequently coadministered to treat hypertension. Utilization data show that approximately 2.4 million of the 57 million hypertensive patients in the United States prescribed antihypertensive treatment receive both a β-blocker and an ARB (IMS, April 2014 data on file, Forest Research Institute, Inc. [FRI]). Beta-blockers are among the most widely prescribed agents for the treatment of hypertension, with an estimated 13 million patients in the United States on a β-blocker for hypertension (IMS, 2014 data on file, FRI). Prescribing information for β-blockers and for ARBs allow for combination therapy with a drug from the other class (Bystolic, 2014; Diovan, 2014). A separate analysis determined that 35% of patients on nebivolol are concomitantly taking an ARB (IMS, April 2014 data on file, FRI). These data highlight the current unmet need for coadministering a β-blocker with an ARB as a single pill.

The 5 FDC doses examined in the nebivolol/valsartan program encompass the most frequently administered doses of nebivolol and valsartan in the United States currently, and include the starting doses and the highest-utilized doses for each component.

5.1.3 Pharmacologic Rationale for the Combination of Nebivolol and Valsartan

The mechanisms for lowering BP of these 2 agents are distinctive and are expected to produce additive results. Nebivolol decreases heart rate, myocardial contractility, and sympathetic outflow, and is vasodilatory via nitric oxide effects on the endothelium, whereas valsartan lowers BP mainly by blocking the vasoconstrictor effects of angiotensin II. Nebivolol also decreases renin release in the kidney, thereby attenuating the effect of valsartan to increase plasma renin activity (PRA) and angiotensin II.

Pharmacologic data confirm the validity of combining nebivolol and valsartan for the treatment of hypertension. Increased PRA is an indicator of an activated renin-angiotensin-aldosterone system (RAAS), vasoconstriction, and elevated BP. Data from this program show that valsartan alone increased PRA while nebivolol alone inhibited PRA, and coadministration of nebivolol prevented the reactive rise in PRA observed with valsartan. Plasma aldosterone levels were also lower following the administration of the combination as compared with nebivolol or valsartan monotherapy treatment. Furthermore, these changes in concentration of biomarkers were associated with reductions in BP, suggesting that these mechanistic changes have a role in the antihypertensive effect from the coadministration of nebivolol and valsartan (Study NAC-MD-01; Study NAC-PK-03).

In the presence of valsartan, approximately 50% and 20% reductions in the nebivolol maximum plasma drug concentration (C_{max}) and area under the plasma concentration versus time curve (AUC), respectively, are observed. Based upon this observed pattern of reductions in exposure of nebivolol, a favorable safety and tolerability profile, without meaningful impingement on BP lowering, is expected (see exposure-response analysis, Section 7.5.3; Study NAC-PP-01).

5.1.4 Components of the Nebivolol/Valsartan Fixed-Dose Combination

5.1.4.1 Nebivolol

Nebivolol is a highly selective β1-adrenergic (cardioselective) receptor antagonist (Bristow et al, 2005). The cardioselectivity of nebivolol (particularly at doses < 20 mg) spares the off-target AEs associated with β2-adrenergic receptor antagonism. Its mechanisms of actions include a number of distinct properties including possible factors of decreased heart rate, decreased myocardial contractility, decreased sympathetic outflow, suppression of renin release in the kidney, and vasodilatation that leads to decreased peripheral vascular resistance (Bystolic, 2014). The vasodilation is mediated through the L-arginine/nitric oxide pathway and an endothelium-dependent mechanism (Bowman et al, 1994; Cockcroft et al, 1995; Gupta and Wright, 2008; Rozec et al, 2009). Although the relative contributions of these mechanisms to the BP-lowering effect of nebivolol have not been definitively established, it is clear that nebivolol has pharmacological properties and β1-selectivity that distinguish it from other β-blockers (Bowman et al, 1994; Bristow et al, 2005; Cockcroft et al, 1995; Tzemos et al, 2001). Older β-blockers such as atenolol and metoprolol, although β1-selective, lack the ability to vasodilate, whereas more recent vasodilatory β-blockers such as carvedilol are nonselective adrenergic receptor blockers.

Data show that properties of nebivolol translate into clinically relevant, hemodynamic changes. For example, in a study in patients with mild-to-moderate hypertension that compared nebivolol with atenolol, both agents reduced brachial BP to a similar extent. However, nebivolol was associated with a decrease in peripheral vascular resistance and a significant increase in stroke volume, with maintenance of cardiac output. In contrast, atenolol was associated with an increase in peripheral vascular resistance and a reduction in cardiac output (Kamp et al, 2003). Similar findings have been demonstrated in hypertensive patients with heart failure (HF) (Nodari et al, 2003).

Additionally, nebivolol's effects on centrally assessed BP, which is a better predictor of CV events than is brachial BP (McEniery et al, 2014), have been examined. For example, in hypertensive patients treated with either nebivolol or atenolol, both agents reduced brachial BP similarly; however, nebivolol reduced aortic pulse pressure and augmentation index to a greater extent than did atenolol (Dhakam et al, 2008; Mahmud and Feely, 2008). Collectively, these data clearly distinguish nebivolol from previously developed β-blockers and support its clinical efficacy coupled with a highly favorable safety and tolerability profile.

The nebivolol United States registration hypertension program, consisting of 2016 patients, demonstrates the safety and efficacy of nebivolol in lowering BP (Bystolic, 2014). At the recommended starting dosage of nebivolol (5 mg once daily), placebo-corrected reductions in seated SBP were 2.6 to 8.1 and in seated DBP were 3.2 to 5.5 mm Hg. Increasing responses to increasing nebivolol doses above 5 mg were observed, with maximum placebo-corrected reductions in SBP/DBP of 11.7/8.3 mm Hg. Throughout clinical trials, nebivolol was well tolerated with a low incidence of β-blocker class related AEs at the commonly prescribed doses (Bystolic, 2014). Moreover, there were no safety issues with nebivolol administered alone or in combination with other antihypertensive medications, including RAAS agents such as angiotensin-converting enzyme (ACE) inhibitors and ARBs.

The worldwide clinical trial exposure to nebivolol comprises 6545 patients, including a large CV outcomes study in elderly patients with HF (further described in Section 5.1.4.1.4). Of those 6545 patients, 5038 patients were treated for hypertension. In this group of trials, patients received nebivolol for up to 24 months, with over 1900 patients treated for at least 6 months, and approximately 1300 patients treated for > 1 year. Thus, as demonstrated in multiple settings, nebivolol has a well-established safety and tolerability profile, similar to that of placebo.

Nebivolol was approved by the FDA in 2007 as a vasodilatory β-blocker for the treatment of hypertension at doses of 5, 10, 20, and 40 mg; a 2.5 mg dose is available as a starting dose for patients with renal or hepatic insufficiency (Bystolic, 2014). It should be noted that the 40 mg dose is used in < 1% of patients, and thus this dosage is not manufactured or marketed. Nebivolol is approved for this indication in 80 countries.

5.1.4.1.1 Further Experience with Nebivolol

A meta-analysis of 12 randomized controlled trials provides useful efficacy and safety information in which low-dose nebivolol (5 mg/day) was compared with the recommended doses of other antihypertensive drugs, placebo, or both. Response rates (percentage of patients achieving target BP or a defined DBP reduction) were higher with nebivolol than with all antihypertensive drugs combined (odds ratio [OR] 1.41; $p = 0.001$). A higher percentage of patients receiving nebivolol achieved target BP levels (BP < 140/90 mm Hg or DBP < 90 mm Hg) compared with patients receiving all antihypertensive drugs combined (OR 1.35; $p = 0.012$). The percentage of patients experiencing AEs did not differ between nebivolol and placebo; AE rates were significantly lower with nebivolol than with all antihypertensive drugs combined (OR 0.59; $p < 0.001$) (Van Bortel et al, 2008).

5.1.4.1.2 Postmarketing Experience with Nebivolol

Nebivolol was first launched in Europe in 1997 for the treatment of hypertension and in 2005 for the treatment of chronic HF. Nebivolol was launched in the United States in 2008 for the treatment of hypertension. Per IMS data (IMS MIDAS, July 2014 data on file, FRI), the cumulative worldwide exposure of nebivolol from Q2 2002 to Q1 2014 is estimated to be 40 million patient-years.

As a result of the extensive postmarketing exposure, substantial data have been acquired on the safety of nebivolol. A search of the FDA adverse event reporting system (AERS) database was conducted to retrieve AEs reported with nebivolol treatment. Cumulatively through Q2 2013, a total of 1860 unique cases were retrieved and, to note, these are spontaneously reported cases. Approximately 55% of the patients were female, and 41% of the patients were > 65 years of age. The 10 most commonly reported AEs were: fatigue (128 events), bradycardia (128 events), dizziness (121 events), dyspnoea (114 events), headache (101 events), drug interaction (101 events), blood pressure increased (99 events), edema peripheral (95 events), hypotension (86 events), and heart rate decreased (72 events). These numbers of events can be viewed in the context of 40 million patient-years of nebivolol treatment.

5.1.4.1.3 Concomitant Treatment with Nebivolol and RAAS Blockers

The efficacy and safety of combining nebivolol and a RAAS blocker has been established in multiple studies, thereby contributing to the basis of the nebivolol/valsartan FDC program.

In Study NEB-MD-321, 669 patients with mild to moderate hypertension who were taking at least 1, but no more than 2, of an ARB, an ACE inhibitor, or a diuretic, were randomized to receive nebivolol or placebo once daily for 12 weeks in addition to continuing their background antihypertensive therapy. In the patients receiving background therapy with an ARB only (including valsartan), the addition of nebivolol led to greater reductions in seated trough SBP (3.5 to 6.2 mm Hg) and DBP (2.7 to 4.0 mm Hg) compared with patients on an ARB without nebivolol. Moreover, adding nebivolol significantly increased the proportion of patients attaining BP treatment goals (53% to 65.1%) compared with placebo (41.3%; $p < 0.028$), and in simultaneously meeting systolic and diastolic BP goals (41.3% to 52.7%) compared with placebo (29.3%; $p < 0.029$). The incidence of AEs with nebivolol was similar to that with placebo (40.2% vs 38.9%, respectively). In the subset of patients receiving background ARB therapy, the rates of AEs were similar between nebivolol- and placebo-treated patients (31.5% and 30.6%, respectively). Among nebivolol-treated patients, there were no new AEs noted that were not already known to be associated with either agent administered as monotherapy (IMS, 2010 data on file, FRI; Neutel and Smith, 2010).

In Study NEB-MD-25, 1126 patients with stage 2 hypertension were randomized to receive nebivolol, lisinopril, or combination therapy with both drugs. Doses were titrated if patients did not achieve goal BP (SBP/DBP < 130/80 mm Hg in diabetics, < 140/90 mm Hg for non-diabetics). The least-squares mean (LSM) difference for DBP between the combination of nebivolol and lisinopril vs placebo (9.0 mm Hg), vs nebivolol alone (3.3 mm Hg), and vs lisinopril alone (5.1 mm Hg) met statistical significance for these comparisons ($p < 0.001$). Results were similar for SBP reductions for nebivolol and lisinopril combination treatment, meeting significance vs placebo (10.0 mm Hg, $p < 0.001$) and vs nebivolol alone (3.5 mm Hg, $p < 0.05$), but not vs lisinopril (3.2 mm Hg, $p = 0.0704$). The rate of achieving BP goal in patients receiving combination therapy was 33.9%, which was significantly greater than vs placebo (7.5%; $p < 0.0001$), vs nebivolol alone (21.6%; $p = 0.003$), or vs lisinopril alone (21.7%; $p = 0.0031$). Both nebivolol monotherapy and the combination of nebivolol plus lisinopril exhibited safety and tolerability; for example, rate of SAEs was lower in the combination therapy group (1.1%) than in placebo (2.1%), nebivolol (1.6%), or lisinopril (2.1%) groups (Weber et al, 2012).

5.1.4.1.4 Nebivolol Use in Other Populations

Nebivolol has been shown to provide beneficial and safe effects in patients with other CV conditions such as HF.

One such study, SENIORS, evaluated mortality and morbidity endpoints in 2135 elderly HF patients (mean age 76 years; left ventricular ejection fraction < 0.35 and/or history of HF), treated with nebivolol or placebo in addition to background therapy (Flather et al, 2005). More than 80% of patients were also on an ACE inhibitor or an ARB. In this double-blind, randomized trial, a 14% reduction was demonstrated in all-cause mortality or CV hospital admission for patients treated with nebivolol compared with placebo (hazard ratio [HR] 0.86; $p = 0.039$). Nebivolol treatment also led to reductions in CV mortality or CV hospitalization by 16% (HR 0.84; $p = 0.027$). The number of patients experiencing an AE was similar between nebivolol and placebo groups (85.4% vs 84.8%). In fact, a slightly lower number of nebivolol patients (40.5%) experienced an SAE compared to placebo (44.1%). Safety data from this study, and from other supportive trials (Dobre et al, 2007), indicate that nebivolol is a well-tolerated β-blocker with a favorable safety profile, even in this highly susceptible patient group.

Nebivolol has demonstrated efficacy and safety in multiple groups, including African-American/Black, Hispanic/Latino, and elderly patients (Bystolic, 2014; Saunders et al, 2007; Punzi et al, 2010).

5.1.4.2 Valsartan

Valsartan is a specific ARB, acting on the angiotensin II type 1 receptor subtype (Black et al, 2009). Angiotensin II, a principal agent of the renin-angiotensin system, acts at multiple levels (eg, vasculature, sympathetic nervous system, adrenal gland) to increase vascular resistance and BP. Valsartan acts by blocking the angiotensin II type 1 receptor subtype, which mediates essentially all currently known effects of angiotensin II (Diovan, 2014). The efficacy, tolerability, and safety of valsartan have been demonstrated in multiple studies in patients with hypertension as well as with other CV diseases for which it is also approved, such as HF and post-myocardial infarction (MI).

For hypertensive patients, valsartan should be administered once-daily, as the antihypertensive effects are sustained over a full 24-hour period. Following daily administration, its antihypertensive effect is substantially present within 2 weeks and maximal reduction is attained after 4 weeks (Diovan, 2014).

Valsartan has been assessed as safe and effective in a number of hypertensive patient populations; including elderly patients (> 65 years of age), diabetic patients, patients with chronic kidney disease, patients at high risk of CV disease, and African Americans/Blacks (Black et al, 2009; Diovan, 2014). Valsartan has been approved to be used in combination with other antihypertensive drugs and has been utilized in a number of FDCs.

Valsartan has been prospectively evaluated in more than 4000 hypertensive patients, including over 400 treated for over 6 months, and more than 160 treated for over 1 year. In total, valsartan has been investigated in more than 60 clinical studies involving over 100,000 patients. More than 50,000 patients have been enrolled in trials involving treatment with valsartan and assessing CV morbidity and mortality outcomes (Black et al, 2009).

Valsartan is approved by the FDA (1996) for the treatment of hypertension at doses of 80, 160, and 320 mg; no initial dose adjustment is required for patients with mild or moderate renal or hepatic insufficiency. It is approved for this indication in > 100 countries.

5.1.4.2.1 Clinical Studies (Hypertension)

The antihypertensive effects of valsartan have been demonstrated principally in 7 placebo-controlled, 4 to 12 week trials using doses ranging from 10 to 320 mg/day. These studies included over 2000 patients randomized to valsartan and approximately 800 patients randomized to placebo. Effects at doses < 80 mg were not consistently distinguished from those of placebo at trough. Doses of 80, 160, and 320 mg produced dose-related decreases in SBP and DBP, with statistically significant differences in SBP/DBP from placebo of approximately 6 to 9/3 to 5 mm Hg at 80 to 160 mg and 9/6 mm Hg at 320 mg (Diovan, 2014).

Furthermore, valsartan is approved as FDCs of valsartan and amlodipine, valsartan and hydrochlorothiazide (HCTZ), and valsartan/amlodipine/HCTZ. In a study of the FDC of valsartan and amlodipine in 944 patients with mild to moderate hypertension, assessments were made after 8 weeks of therapy. Treatment effects between amlodipine/valsartan 10/160 mg FDC and amlodipine 10 mg monotherapy were SBP/DBP reductions of 2.9/2.1 mm Hg.

Registration studies of valsartan have shown safety findings including adverse reactions that generally have been mild, transient, and only infrequently requiring discontinuation of therapy. The incidence of adverse reactions with valsartan is similar to placebo. The frequency of adverse reactions is not related to dose, gender, age, race, or regimen. The most common reasons for discontinuation of valsartan are headache and dizziness. Dose-related orthostatic effects are seen in fewer than 1% of patients. Patients treated with valsartan 320 mg have an increased incidence of dizziness (8%) compared to those receiving doses of 10 mg to 160 mg (2% to 4%) (Diovan, 2014).

5.1.4.2.2 Clinical Studies (Mortality and Morbidity Outcomes Trials)

Benefits of valsartan have been demonstrated in 3 large-scale outcome trials in patients with hypertension, HF, and following a recent MI.

In over 15,000 hypertensive patients at high risk for CV events randomized to either valsartan or amlodipine in the VALUE trial, the rates of first cardiac event were similar between treatment groups over a mean 4.2-year follow-up. The frequency of AEs was low in the valsartan-treated patients. Of relevant interest, 48% of patients in the valsartan group were also on a β-blocker (Julius et al, 2004).

In a randomized, controlled trial of over 5000 patients with chronic HF (Val-HeFT), valsartan treatment was compared with placebo in patients on standard-of-care therapy; valsartan significantly reduced all-cause mortality by 13% over a mean follow-up of 23 months ($p < 0.05$). Valsartan treatment was generally well tolerated. AEs leading to discontinuation of study drug occurred in 249 of the patients receiving valsartan (9.9%) and 181 of the patients receiving placebo (7.2%). Of note, 34.5% of patients in the valsartan group were also taking a β-blocker (Cohn and Tognoni, 2001).

In a randomized, controlled trial of over 14,700 patients following an acute MI (VALIANT), valsartan demonstrated non-inferiority to the ACE inhibitor, ramipril, on rates of all-cause mortality over a mean follow-up of 25 months. Tolerability was better for the patients in the valsartan group compared with those in the ramipril group. Approximately 70% of patients were also taking a β-blocker (Pfeffer et al, 2003) and no evidence was found of adverse interactions between valsartan and β-blockers when analyzed separately from the overall population treated. In fact, patients treated with a β-blocker had lower 3-year mortality rate (17.7% to 30.7%) than patients who were not treated with a β-blocker (35.1%). These results further confirmed that β-blockers reduce the risk of death and nonfatal CV events in patients with HF or systolic left ventricular dysfunction post-MI (Califf et al, 2009).

5.1.4.2.3 Postmarketing Experience with Valsartan

Per IMS data (IMS MIDAS, July 2014 data on file, FRI), the cumulative worldwide exposure of valsartan from Q2 2002 to Q1 2014 is estimated to be 180 million patient-years. As a result of the extensive postmarketing exposure, a significant amount of data has been acquired on the safety of valsartan. A search of the FDA AERS database was conducted to retrieve AEs reported to valsartan.

Cumulatively through 14 October 2013, a total of 13,234 unique cases were retrieved. Approximately 55% of the patients were female and around 41% of the patients were elderly (> 65 years). The most commonly reported AEs were BP increased (793 events), hypertension (773 events), dizziness (747 events), death (659 events), dyspnoea (608 events), hypotension (515 events), malaise (476 events), cerebrovascular accident (475 events), fall (474 events), and headache (464 events). These numbers of events can be viewed in the context of 180 million patient-years of valsartan treatment.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. This review of safety data from the FDA AERS database showed that the safety profile of valsartan generally appeared to be consistent with its pharmacologic effects, the patient populations treated with valsartan (hypertension, HF, and post-MI) and/or the current labeling.

5.2 CLINICAL RELEVANCE OF BLOOD PRESSURE CONTROL AND BLOOD PRESSURE REDUCTIONS

The main goal of antihypertensive therapy is to attain and maintain goal BP (James et al, 2014), thereby reducing the risk of unfavorable outcomes. Current hypertension guidelines set the BP goal for most patients at < 140/90 mm Hg (James et al, 2014; Weber et al, 2014).

Although control of both systolic and diastolic BP is important, a review of the literature indicates that changes in SBP are a stronger predictor than changes in DBP for CV risk in most patients (He and Whelton, 1999; Leonetti el al, 2000; Mancia et al, 2002; Nielsen et al, 1997; Sega et al, 2005; SHEP Cooperative Research Group, 1991; Tin et al, 2002; Williams et al, 2008). However, it is also clear that concomitant reductions in both compartments of the BP are important. Reductions in SBP have been clearly associated with favorable reductions in CV events and are supported by multiple findings (Fagard et al, 2007; Leonetti et al, 2000; Nielsen et al, 1997; Rapsomaniki et al, 2014; Staessen et al, 2000; Tin et al, 2002). The smallest amount of mean SBP reduction associated with a distinct, favorable reduction in CV risk is regarded as 2 mm Hg (Gradman et al, 2013; Grossman, 2011; Lewington et al, 2002; Mancia, 2007; Sega et al, 2005; Stamler et al, 1991). As well, epidemiological data from the World Health Organization show that for every 1 mm Hg reduction in mean SBP across the United States population, approximately 10,000 coronary heart disease deaths could be prevented (Capewell et al, 2010).

With regards to the clinical meaningfulness of overall BP reductions, it is useful to consider a meta-analysis that compared different classes of antihypertensives on the prevention of CV events (Turnbull et al, 2003). This meta-analysis included 4 randomized, long-term studies in which ARB-based therapy was compared with the addition of either placebo or an active comparator. The meta-analysis demonstrated statistically significant, favorable reductions in CV events, even though only small additional reductions in BP were detected (mean reduction, SBP/DBP: 2/1 mm Hg).

6.0 PRODUCT DEVELOPMENT

6.1 OVERVIEW

The nebivolol/valsartan FDC clinical program consisted of 6 Phase 1 studies in healthy subjects and 2 Phase 3 studies in patients with stage 1 or stage 2 hypertension. These studies are tabulated in Appendix 1, Table 14–1.

The Phase 3 studies were a pivotal efficacy, 8-week study (Study NAC-MD-01) and an open-label, long-term 52-week safety study (Study NAC-MD-02). Approximately 5000 patients participated in these 2 studies. Study NAC-MD-01 was designed to fulfill requirements of the regulatory "combination rule" (ie, each component must demonstrate its contributions to the effects of the FDC) when compared to the highest approved monotherapy doses. This study utilized a standard factorial design to evaluate the use of this FDC as initial therapy. The design allowed for examination of multiple FDCs as well as providing information on the up-titration from lower to higher doses of these FDCs.

6.2 SELECTION OF DOSES FOR THE PHASE 3 PROGRAM

The doses of FDC studied in the Phase 3 program are nebivolol/valsartan 5/80, 5/160, 10/160, 10/320, and 20/320 mg. All of the doses of the nebivolol and valsartan components of these 5 FDCs include the most commonly prescribed doses of the monotherapies, including starting doses, in the United States. Nebivolol is marketed at doses of 2.5, 5, 10, and 20 mg. Nebivolol is approved up to a maximum dose of 40 mg, although the highest marketed dose is 20 mg; nebivolol 40 mg is not currently available, and this dose, which would require the administration of two 20 mg tablets, is rarely utilized (< 1%). The recommended starting daily dose for nebivolol is 5 mg in all patients, except those with severe renal impairment or moderate hepatic impairment, in whom the recommended starting daily dose is 2.5 mg. Valsartan is currently marketed in the United States at doses of 80, 160, and 320 mg. The recommended starting dose is 80 or 160 mg. Thus, the 5 FDCs examined in this Phase 3 program encompass the most frequently administered doses of nebivolol and valsartan in the United States currently, and include the starting doses and the highest-utilized doses for each component.

6.3 REGULATORY HISTORY

Forest has developed a FDC of nebivolol and valsartan and is seeking its approval for the treatment of hypertension. Both nebivolol (Bystolic) and valsartan (Diovan) are well tolerated, efficacious, and highly utilized antihypertensive agents, approved to be used alone or in combination with other classes of antihypertensive agents for the treatment of hypertension. NDA 21-742 was approved for nebivolol (Bystolic) on 17 Dec 2007, NDA 20-665 was approved for valsartan (Diovan capsules) on 23 Dec 1996, and NDA 21-283 was approved for valsartan (Diovan tablets) on 18 Jul 2001.

The nebivolol/valsartan FDC has been studied for the treatment of hypertension under Investigational New Drug 109,771 submitted to the Division of Cardiovascular and Renal Products on 27 May 2011. A pre-Investigational New Drug meeting took place on 15 Feb 2011, at which time the FDA indicated that each component must demonstrate its contributions to the effect of the FDC when compared to the highest approved monotherapy doses (the "combination rule" for approval of a FDC). Study NAC-MD-01 was conducted in accordance with this advice. Study NAC-MD-02 was a long-term safety trial utilizing a free-tablet combination, the use of which was justified by Study NAC-PK-05 which demonstrated bioequivalence between the 20/320 mg FDC and the coadministration of the separate 20 mg nebivolol and 320 mg valsartan tablets. FDA agreed that long-term safety data collected on the free-tablet combination would be adequate to support the approval of the FDC.

The application is covered under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, which allows the Sponsor to rely on the Agency's previous findings of safety and effectiveness for the listed drug Diovan (valsartan). The Sponsor is also relying on the Agency's previous findings of safety and effectiveness for Bystolic (nebivolol), for which the Sponsor is the owner of the approved NDA.

A Pre-NDA Meeting was granted for 12 Sep 2013 and following receipt of the premeeting comments the meeting was canceled. The nebivolol/valsartan FDC NDA was filed on 24 Feb 2014. Based on the positive results of Study NAC-MD-01, the Sponsor is seeking the following indications:

Add-on therapy: patients whose BP is not adequately controlled on monotherapy

Replacement therapy: the nebivolol/valsartan FDC may be substituted for the titrated components

Initial therapy: the nebivolol/valsartan FDC may be used as initial therapy in patients who are likely to need multiple drugs to achieve their BP goals

The proposed clinical doses, investigated in the nebivolol/valsartan FDC program, are 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg per day.

7.0 OVERVIEW OF CLINICAL PHARMACOLOGY

The clinical pharmacology of nebivolol and valsartan monotherapies has been well characterized (NDA 21-742; Bystolic, 2014; and Diovan, 2014). Therefore, the Sponsor is relying on FDA's previous findings of safety and effectiveness for the listed drugs to support the application. In addition, 6 Phase 1 studies were conducted in healthy subjects as well as population pharmacokinetic (PK) and PK/pharmacodynamic (PD) analyses in hypertensive patients, to supplement this information and to demonstrate bioequivalence between the FDC and coadministration of the individual components.

Based on the similar bioavailability of the FDC to coadministration of the individual components (Study NAC-PK-05), clinical pharmacology studies to evaluate the influence of intrinsic factors (age, gender, race, renal impairment, hepatic impairment) on PK properties, the potential for QTc prolongation, or further drug-drug interactions are not warranted for this program, as agreed upon with the FDA.

Main findings from Phase 1 studies as well as population PK and PK/PD analyses in hypertensive patients are summarized below, and study descriptions are presented in Appendix 1, Table 14–1. As documented in the pre-NDA meeting minutes, the FDA has agreed that the clinical pharmacology program was sufficient to support this application.

7.1 PHARMACOKINETICS

Following coadministration (single and multiple doses) of 20 mg nebivolol and 320 mg valsartan in healthy subjects, an approximately 50% reduction in C_{max} and an approximately 20% reduction in AUC, were observed for *d,l*-nebivolol, and the glucuronide metabolite compared with administration of nebivolol alone (see Appendix 1, Figure 14–1 for multiple-dose treatments). The valsartan C_{max} and AUC were approximately 20% lower with coadministration of 20 mg nebivolol compared with the administration of valsartan alone (Appendix 1, Figure 14–2). The more pronounced decrease in nebivolol C_{max} compared to AUC, the small change in the apparent clearance for coadministration compared to nebivolol alone, and the similar reductions in plasma exposure of nebivolol and its metabolites suggest that the PK interaction occurs at the absorption site rather than in the distribution or elimination phases (Study NAC-PK-01; Study NAC-PK-03).

This is supported by the concentration-time profiles of *d,l*-nebivolol following multiple-dose treatments on Day 7 (Appendix 1, Figure 14–1) that show differences in plasma exposure during the absorption phase, but similar mean profiles for the majority of the dosing interval, past the absorption phase.

Given the observed intersubject variability in nebivolol and valsartan PK (~50% coefficient variation), the observed PD effects of the combination (Study NAC-PK-03), modeling/simulation results (Study-NAC-PP-01, Section 7.5.2), and the results from the pivotal clinical studies (Study-NAC-MD-01), no clinically meaningful loss of BP-lowering effect was expected from the PK interaction with valsartan.

7.2 BIOEQUIVALENCE OF NEBIVOLOL/VALSARTAN FDC AND FREE-TABLET COMBINATION

Bioequivalence was demonstrated between the 20/320 mg FDC and the coadministration of the separate 20 mg nebivolol and 320 mg valsartan tablets, serving as the bridge between the FDC and the approved monotherapy products and substantiating that nebivolol/valsartan FDC may be substituted for the individual monotherapy components (Study NAC-PK-05). This justifies both the use of free-tablet combination in the long-term safety study, NAC-MD-02, and the replacement claim indication for the FDC.

7.3 OTHER PHARMACOKINETIC CHARACTERISTICS

Statistically significant differences in the rate and extent of exposure (AUC, C_{max}) were demonstrated for *d,l*-nebivolol (up to 15% increase in the presence of food), and valsartan (up to 15% decrease in the presence of food) but were of small magnitude, indicating that the minor food effect on exposure should not be clinically relevant (Study NAC-PK-04). These food effects are consistent with those seen for the nebivolol (Bystolic, 2014) and valsartan (Diovan, 2014) monotherapies, with no dosing adjustments due to food intake needed.

The PK of nebivolol, its metabolites, and valsartan were proportional over the dose ranges of nebivolol/valsartan 5/80 mg to 20/320 mg (Study NAC-PK-06).

7.4 PHARMACODYNAMICS

In the multiple-dose PK/PD interaction study with healthy subjects (Study NAC-PK-03), a sharp increase in mean Day 7 PRA and angiotensin II concentration occurred during the period when subjects received valsartan and was significantly attenuated in the period when nebivolol was concomitantly administered. Mean Day 7 24-hour urine aldosterone was substantially decreased after combined treatment as compared to either monotherapy treatment. The mean heart rate after treatment with nebivolol alone, and after the combined treatment, was consistently lower than the mean heart rate following valsartan monotherapy. SBP and DBP decreased after all treatments with the most pronounced effect observed following combined treatment.

In patients with stage 1 or 2 hypertension (Study NAC-MD-01), valsartan alone increased PRA while nebivolol alone inhibited PRA. Coadministration of nebivolol prevented the reactive rise in PRA observed with valsartan. Plasma aldosterone levels were also lower following the administration of the combination as compared with nebivolol or valsartan monotherapy treatment. Decreases in pulse rate from baseline were observed in the FDC and nebivolol treatment groups. Collectively, these PD results were consistent with the concomitant administration of a β-blocker and an ARB.

7.5 POPULATION PHARMACOKINETICS AND PHARMACOKINETIC-PHARMACODYNAMIC ANALYSES

7.5.1 Population Pharmacokinetics

Population PK analysis used data from 7 clinical studies (6 Phase 1 and 1 Phase 3) in healthy adults and patients with stage 1 and 2 hypertension for *d*-nebivolol, *l*-nebivolol, glucuronide, and valsartan. The PK Population included 254 healthy volunteers (135 male, 119 female) from Phase 1 trials and 639 patients (371 male, 268 female) with stage 1 and 2 hypertension from the Phase 3 Study NAC-MD-01. The PK of *d*-nebivolol, *l*-nebivolol, and valsartan were well described by 2-compartment models with first-order absorption. The glucuronide data were well described by a 2-compartment model with a combined zero and first-order absorption model. Among the covariates that were of statistical significance, the main predictors for AUC and/or C_{max} at steady state were cytochrome P-450 isoenzyme 2D6 (CYP 2D6) genotype followed by valsartan coadministration for *d*-nebivolol, *l*-nebivolol, and the glucuronide, followed by study phase (Phase 3 studies versus Phase 1 studies) for valsartan.

7.5.2 Exposure-Response Analysis to Explore the Impact of Pharmacokinetic Drug Interaction on Expected Blood Pressure Lowering Effect

In healthy subjects, coadministration of valsartan reduced mean *d,l*-nebivolol C_{max} and AUC by approximately 50% and 20%, respectively. Therefore, data from nebivolol monotherapy in hypertensive patients were used to assess any potential clinical impact of the reduced nebivolol exposures, when coadministered with valsartan, on reducing DBP. A saturable E_{max} model best described the relationship between *d,l*-nebivolol observed concentrations and DBP measurement in hypertensive patients. Simulations were performed over a range of reductions in C_{max} at steady state (20%-80%) and average plasma concentration at steady state (20%-50%) for approved nebivolol doses of 5, 10, and 20 mg. Simulation results for 20% reduction in average plasma concentration at steady state at 5, 10, and 20 mg nebivolol doses indicated a median (95% CI) decrease in the typical DBP treatment effect (mm Hg) of 0.049 (0.012, 0.12), 0.026 (0.0063, 0.066), and 0.013 (0.0032, 0.035), respectively. Simulation results for 50% reduction in C_{max} at steady state at 5, 10, and 20 mg nebivolol doses indicated a median (95% CI) decrease in the typical DBP treatment effect (mm Hg) of 0.05 (0.012, 0.13), 0.025 (0.006, 0.069), and 0.013 (0.003, 0.035), respectively. Based on the results of this study, no clinically meaningful effect on the DBP-lowering effect of nebivolol was expected from the PK interaction with valsartan (Study NAC-PP-01).

7.5.3 Exposure-Response Analysis for Stage 1 and 2 Hypertension

Population exposure-response models were developed from Study NAC-MD-01 data. Models were developed for both seated cuff-measured BP and 24-hour ambulatory-measured BP (DBP and SBP). The exposure-response population included 761 patients (442 male, 319 female) for the seated cuff-measured BP and 746 patients (436 male, 310 female) for ambulatory-measured BP. The BP-lowering drug effects of nebivolol and valsartan for the seated cuff-measured and 24-hour ambulatory-measured BP were described by E_{max} models with a parameter (α) to account for the interaction between the compounds. The exposure-response relationships were statistically significant in the valsartan and nebivolol monotherapy arms as well as in all FDC arms.

The model was used to further simulate possible combinations of dosages in monotherapy and dual combination therapy, including that of dosing strengths (eg, nebivolol 20 mg and nebivolol/valsartan FDC 40/320 mg at Week 8) that were not studied in Study NAC-MD-01. The model-predicted change from baseline in DBP and SBP demonstrated that all FDC doses (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, 20/320 mg, and 40/320 mg) had greater BP reductions compared with their monotherapy components. SBP and DBP reductions when compared with FDC 20/320 mg versus nebivolol 20 mg at Week 8 were –2.5/–2.2 mm Hg (Study NAC-MS-01/02).

8.0 OVERVIEW OF EFFICACY

8.1 8-WEEK PLACEBO-CONTROLLED STUDY (NAC-MD-01)—STUDY DESIGN

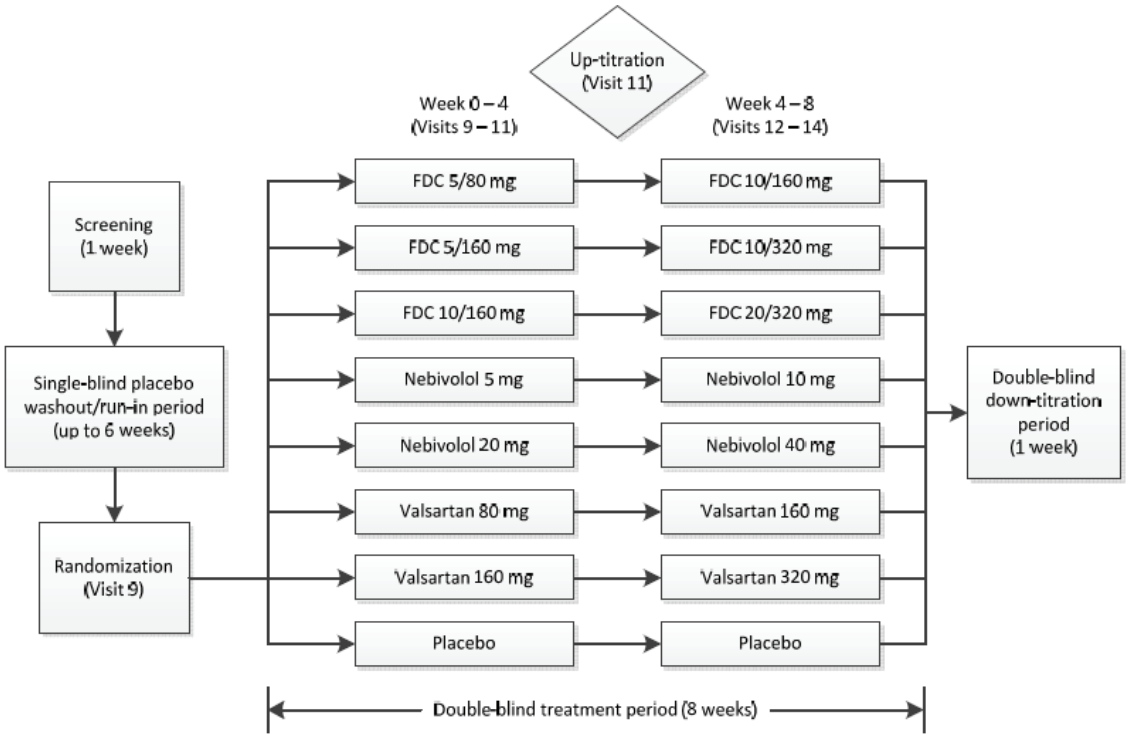
Study NAC-MD-01 (Giles et al, 2014; Waeber and Feihl, 2014) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 8-arm, multiple-dose study of nebivolol and valsartan given either in combination as an FDC or as monotherapy in patients with a diagnosis of stage 1 or stage 2 hypertension. The study was conducted in 460 centers in the United States and 4161 patients were randomized.

Study NAC-MD-01 was designed to fulfill the "combination rule," as described in the regulatory guidance for approval of an FDC treatment, and the regulatory expectations of a factorial design in the registration study. Demonstration of positive results in only 1 FDC dose compared with maximum-dose monotherapy is required, however this trial's design allowed for examination of multiple FDC doses as initial therapy and yielded safety and efficacy data upon up-titration to higher doses. The 5 FDC doses studied encompass the most frequently utilized doses of nebivolol and valsartan, including starting doses, in the United States.

The primary objectives of this study were to evaluate the efficacy and safety of the nebivolol and valsartan FDC compared with the monotherapy components and placebo.

The study consisted of 1 week of screening followed by a single-blind, placebo washout/run-in period of up to 6 weeks, an 8-week double-blind treatment period (separated into two 4-week periods, with a forced up-titration in all doses after the first 4 weeks), and a 1-week down-titration period. An overview is shown in Figure 8.1–1.

Figure 8.1–1. Study NAC-MD-01 Study Design



FDC = fixed-dose combination.

The single-blind placebo washout/run-in phase served as a washout phase for patients on antihypertensive therapy at enrollment and to measure treatment compliance as the patients became familiar with study medication.

At the end of the single-blind placebo washout/run-in period, patients who met the entry criteria were randomized to 1 of 8 double-blind treatment groups in a 2:2:2:2:2:2:2:1 ratio. All study medication was given once daily, between 8AM and 10AM.

The double-blinded treatment period during the first 4 weeks of Study NAC-MD-01 yielded safety and efficacy data on the administration of this FDC as initial therapy. The dose-doubling at 4 weeks provided information on the safety and efficacy upon up-titration of the FDC doses. At Week 8, efficacy and safety information was collected on the higher-dose FDCs. Patients completing the double-blind treatment period, or after early termination, entered a 1-week double-blind down-titration period. During the down-titration period, nebivolol doses were reduced while the dose of valsartan remained constant.

To investigate the PK and PD of the nebivolol/valsartan FDC in hypertensive patients, a substudy was conducted within Study NAC-MD-01 to assess 24-hour ambulatory blood pressure monitoring (ABPM), sparse PK measurements, and biomarkers (including PRA and plasma aldosterone). The ABPM assessments provided supportive data over a 24-hour interval for the BP-lowering effects of the nebivolol/valsartan FDC.

8.1.1 Key Inclusion/Exclusion Criteria in Study NAC-MD-01

The key inclusion criteria were:

- Male or female outpatients, age 18 years and above
- Patients diagnosed with stage 1 or stage 2 hypertension who met 1 of the following criteria:
  - Currently being treated for hypertension with at least 1 documented DBP value ≥ 90 mm Hg and < 110 mm Hg in their medical history or at a recent time during prescreening (ie, before signing the study-specific informed consent form)
  - Newly diagnosed with hypertension and who have never received treatment must have had a mean seated diastolic blood pressure (msDBP) ≥ 95 mm Hg and < 110 mm Hg at screening
  - Previously diagnosed with hypertension and who had not received antihypertensive medications for at least 4 weeks before screening must have had a msDBP ≥ 95 mm Hg and < 110 mm Hg at screening
- Seated pulse rate of at least 55 bpm at screening, except for patients on β-blockers
- Normal physical examination findings and electrocardiogram (ECG) results or abnormal findings judged by the Investigator to be not clinically significant. Patients with QTcF ≥ 430 msec for male patients or ≥ 450 msec for female patients were excluded

The key randomization criteria were:

- Compliance with single-blind placebo within the last 2 visit periods ≥ 80% and ≤ 120%

- Patients were eligible for early randomization (at least 4 weeks after Visit 2) if either:
  - During the single-blind run-in period the safety BP value (mean seated systolic blood pressure [msSBP] ≥ 180 mm Hg or msDBP ≥ 110 mm Hg) was obtained at any visit on or after Visit 6 (ie, Visit 7), and the repeat BP within 1 to 2 days of the visit was below the safety value (msSBP < 180 mm Hg and msDBP < 110 mm Hg, but ≥ 95 mm Hg), or
  - Patients had DBP ≥ 95 mm Hg at 2 out of 3 visits beginning with Visit 5. In addition patients must have had an office cuff msDBP < 110 mm Hg at these visits and an msSBP < 180 mm Hg
- Had a difference of ≤ 10 mm Hg in msDBP between the Randomization Visit and the visit prior to randomization
- Had an office cuff msDBP ≥ 95 and < 110 mm Hg at the Randomization Visit and at the visit prior to randomization (Day –7) or an office cuff msDBP ≥ 95 and < 110 mm Hg at 1 of 2 prior visits if qualified for early randomization

The key exclusion criteria were:

- Secondary hypertension (eg, renal artery stenosis, chronic renal disease, pheochromocytoma, primary hyperaldosteronism) or severe hypertension (msSBP ≥ 180 mm Hg or msDBP ≥ 110 mm Hg)
- Taking 4 or more antihypertensive agents. FDC products were counted as the number of their individual agents
- Coronary artery disease requiring treatment with a β-blocker, calcium channel blocker, or chronic nitrates
- Evidence of renal impairment as determined by any of the following: estimated glomerular filtration rate < 60 mL/min, serum creatinine > 1.5 × upper limit of normal, a history of dialysis, or a history of nephritic syndrome
- Evidence of hepatic disease as determined by any of the following: aspartate aminotransferase or alanine aminotransferase values exceeding 3 × upper limit of normal, total bilirubin exceeding 2 × upper limit of normal, a history of hepatic encephalopathy, a history of esophageal varices, a history of portacaval shunt, or a history of hepatitis B or C

8.1.2 Efficacy Endpoints

8.1.2.1 Rationale for Study Endpoints

This study was conducted to support the registration of the nebivolol/valsartan FDC. At the time that the study was designed, DBP was the accepted standard clinical endpoint in hypertension studies and thus was chosen as the primary endpoint. SBP has strong importance in the evaluation of treatment for hypertension and thus was chosen as the key secondary endpoint. It was also recognized that a full assessment of antihypertensive efficacy requires that both DBP and SBP be analyzed, providing the rationale of the BP control endpoint (Section 5.2). Because doses of nebivolol and valsartan are known to achieve their maximal effect after 2-4 weeks of therapy, assessments made after 4 or 8 weeks of therapy are valid (Bystolic, 2014; Diovan, 2014).

8.1.2.2 Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in seated trough DBP at Week 8. Statistical methods for the endpoints are described in Section 8.1.3.

8.1.2.3 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint was the change from baseline in seated trough SBP at Week 8.

8.1.2.4 Other Secondary and Additional Efficacy Endpoints

Some of the other secondary and additional efficacy endpoints included:

- Change in seated trough DBP and SBP from baseline to Week 4 (FDC 5/80 mg and FDC 5/160 mg compared with respective monotherapies)
- Proportion of patients achieving a target seated trough BP goal (ie, < 140/90 mm Hg for non-type 2 diabetics and < 130/80 mm Hg for type 2 diabetics) at Week 4 and at Week 8
- Change in mean 24-hour ambulatory DBP and SBP from baseline to Week 8 (FDC 20/320 mg compared with 40 mg nebivolol and 320 mg valsartan)

8.1.3 Statistical Methods for Study NAC-MD-01

The primary population for analysis of efficacy variables in Study NAC-MD-01 was the Intent-to-Treat (ITT) Population, defined as all randomized patients who took at least 1 dose of investigational product and who had at least 1 postbaseline seated BP measurement.

As agreed upon with FDA, and to test the regulatory "combination rule," the FDC of 20/320 mg was compared with the highest approved doses of nebivolol (40 mg) and valsartan (320 mg). If the adjusted p-value for the FDC for the primary efficacy comparison of FDC 20/320 mg and monotherapy (ie, the maximum of p-values for the comparisons of FDC 20/320 mg versus nebivolol 40 mg and FDC 20/320 mg versus valsartan 320 mg) was less than 0.05, the study would be deemed successful. Subsequently, the FDC doses of 10/160 mg and 10/320 mg would be compared with their corresponding monotherapy components with multiplicity controlled by Hochberg procedure on the adjusted p-values (ie, the maximum of p-values for the comparisons of the FDC group versus its corresponding monotherapy groups). For the key secondary efficacy parameter (mean change from baseline in SBP), each FDC compared with its respective monotherapies was to be tested only after the same FDC was determined to be positive in the primary efficacy parameter. Comparison of each active treatment group vs placebo was also analyzed as supportive analysis.

For all analyses with continuous variables, the between–treatment-group comparisons were performed by means of an analysis-of-covariance model, with treatment group and diabetic status as the factors and baseline value as a covariate. For binary secondary efficacy parameters, summary statistics (number and percentage) were presented by treatment group, and the between–treatment-group comparisons were performed by means of a logistic regression model with treatment group as class variable and baseline BP value as covariate. The last-observation-carried-forward approach was used to impute missing values.

To assess the robustness of the primary analysis using the prespecified last-observation-carried-forward method for missing data imputation, sensitivity analyses using baseline-observation-carried-forward and observed-case values at Week 8 were also performed using the same analysis of covariance model as used for the primary analysis. In addition, a sensitivity analysis using the mixed model for repeated measurement (MMRM) model was also performed based on observed data from all visits. The MMRM model included treatment group, diabetic status, visit, and treatment group by visit interaction as fixed effects and baseline and baseline by visit interaction as covariates. An unstructured covariance matrix was used to model the within patient correlation.

The above described MMRM model was also used to perform the post hoc analysis comparing FDC 20/320 mg at Week 8 and nebivolol 20 mg at Week 4 adjusting for time (ie, visit) effect.

8.2 NAC-MD-01 STUDY RESULTS

8.2.1 Patient Disposition From Study NAC-MD-01

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); and 4118 patients had at least 1 postbaseline trough seated DBP assessment (ITT Population).

A total of 3715 patients (89.3%) completed the double-blind treatment period, which reflects the tolerability of the nebivolol/valsartan FDC. The reasons for discontinuation are presented in Appendix 1, Table 14–2. The most frequent reasons for discontinuation during the double-blind treatment period were withdrawal of consent (2.9%), AE (2.3%), and lost to follow-up (1.7%).

8.2.2 Key Demographics of Study NAC-MD-01

As shown in Appendix 1, Table 14–3, the average patient age in the Safety Population of Study NAC-MD-01 was 51.3 years; 84.7% of patients were white, and 55.5% of patients were male. Diabetic patients consisted of 15.3% of the patient population. The mean baseline seated trough BP was 155/100 mm Hg. All baseline characteristics were well balanced among the treatment groups with respect to age, age group, sex, diabetic category, race, ethnicity, weight, height, body mass index, and participation in the substudy.

8.2.3 Efficacy Results of Study NAC-MD-01

8.2.3.1 Blood Pressure Reductions: FDC 20/320 mg vs Nebivolol 40 mg and Valsartan 320 mg—Primary and Key Secondary Efficacy Results

Study NAC-MD-01 (Giles et al, 2014; Waeber and Feihl, 2014) successfully met its primary endpoint, based on prespecified criteria in the protocol and statistical analysis plan, and it met the regulatory "combination rule" for a FDC, namely that the nebivolol/valsartan FDC reduced BP to a greater and statistically significant extent compared with the highest approved monotherapy doses, demonstrating that both of the monotherapy components contributed to the effect of the FDC (Section 6.1). This is the first Phase 3, registration study to demonstrate significant reductions in BP when combining a β-blocker and an ARB compared with monotherapy alone.

As shown in Table 8.2.3.1–1, statistically significantly greater reductions in both DBP and SBP occurred with the highest-dose FDC (20/320 mg) as compared with the highest approved monotherapy doses (nebivolol 40 mg and valsartan 320 mg).

Table 8.2.3.1–1. FDC 20/320 mg Versus Highest-Dose Monotherapy (Nebivolol 40 mg and Valsartan 320 mg): Primary and Key Secondary Endpoints of Study NAC-MD-01 (LOCF)—Intent-to-Treat Population

Comparison	*LSM Reductions in SBP/DBP, mm Hg*	*95% Confidence Intervals of Reductions in SBP/DBP, mm Hg*	*p-Value for SBP Reduction; p-Value for DBP Reduction*
FDC 20/320 mg vs nebivolol 40 mg	–2.9/–1.2	(–4.7, –1.1)/(–2.3, –0.1)	0.0013; 0.03
FDC 20/320 mg vs valsartan 320 mg	–3.1/–4.4	(–4.9, –1.4)/(–5.4, –3.3)	0.0005; < 0.0001

Note: Reduction in DBP was the primary endpoint of Study NAC-MD-01 and reduction in SBP was the key secondary endpoint.

Analyses are based on analysis of covariance model with treatment group and diabetes status as factors and baseline value as a covariate.

DBP = diastolic blood pressure; FDC = fixed-dose combination; LOCF = last observation carried forward; LSM = least squares mean; SBP = systolic blood pressure.

In addition to the primary and key secondary efficacy analyses using a prespecified last-observation-carried-forward method for missing data imputation, sensitivity analyses based on methods of MMRM, baseline-observation-carried-forward, and observed-case values at Week 8 all show consistent results when comparing FDC 20/320 mg vs. nebivolol 40 mg (Table 8.2.3.1–2).

Table 8.2.3.1–2. FDC 20/320 mg Versus Highest-Dose Monotherapy (Nebivolol 40 mg and Valsartan 320 mg): Primary and Key Secondary Endpoints of Study NAC-MD-01—Post Hoc Sensitivity Analysis

Endpoint	*Method*	*FDC 20/320 mg vs Nebivolol 40 mg*		*FDC 20/320 mg vs Valsartan 320 mg*	
		LSMD (95% CI)	*p-Value*	*LSMD (95% CI)*	*p-Value*
SBP	MMRM	–2.9 (–4.6, –1.1)	0.0018	–3.1 (–4.9, –1.3)	0.0006
	BOCF	–2.8 (–4.5, –1.0)	0.0017	–2.8 (–4.5, –1.1)	0.0014
	OC	–2.6 (–4.4, –0.8)	0.0045	–3.0 (–4.8, –1.2)	0.0010
DBP	MMRM	–1.2 (–2.3, –0.1)	0.0313	–4.4 (–5.5, –3.3)	< 0.0001
	BOCF	–1.6 (–2.8, –0.5)	0.0045	–4.1 (–5.3, –3.0)	< 0.0001
	OC	–1.2 (–2.4, –0.1)	0.0310	–4.4 (–5.5, –3.3)	< 0.0001

Note: Reduction in DBP was the primary endpoint of Study NAC-MD-01 and reduction in SBP was the key secondary endpoint.

BOCF = baseline observation carried forward; CI = confidence interval; DBP = diastolic blood pressure; FDC = fixed-dose combination; LSMD = least squares mean difference; MMRM = mixed model for repeated measurement; OC = observed cases; SBP = systolic blood pressure.

8.2.3.1.1 Blood Pressure Reductions: FDC 20/320 mg vs Nebivolol 20 mg—Post Hoc Results

Notably, the efficacy comparison of FDC 20/320 mg vs nebivolol 40 mg was particularly stringent, as nebivolol 40 mg is a dose which is double that of this FDC's nebivolol component. Furthermore, nebivolol 40 mg is not a clinically utilized dose (prescribed in < 1% of all nebivolol patients), and therefore a post hoc analysis based on MMRM was conducted to provide a comparison of FDC 20/320 mg against the component monotherapy of nebivolol 20 mg (Table 8.2.3.1.1–1). Due to the up-titration design of the study, the efficacy of nebivolol 20 mg and FDC 20/320 mg was assessed after 4 weeks of treatment (Week 4 for nebivolol 20 mg and Week 8 for FDC 20/320 mg).

The results of this analysis show that FDC 20/320 mg demonstrates statistically significant and clinically meaningful differences in BP reductions as compared with nebivolol 20 mg. SBP/DBP reductions when compared with nebivolol 20 mg were –3.7/–2.2 mm Hg. These results are consistent with the prespecified analysis against the higher dose nebivolol 40 mg and support the overall efficacy data.

Table 8.2.3.1.1–1. FDC 20/320 mg Versus Nebivolol 20 mg in Study NAC-MD-01

Comparison	*LSM Change in SBP/DBP, mm Hg*	*95% Confidence Intervals of Reductions in SBP/DBP, mm Hg*	*p-Value for SBP Reduction; p-Value for DBP Reduction*
FDC 20/320 mg vs nebivolol 20 mg	–3.7/–2.2	(–5.4, –2.0)/(–3.3, –1.1)	p < 0.0001; p < 0.0001

Note: Nebivolol 20 mg data at Week 4.
DBP = diastolic blood pressure; FDC = fixed-dose combination; LSM = least squares mean; SBP = systolic blood pressure.

8.2.3.2 Blood Pressure Reductions: All Fixed-Dose Combinations vs Monotherapy Components—Primary, Key Secondary, and Other Secondary Results

Study NAC-MD-01 demonstrated consistently greater SBP and DBP reductions from baseline for all 5 of the FDCs as compared with their corresponding monotherapy components or, in the case of FDC 20/320 mg, with a higher dose of nebivolol (primary, key secondary, and other secondary endpoints).

There were a total of 20 comparisons of FDC with monotherapies for SBP and DBP; and of these 20 comparisons, 19 met statistical significance (Table 8.2.3.2–1). These reductions were of a magnitude customarily associated with clinically meaningful benefits (for example, 18 of 20 comparisons demonstrated reductions of > 2 mm Hg) (Section 5.2). Thus, broad consistency is demonstrated in the array of these 20 BP comparisons in terms of both statistically significant BP reductions and clinical meaningfulness.

Table 8.2.3.2–1. Blood Pressure Comparisons in Study NAC-MD-01—Intent-to-Treat Population

FDC, mg	*Comparator Monotherapy, mg*	*LSM Change in SBP[a]/DBP[b], mm Hg*	*p-Value*
8 weeks			
20/320	Nebivolol 40	–2.9/–1.2	0.0013/0.030
	Valsartan 320	–3.1/–4.4	0.0005/< 0.0001
10/320	Nebivolol 10	–3.6/–2.4	< 0.0001/< 0.0001
	Valsartan 320	–3.0/–3.7	0.0011/< 0.0001
10/160	Nebivolol 10	–3.6/–2.2	< 0.0001/< 0.0001
	Valsartan 160	–3.9/–4.1	< 0.0001/< 0.0001
4 weeks			
5/160	Nebivolol 5	–4.1/–3.0	< 0.0001/< 0.0001
	Valsartan 160	–1.4/–2.9	0.1097/< 0.0001
5/80	Nebivolol 5	–3.6/–2.7	< 0.0001/< 0.0001
	Valsartan 80	–2.9/–3.3	0.0007/< 0.0001

Note: Primary and key secondary endpoints; hierarchically tested.

a Key secondary endpoint.

b Primary endpoint.

DBP = diastolic blood pressure; FDC = fixed-dose combination; LSM = least squares mean; SBP = systolic blood pressure.

8.2.3.2.1 Blood Pressure Reductions From Baseline: FDC Treatment Compared With Placebo

Reductions from baseline in DBP and SBP for all FDCs and monotherapies at Week 4 and Week 8 are displayed in Table 8.2.3.2.1–1 and Table 8.2.3.2.1–2. All comparisons with placebo achieved statistical significance ($p < 0.0001$).

Table 8.2.3.2.1–1. Change From Baseline in Trough Seated Systolic and Diastolic Blood Pressure (mm Hg) at Week 4 (LOCF)—Intent-to-Treat Population

Treatment Group	*SBP/DBP Change From Baseline, mm Hg*	*Placebo Adjusted SBP/DBP Change, mm Hg*	*p-Value vs Placebo*
Placebo	–6.5/–6.4	—	—
FDC 10/160 mg	–15.5/–14.3	–9.0/–7.9	< 0.0001/< 0.0001
FDC 5/160 mg	–15.3/–13.8	–8.8/–7.4	< 0.0001/< 0.0001
FDC 5/80 mg	–14.8/–13.5	–8.3/–7.2	< 0.0001/< 0.0001
Nebivolol 20 mg	–13.8/–13.8	–7.4/–7.5	< 0.0001/< 0.0001
Nebivolol 5 mg	–11.2/–10.8	–4.7/–4.4	< 0.0001/< 0.0001
Valsartan 160 mg	–13.9/–10.9	–7.5/–4.6	< 0.0001/< 0.0001
Valsartan 80 mg	–11.9/–10.2	–5.4/–3.9	< 0.0001/< 0.0001

DBP = diastolic blood pressure; FDC = fixed-dose combination; LOCF = last observation carried forward; SBP = systolic blood pressure.

Table 8.2.3.2.1–2. Change From Baseline in Trough Seated Systolic and Diastolic Blood Pressure (mm Hg) at Week 8 (LOCF)—Intent-to-Treat Population

Treatment Group	*SBP/DBP Change From Baseline, mm Hg*	*Placebo Adjusted SBP/DBP Change, mm Hg*	*p-Value vs Placebo*
Placebo	–7.2/–7.1	—	—
FDC 20/320 mg	–17.1/–15.7	–9.9/–8.7	< 0.0001/< 0.0001
FDC 10/320 mg	–17.0/–15.1	–9.7/–8.1	< 0.0001/< 0.0001
FDC 10/160 mg	–17.0/–15.0	–9.8/–7.9	< 0.0001/< 0.0001
Nebivolol 40 mg	–14.2/–14.5	–7.0/–7.5	< 0.0001/< 0.0001
Nebivolol 10 mg	–13.4/–12.8	–6.2/–5.7	< 0.0001/< 0.0001
Valsartan 320 mg	–14.0/–11.4	–6.8/–4.3	< 0.0001/< 0.0001
Valsartan 160 mg	–13.1/–10.9	–5.9/–3.9	< 0.0001/< 0.0001

DBP = diastolic blood pressure; FDC = fixed-dose combination; LOCF = last observation carried forward; SBP = systolic blood pressure.

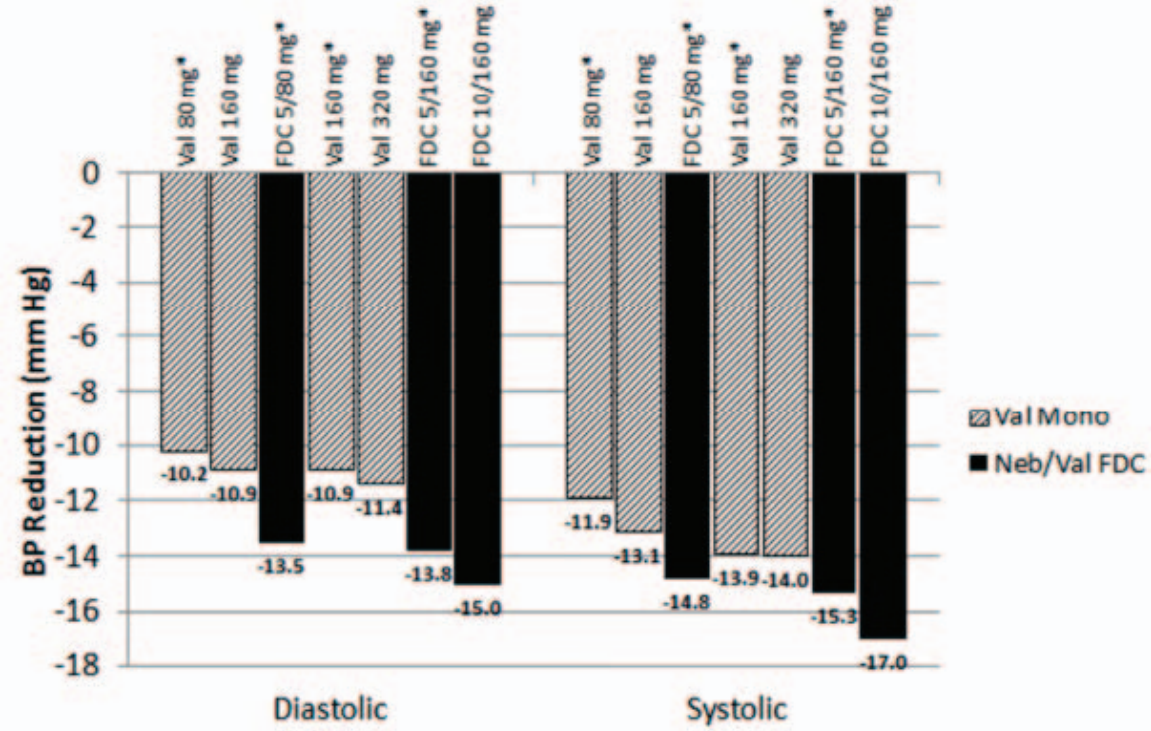
Figure 8.2.3.2.1–1 and Figure 8.2.3.2.1–2 graphically display BP reductions from baseline for select active treatment groups with FDC shown in black bars and monotherapies in cross-hatched bars.

An important finding is that all FDCs provide numerically greater BP reductions compared with the incremental reductions seen with doubling the dose of individual monotherapy. For example, patients who were initiated on 80 mg of valsartan and were up-titrated to 160 mg of valsartan after 4 weeks, experienced an incremental BP reduction of only 1.2/0.7 mm Hg. Patients who were initiated on FDC 5/80 mg experienced BP reductions that were 2.9/3.3 mm Hg greater than the BP reductions in patients on valsartan 80 mg (Figure 8.2.3.2.1–1).

As a second example, patients who were initiated on 20 mg of nebivolol and were up-titrated to 40 mg of nebivolol after 4 weeks, experienced an incremental BP reduction of 0.4/0.7 mm Hg. Patients who received FDC 20/320 mg experienced BP reductions that were 1.9/3.3 mm Hg greater than the BP reductions in patients on nebivolol 20 mg (Figure 8.2.3.2.1–2).

These data demonstrate that both components, nebivolol and valsartan, contribute to the antihypertensive effect of the FDC and that this combination leads to greater reductions in BP as compared to increasing the dose of monotherapy.

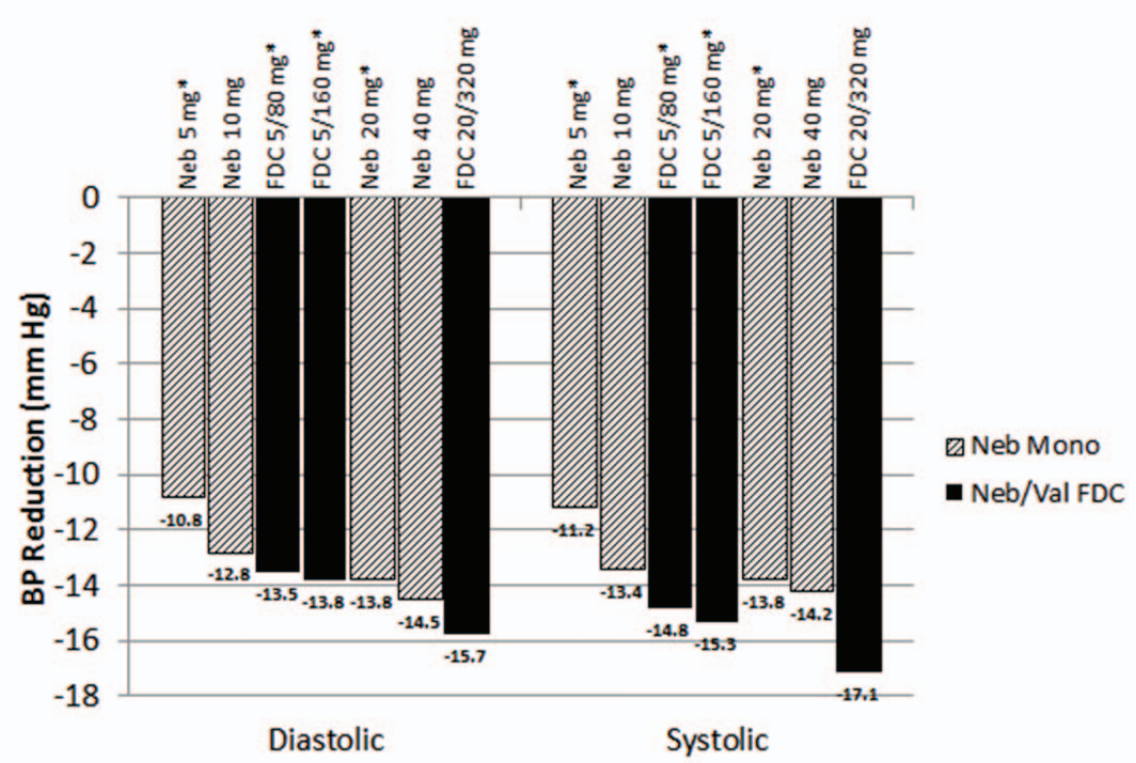
Figure 8.2.3.2.1–1. Study NAC-MD-01: Blood Pressure Reductions From Baseline by Treatment Group for FDC Treatment Groups Versus Valsartan Monotherapy—Intent-to-Treat Population



Note: This figure shows the mean DBP and SBP reductions from baseline for FDCs 5/80 mg, 5/160 mg, and 10/160 mg and valsartan monotherapies (80 mg, 160 mg, and 320 mg). DBP and SBP reduction from baseline are denoted directly below each bar. An asterisk indicates data collected at Week 4.

BP = blood pressure; FDC = fixed-dose combination; Neb = nebivolol; Val = valsartan.

Figure 8.2.3.2.1–2. Study NAC-MD-01: Blood Pressure Reductions From Baseline by Treatment Group for FDC Treatment Groups Versus Nebivolol Monotherapy—Intent-to-Treat Population



Note: This figure shows the mean DBP and SBP reductions from baseline for FDCs 5/80 mg, 5/160 mg, and 20/320 mg and nebivolol monotherapies (5 mg, 10 mg, 20 mg, and 40 mg). DBP and SBP reductions from baseline are denoted directly below each bar. An asterisk indicates data collected at Week 4.

BP = blood pressure; FDC = fixed-dose combination; Neb = nebivolol; Val = valsartan.

8.2.3.3 Blood Pressure Control—Additional Results

In this prespecified analysis, patients achieving BP control were defined as those who met the goal of SBP < 140 mm Hg *and* DBP < 90 mm Hg for non-type 2 diabetic patients, or SBP < 130 mm Hg *and* DBP < 80 mm Hg for type 2 diabetic patients. This definition was based on the available guidelines when the study was designed (Chobanian et al, 2003). Statistically significantly more patients receiving any FDC achieved BP control than did patients receiving the corresponding monotherapies or placebo (Table 8.2.3.3–1; placebo not shown). The FDC 20/320 mg group was the only group to achieve more than 50% BP control rate in patients.

Table 8.2.3.3–1. Study NAC-MD-01 Efficacy Parameters: Percentage of Patients at Diastolic and Systolic Treatment Goals by Treatment Group—Intent-to-Treat Population

Time Point	***FDC Dose, mg***	***FDC***		***Comparator Monotherapy***			
				Nebivolol		*Valsartan*	
		BP Control %	*p-Value*[a]	BP Control %	p-Value[b]	BP Control %	p-Value[c]
Week 4	5/80	42.4	< 0.0001	31.0	< 0.0001	32.8	0.0027
	5/160	41.4	< 0.0001	31.0	< 0.0001	31.8	0.0002
Week 8	10/160	48.8	< 0.0001	38.6	0.0005	36.5	0.0001
	10/320	46.7	< 0.0001	38.6	0.0013	35.6	< 0.0001
	20/320	51.8	< 0.0001	45.2	0.0231	35.6	< 0.0001

Note: *Blood Pressure Control* was defined as SBP < 140 mm Hg and DBP < 90 mm Hg for non-type 2 diabetes patients, and SBP < 130 mm Hg and DBP < 80 mm Hg for type 2 diabetes patients.

BP control % data tabulated in the *Nebivolol BP Control* and *Valsartan BP Control* columns refer to treatment with each monotherapy, at the dose of that drug denoted in the *FDC Dose* column (except for FDC 20/320 mg which was compared with nebivolol 40 mg and valsartan 320 mg).

The percentages of placebo patients achieving BP control were 17.0% at Week 4 and 20.9% at Week 8.

a p-Value is based on a logistic regression model comparing the FDC dose versus placebo.

b p-Value is based on a logistic regression model comparing the FDC dose versus the corresponding nebivolol monotherapy.

c p-Value is based on a logistic regression model comparing the FDC dose versus the corresponding valsartan monotherapy.

BP = blood pressure; DBP = diastolic blood pressure; FDC = fixed-dose combination; SBP = systolic blood pressure.

Following completion of Study NAC-MD-01, hypertension guidelines were updated with new SBP/DBP goals of < 140/90 mm Hg, without distinction based on diabetic status. Therefore a post hoc analysis examined BP control using SBP of < 140 mm Hg *and* DBP < 90 mm Hg for all patients, as described in the most recent hypertension guidance documents (James et al, 2014; Weber et al, 2014). The results using these criteria are consistent with those using the prespecified criteria.

As shown in Table 8.2.3.3–2, the percentages of patients achieving BP control were statistically significantly greater with each FDC dose as compared with the highest approved doses of monotherapies or placebo (placebo not shown in Table 8.2.3.3–2). Additionally, more than 50% of patients treated with the FDC 20/320 mg, 10/320 mg, and 10/160 mg at Week 8 achieved BP control. This level of BP control was not observed with any of the monotherapies, even at the highest approved doses.

Table 8.2.3.3–2. Study NAC-MD-01 Post Hoc Analysis: Number (%) of Patients at Diastolic and Systolic Treatment Goals by Treatment Group—Intent-to-Treat Population

Time Point	***FDC Dose, mg***	***FDC***		***Comparator Monotherapy***			
				Nebivolol		*Valsartan*	
		BP Control %	*p-Value*[a]	BP Control %	p-Value[b]	BP Control %	p-Value[c]
Week 4	5/80	45.7	< 0.0001	34.8	0.0003	35.9	0.0033
	5/160	46.5	< 0.0001	34.8	< 0.0001	36.2	0.0001
Week 8	10/160	52.1	< 0.0001	42.8	0.0025	39.4	0.0001
	10/320	52.2	< 0.0001	42.8	0.0006	40.4	< 0.0001
	20/320	55.3	< 0.0001	48.8	0.0397	40.4	< 0.0001

Note: *Blood Pressure Control* was defined SBP < 140 mm Hg and DBP < 90 mm Hg.

BP control % data tabulated in the *Nebivolol BP Responder* and *Valsartan BP Responder* columns refer to treatment with each monotherapy, at the dose of that drug denoted in the *FDC Dose* column (except for FDC 20/320 mg which was compared with nebivolol 40 mg and valsartan 320 mg).

The percentages of placebo patients achieving BP control were 18.4% at Week 4 and 23.5% at Week 8.

a p-Value is based on a logistic regression model comparing the FDC dose versus placebo.

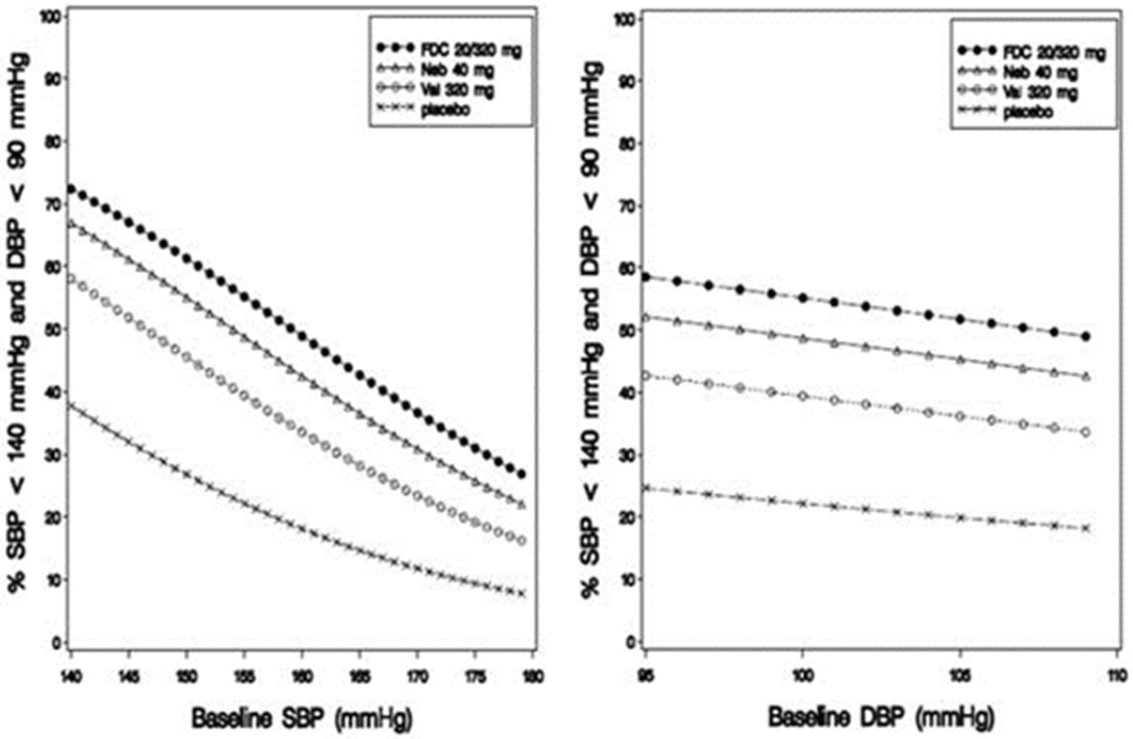
b p-Value is based on a logistic regression model comparing the FDC dose versus the corresponding nebivolol monotherapy.

c p-Value is based on a logistic regression model comparing the FDC dose versus the corresponding valsartan monotherapy.

BP = blood pressure; DBP = diastolic blood pressure; FDC = fixed-dose combination; SBP = systolic blood pressure.

The greater BP control rates seen with the FDC 20/320 mg dose compared with the highest-dose monotherapies were consistent, regardless of baseline DBP or SBP, as demonstrated in Figure 8.2.3.3–1.

Figure 8.2.3.3–1. Probability of Achieving BP Control (SBP < 140 mm Hg and DBP < 90 mm Hg at Week 8) Versus Baseline SBP and DBP in Study NAC-MD-01—Conditional on Mean Baseline DBP and SBP, Respectively



Note: These figures show the probability of patients achieving BP control based on baseline SBP or DBP for the FDC 20/320 mg, nebivolol 40 mg, valsartan 320 mg, and placebo groups. The probability of achieving BP control was derived from a logistic regression model with treatment group as a class variable and baseline SBP and DBP as covariates.

BP = blood pressure; DBP = diastolic blood pressure; FDC = fixed-dose combination; Neb = nebivolol; SBP = systolic blood pressure; Val = valsartan.

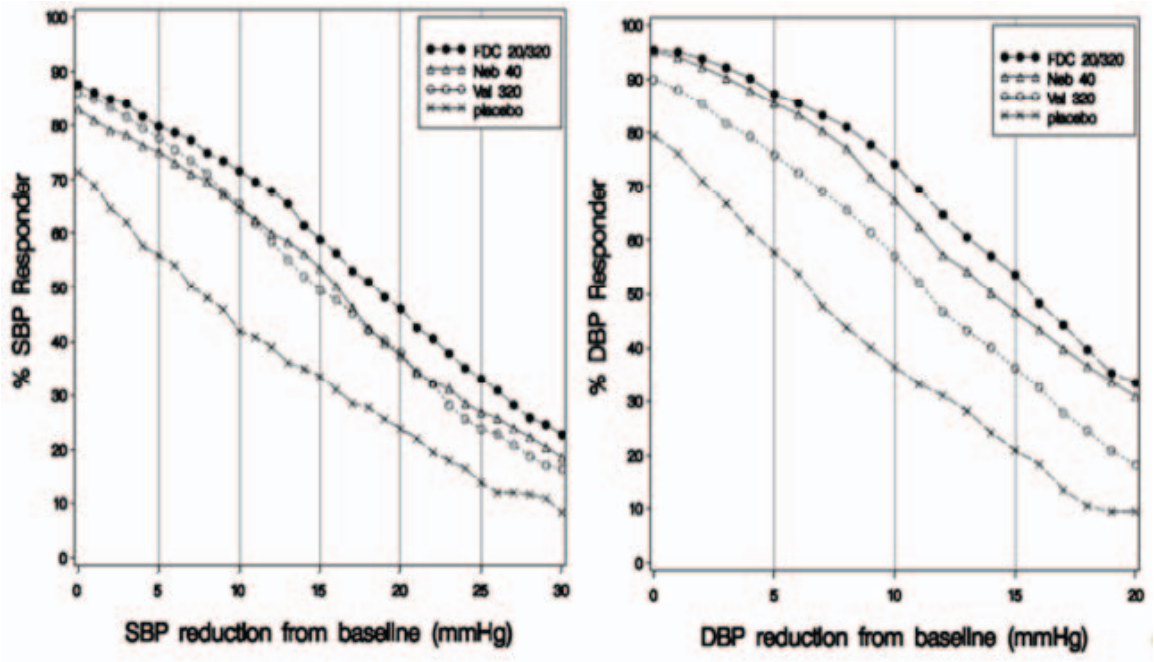
8.2.3.3.1 Percentage of Patients Achieving Distinct Reductions in BP: FDC 20/320 mg, Nebivolol 40 mg, Valsartan 320 mg, and Placebo—Post Hoc Results

The percentage of patients achieving distinct BP reductions from baseline in the FDC 20/320 mg, nebivolol 40 mg, valsartan 320 mg, and placebo groups was determined for both SBP and DBP. In this analysis, patients who achieved a BP reduction that was greater than or equal to the distinct BP reduction value were considered responders. For example, all patients with a reduction from baseline in SBP of ≥ 20 mm Hg would be considered responders at 20 mm Hg.

This analysis found that more patients in the FDC 20/320 mg treatment group consistently achieved distinct reductions in SBP from baseline as compared with the monotherapies and placebo (Figure 8.2.3.3.1–1). Specifically, a greater percentage of patients in the FDC 20/320 treatment group achieved reductions in SBP of 10 mm Hg, 20 mm Hg, and 30 mm Hg as compared with both monotherapies (achieving statistical significance for reductions of SBP of 10, 15, and 20 mm Hg [$p < 0.05$]).

In addition, for DBP, more patients in the FDC 20/320 mg treatment group consistently achieved distinct reductions in DBP from baseline as compared with both monotherapies (Figure 8.2.3.3.1–1) (achieving statistical significance for reductions of DBP at 10 and 15 mm Hg [$p < 0.05$]).

Figure 8.2.3.3.1–1. Study NAC-MD-01: Percentage of Patients Achieving Distinct BP Reductions From Baseline by Treatment Group—Intent-To-Treat Population



Note: These figures show the percentage of patients achieving distinct BP reductions from baseline in the FDC 20/320 mg, nebivolol 40 mg, valsartan 320 mg, and placebo groups.

Post hoc assessment of the difference between FDC 20/320 mg vs both maximum-dose monotherapies were statistically significant for SBP at 10, 15, and 20 mm Hg ($p < 0.05$) and for DBP at 10 and 15 mm Hg ($p < 0.05$).

BP = blood pressure; DBP = diastolic blood pressure; FDC = fixed-dose combination; Neb = nebivolol; SBP = systolic blood pressure; Val = valsartan.

Although not shown in the figures, the percentage of patients achieving reductions in both SBP and DBP was measured. For FDC 20/320 mg, 69.1% of patients achieved an SBP/DBP reduction from baseline of at least 10/5 mm Hg, which was statistically greater than patients in the nebivolol 40 mg (62.5%) and valsartan 320 mg (60.0%) groups ($p < 0.05$). In addition, the number of patients achieving an SBP/DBP reduction from baseline of at least 20/10 mm Hg was statistically significantly greater in the FDC 20/320 mg group (43.8%) compared with the nebivolol 40 mg (34.6%) and valsartan 320 mg (34.4%) groups ($p < 0.01$).

8.2.3.4 Blood Pressure Reductions Upon Dose Up-titration—Within-Arm Comparisons for Study NAC-MD-01

In order to assess the effect of up-titration among FDC dosages, comparisons were also made *within* FDC treatment groups. This allows a comparison of BP reduction observed over Weeks 0 to 4 and the incremental effect after dosage up-titration during Weeks 4 to 8, all based on data from the same patients within a single treatment group. This within-treatment-group comparison was performed directly based on data from the primary, key secondary, and other secondary analyses.

The results of this comparison demonstrate that all FDC treatment groups experienced a further reduction in both DBP and SBP from Week 4 to Week 8, with the amount of incremental reduction meeting statistical significance (Appendix 1, Table 14–4).

8.2.3.5 Results in Subgroups

Prespecified analyses of the Study NAC-MD-01 primary and key secondary endpoints were performed in subgroups defined by diabetes status, baseline seated DBP category, race, age group, body mass index category, sex, and ethnicity; and on subgroups of stage 1 and 2 hypertension defined post hoc. These analyses assessed reductions in DBP and SBP for each FDC, as compared with monotherapies, at 8 weeks. The subgroup analyses were not designed to be powered to show statistical differences. The results demonstrated broad consistency with the overall results of the study (Appendix 1: Figure 14–3, Figure 14–4, Figure 14–5, and Figure 14–6). BP reductions were generally greater in patients receiving FDCs than in those receiving highest approved doses of monotherapies.

8.2.3.6 Substudy Results

8.2.3.6.1 Change From Baseline in 24-Hour Ambulatory Blood Pressure Monitoring

Twenty-four-hour ambulatory BP was assessed at baseline and at Week 8 in the substudy of NAC-MD-01. These results are supportive of the primary and key secondary efficacy results observed in the overall ITT Population.

The results of the secondary and additional analyses for the change from baseline to Week 8 in 24-hour ABPM are displayed in Table 8.2.3.6.1–1. The mean changes in 24-hour ambulatory SBP/DBP after 8 weeks of treatment demonstrate that treatment with the 3 FDCs lowered 24-hour mean SBP by 14.4 to 17.1 mm Hg and DBP by 10.3 to 12.5 mm Hg, meeting statistical significance compared with placebo treatment. Patients in the placebo group experienced small increases in both mean ambulatory SBP and DBP.

Table 8.2.3.6.1–1. Study NAC-MD-01 Analysis: Changes in Mean 24-Hour Ambulatory SBP and DBP from Baseline to Week 8 (LOCF)—Substudy Population

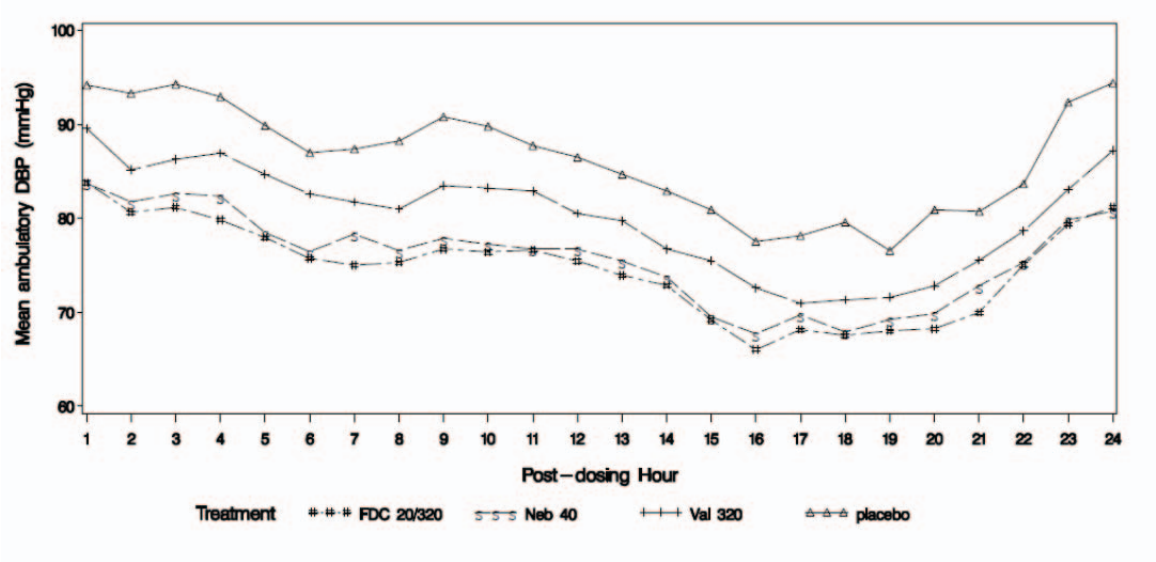
Treatment Group	*n*	*Mean Change in SBP From Baseline, mm Hg*	*Mean Change in DBP From Baseline, mm Hg*
Placebo	39	0.1	0.6
FDC 20/320 mg	86	–17.1	–12.5
FDC 10/320 mg	83	–14.4	–10.3
FDC 10/160 mg	78	–15.3	–12.1
Nebivolol 40 mg	77	–14.6	–10.8
Nebivolol 10 mg	87	–11.2	–8.6
Valsartan 320 mg	82	–12.0	–8.5
Valsartan 160 mg	78	–8.9	–5.7

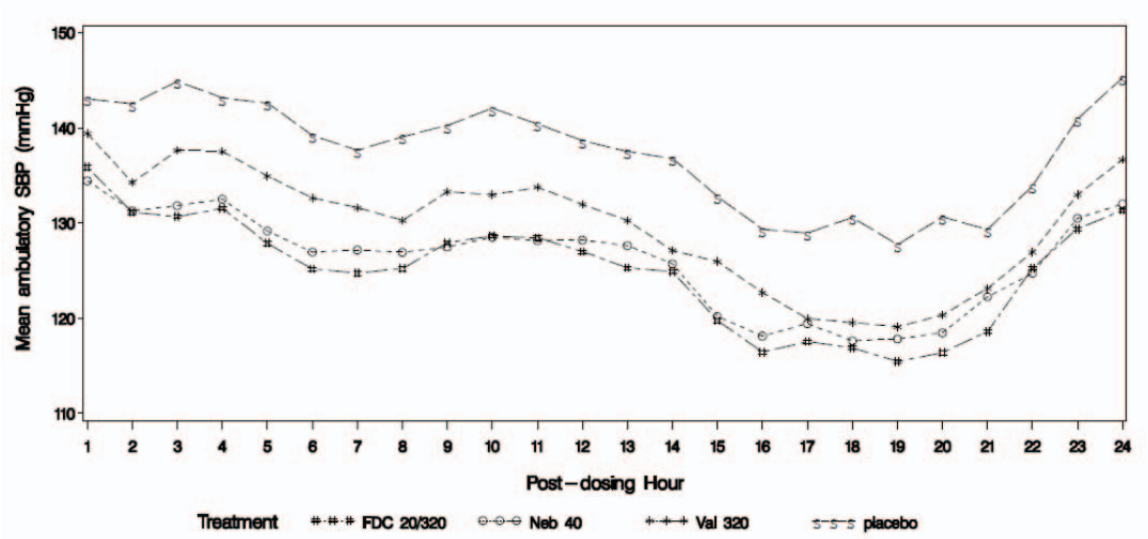
Note: This table shows mean reductions in 24-hour ambulatory SBP and DBP at Week 8 from the Substudy Population of Study NAC-MD-01. The n represents the number of patients who entered the substudy and had an ABPM measurement at baseline and Week 8 of the study.

ABPM = ambulatory blood pressure monitoring; DBP = diastolic blood pressure; FDC = fixed-dose combination; LOCF = last observation carried forward; SBP = systolic blood pressure.

Figure 8.2.3.6.1–1 shows the ambulatory SBP and DBP data, graphed by hour following drug administration, for FDC 20/320 mg compared with the highest approved doses of monotherapies and placebo. These data indicate that treatment with FDC 20/320 mg consistently reduced SBP and DBP to a greater extent as compared with highest dose valsartan therapy or placebo over the 24-hour period, with slightly greater reductions compared with highest dose nebivolol over the majority of the 24-hour period. These data are confirmatory of prior studies, which show the appropriateness of once-daily dosing of the nebivolol/valsartan FDC.

Figure 8.2.3.6.1–1. Study NAC-MD-01 Analysis: Changes in Mean 24-Hour Ambulatory DBP and SBP by Post-Dosing Hour at Week 8 for FDC 20/320 mg, Nebivolol 40 mg, and Valsartan 320 mg—Substudy Population





Note: This figure shows the 24-hour ambulatory DBP (upper panel) and SBP (lower panel) from baseline to Week 8 for FDC 20/320 mg, nebivolol 40 mg, valsartan 320 mg, and placebo groups over a 24-hour period. The order of BP reductions for these groups follows the general trend, the smallest reductions observed in placebo, then valsartan 320 mg, then nebivolol 40 mg, with the greatest reductions in FDC 20/320 mg.

BP = blood pressure; DBP = diastolic blood pressure; FDC = fixed-dose combination; Neb = nebivolol; SBP = systolic blood pressure; Val = valsartan.

Table 8.2.3.6.1–2 presents greater reductions in 24-hour mean SBP/DBP with each FDC treatment compared with treatment with corresponding monotherapy, including the comparisons with highest dose monotherapy (nebivolol 40 mg, valsartan 320 mg), with some comparisons achieving statistical significance. Thus, the consistency of these findings is supportive of the primary and key secondary endpoints of the ITT analysis, which also demonstrated consistently greater reductions with the FDCs compared with corresponding monotherapy.

Table 8.2.3.6.1–2. Study NAC-MD-01 Analysis: LSM Changes in Mean 24-Hour Ambulatory SBP and DBP from Baseline to Week 8 (LOCF)—Substudy Population

Comparison	*n (FDC, Mono)*	*LSM Difference in SBP/DBP from Baseline, mm Hg*	*p-Value SBP Comparison/ DBP Comparison*
FDC 20/320 mg vs Val 320 mg	86, 82	–5.1/–4.6	0.0027/< 0.0001
FDC 20/320 mg vs Neb 40 mg	86, 77	–2.1/–1.6	0.2312/0.1486
FDC 10/320 mg vs Val 320 mg	83, 82	–2.2/–1.9	0.1910/0.0828
FDC 10/320 mg vs Neb 10 mg	83, 87	–2.0/–1.1	0.2294/0.2893
FDC 10/160 mg vs Val 160 mg	78, 78	–6.2/–6.3	0.0005/< 0.0001
FDC 10/160 mg vs Neb 10 mg	78, 87	–2.7/–3.0	0.1112/0.0053

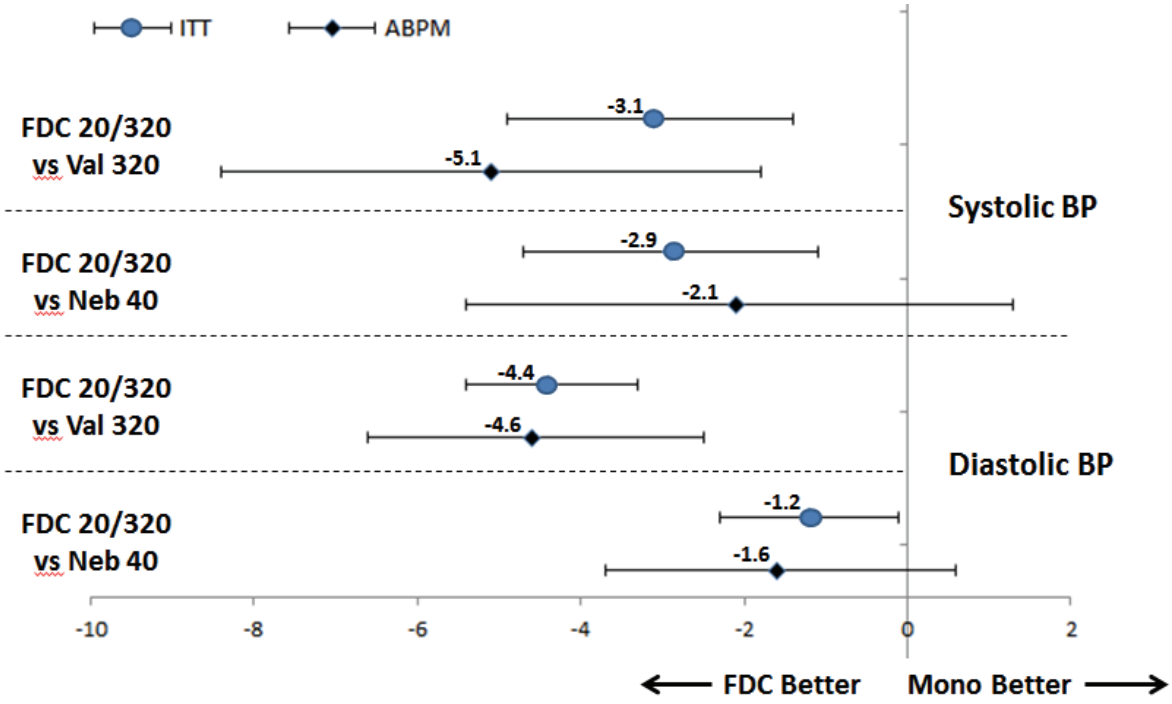
Note: This table shows LSM reductions in 24-hour ambulatory SBP/DBP at Week 8 for the comparisons of FDC with corresponding monotherapy from the substudy of Study NAC-MD-01.

Analyses are based on analysis of covariance model with treatment group and diabetes status as factors and baseline value as a covariate.

DBP = diastolic blood pressure; FDC = fixed-dose combination; ITT = intent to treat; LOCF = last observation carried forward; LSM = least squares mean; Mono = monotherapy; n = number of patients (in the substudy) with available analysis value at both baseline and a specific time point in the ITT Population; Neb = nebivolol; SBP = systolic blood pressure; Val = valsartan.

Figure 8.2.3.6.1–1 provides a comparison of SBP and DBP reductions observed with cuff assessments (primary and key secondary endpoints, from ITT Population) with those observed via ABPM (secondary endpoints, from Substudy Population).
Figure 8.2.3.6.1–2 illustrates that the ABPM results were supportive of the primary and key secondary endpoints from the ITT analysis. As shown in this figure, the LSM differences between FDC 20/320 mg and nebivolol 40 mg and valsartan 320 mg were similar between the ITT and ABPM-Substudy Populations.

Figure 8.2.3.6.1–2. Study NAC-MD-01 Analysis: Comparison of the Reductions in Mean 24-Hour Ambulatory SBP and DBP With Reductions in SBP and DBP from the Intent-to-Treat Analysis at Week 8



This figure shows primary and key secondary endpoints of the ITT analysis (blue circles) and the LSMD changes in the 24-hour ambulatory BP reduction (black diamonds) for the FDC 20/320 mg compared with the highest-dose monotherapies (nebivolol 40 mg and valsartan 320 mg). Point estimates to the left of 0 are favorable for the FDC and point estimates to the right of 0 are favorable for the monotherapy. The error bars represent the 95% confidence intervals for each point estimate. As shown in this figure, all point estimates, for both the ITT analysis and ABPM analysis favor the FDC, with similar findings for all comparisons of FDC and monotherapy.

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; FDC = fixed-dose combination; ITT = intent to treat; LSMD = least squares mean difference; Mono = monotherapy; Neb = nebivolol; Val = valsartan.

8.2.3.6.2 Biomarkers

As discussed in Section 7.4, PRA and aldosterone are important markers of the RAAS and have important implications in hypertension and CV disease. Increased PRA and aldosterone suggests increased BP and reduced endothelial function, while reductions in these biomarkers suggest a favorable biological response in reducing BP.

After 8 weeks of double-blind treatment, PRA increased from baseline in the groups treated with valsartan monotherapy (range: 53.8% to 72.8%), and decreased from baseline in the groups treated with nebivolol monotherapy (range: 51.3% to 65.4%) and FDC (range: 3.2% to 39.0%). Changes in PRA were consistent with the expected changes from the antihypertensive effect from the administration of a β-blocker and an ARB.

At 8 weeks, the greatest decrease from baseline in aldosterone was seen in the FDC 20/320 mg group (35.1%), which exceeded the reductions observed in the nebivolol 40 mg (26.5%) and valsartan 320 mg (22.1%) groups. Therefore, the FDC provides the greatest decrease in aldosterone compared with monotherapy components.

8.2.3.7 52-Week, Open-label Safety Study (NAC-MD-02)

Study NAC-MD-02 was a Phase 3, open-label, 52-week study to evaluate the safety of nebivolol and valsartan in free-tablet combination in patients with hypertension. Details on study design, conduct, and results are in the safety section (Section 10.0). In the study, 810 patients were enrolled to receive treatment, and 799 patients received at least 1 dose of open-label investigational product and had at least 1 postbaseline assessment of trough seated DBP or SBP (ITT Population).

BP reductions were assessed in Study NAC-MD-02 and were a prespecified endpoint. The reduction from baseline in mean SBP/DBP was 16.9/14.4 mm Hg at Week 10, and 25.5/19.0 mm Hg at Week 52. Patients not achieving BP goals (< 130/80 mm Hg for diabetics, < 140/90 mm Hg for others) were administered 12.5 mg HCTZ in addition to nebivolol and valsartan; HCTZ could be titrated to 25 mg if needed to reach BP goal. Among patients who did not require HCTZ (N = 380), the mean SBP/DBP reduction at 52 weeks was 26.2/19.3 mm Hg, among patients who required and received HCTZ (N = 419), the mean SBP/DBP reduction was 25.0/18.7 mm Hg. Of note, the mean reduction in SBP/DBP observed at Week 10 of treatment in Study NAC-MD-02 was similar in magnitude to those demonstrated by the FDC groups in Study NAC-MD-01 at Week 8.

8.2.4 Summary and Discussion of Study NAC-MD-01 Efficacy Data

The current development program was the first to systematically examine the combination of a β-blocker and an ARB, 2 classes of drugs that are already commonly coadministered. Study NAC-MD-01 (Giles et al, 2014; Waeber and Feihl, 2014) successfully fulfilled the regulatory “combination rule” requirement for approval of an FDC. FDC 20/320 mg treatment reduced BP to a greater and statistically significant extent compared to the highest approved monotherapy doses (nebivolol 40 mg and valsartan 320 mg), thereby demonstrating that both of the monotherapy components contributed to the effect of the FDC. Furthermore, 5 FDCs were studied, and treatment with each FDC reduced BP to a greater extent than did the corresponding monotherapies. These BP reductions were of a magnitude that has been shown in the literature to be clinically meaningful and associated with improvements in CV outcomes (Section 5.2). Study NAC-MD-01 demonstrated consistent efficacy in the reduction of BP with the FDC of nebivolol and valsartan for the treatment of stage 1 or 2 hypertension.

Of note, the main efficacy comparison that addressed the regulatory "combination rule" (FDC 20/320 mg vs the highest-dose monotherapies, thereby showing that each component contributed to the effect of the FDC) used a dose of nebivolol 40 mg; however, this dose is very rarely used (< 1%) in practice. Therefore, an analysis was conducted post hoc to compare FDC 20/320 mg with nebivolol 20 mg (a much more utilized dose and the nebivolol component with this FDC). Results were consistent with the prespecified endpoint, showed an increased treatment effect size with statistical significance, and confirmed the robustness of the efficacy data.

The consistency of the study data are further supported by other secondary and additional efficacy findings. Regardless of the BP control criteria utilized, statistically significantly more patients receiving any FDC (at Week 4 or Week 8) achieved BP control as compared to patients receiving monotherapies or placebo. The FDC 20/320 mg group was the only group to achieve more than 50% BP control in patients using both BP control criteria (Chobanian et al, 2003; James et al, 2014) and specifically demonstrated statistically more patients achieving BP control as compared with maximum-dose monotherapy. In addition, more patients in the FDC 20/320 mg treatment group consistently achieved distinct reductions in SBP and DBP from baseline as compared with the monotherapies and placebo.

In the substudy of NAC-MD-01, ABPM analyses confirmed 24-hour antihypertensive coverage and showed that the FDC reduced 24-hour BP to a greater extent as compared to the monotherapy components, which is confirmatory and supportive of once-daily dosing and the overall efficacy results. In addition, data from this program show that valsartan alone increased PRA while nebivolol alone inhibited PRA. Coadministration of nebivolol prevented the reactive rise in PRA observed with valsartan. Plasma aldosterone levels were also lower following the administration of the combination as compared with nebivolol or valsartan monotherapy treatment. Furthermore, these changes in biomarkers were associated with a reduction in BP, suggesting that these mechanistic changes have a role in the antihypertensive effect from the coadministration of nebivolol and valsartan.

In summary, Study NAC-MD-01 demonstrated statistically significant and clinically meaningful efficacy for FDC of nebivolol and valsartan as compared with the monotherapy components. The FDC groups showed greater reductions from baseline BP, higher rates of BP response, and higher rates of BP control than monotherapy. The results from this large (> 4000 patients) study demonstrate the effectiveness of this FDC.

9.0 OVERVIEW OF SAFETY AND TOLERABILITY

The safety and tolerability of nebivolol/valsartan FDC and free-tablet combination were evaluated in the Safety Populations of an 8-week placebo-controlled study (NAC-MD-01) and a long-term safety study (NAC-MD-02) by customary monitoring of AEs, TEAEs, SAEs, AEs leading to discontinuations, AEs of potential interest, vital signs, laboratory tests, and ECG measurements. The Safety Populations consisted of all patients who took at least 1 dose of investigational product. A total of 4966 patients were studied in the Phase 3 Safety Populations, with 1664 patients exposed to the nebivolol/valsartan FDCs in Study NAC-MD-01 (Giles et al, 2014; Waeber and Feihl, 2014) and 807 patients exposed to the free-tablet combination in Study NAC-MD-02. ICH requirements of long-term exposure to an investigational product were fully met and exceeded.

Studies NAC-MD-01 and NAC-MD-02 were conducted in parallel on separate hypertensive patients (ie, separate Safety Populations) with equivalent baseline characteristics. In both studies, prior to initiating nebivolol/valsartan combination therapy, there was a washout of prior antihypertensive agents; thus, the described treatments were administered as initial therapy.

9.1 8-WEEK PLACEBO-CONTROLLED STUDY (NAC-MD-01) SAFETY RESULTS

9.1.1 Safety Population and Exposure

The Safety Population in Study NAC-MD-01 comprised 4159 patients, of whom 1664 received one of the nebivolol/valsartan FDCs.

The mean treatment duration was 59.9 days in the combined FDC treatment groups, 59.7 days in the combined nebivolol monotherapy treatment groups, 59.9 days in the combined valsartan monotherapy treatment groups, and 58.8 days in the placebo group. The total exposure in the combined FDC treatment groups was 273.1 patient-years.

9.1.2 Summary of Adverse Events

Table 9.1.2–1 provides a summary of AEs that occurred during the 8-week, double-blind treatment period and 1-week double-blind down-titration period. No deaths were reported during the double-blind periods. Two patients had SAEs that resulted in death during the single-blind placebo run-in period, prior to administration of investigational product; although they were not in the Safety Population, information is given on these 2 patients (Section 9.1.6). Thirty-one patients reported on-therapy SAEs, and 102 patients discontinued from the double-blind treatment and down-titration periods due to AEs.

Table 9.1.2–1. Overall Summary of Adverse Events in Study NAC-MD-01—Safety Population

Event	*Placebo (N = 277, M = 244) n (%)*	*FDC 10/160 (N = 555, M = 505) n (%)*	*FDC 10/320 (N = 555, M = 495) n (%)*	*FDC 20/320 (N = 554, M = 520) n (%)*	*NEB 10 (N = 555, M = 515) n (%)*	*NEB 40 (N = 554, M = 501) n (%)*	*VAL 160 (N = 555, M = 508) n (%)*	*VAL 320 (N = 554, M = 507) n (%)*
Patients who died[a]	0	0	0	0	0	0	0	0
Patients with SAEs	4 (1.4)	4 (0.7)	3 (0.5)	1 (0.2)	4 (0.7)	4 (0.7)	6 (1.1)	5 (0.9)
Patients with ADOs occurring during the DBTP	10 (3.6)	15 (2.7)	9 (1.6)	9 (1.6)	12 (2.2)	22 (4.0)	10 (1.8)	10 (1.8)
Patients with ADOs occurring during the DBDP	0	0	0	0	1 (0.2)	0	1 (0.2)	1 (0.2)
Patients with ADOs occurring after completing the DBTP but before entering the DBDP	0	0	0	1 (0.2)	0	0	0	1 (0.2)
Patients with TEAEs	104 (37.5)	204 (36.8)	192 (34.6)	196 (35.4)	205 (36.9)	205 (37.0)	175 (31.5)	202 (36.5)

Note: Deaths, SAEs, and TEAEs are those that occurred on or after the date of the first dose of double-blind investigational product and within 30 days of last dose of double-blind investigational product.

% = n/M × 100 if counting the number in double-blind down-titration period; otherwise % = n/N × 100.

a Two patients died during the single-blind placebo run-in period, prior to administration of investigational product. See Section 9.1.6.

ADO = adverse event leading to dropout (ie, premature discontinuation from the study); DBDP = double-blind down-titration period; DBTP = double-blind treatment period; FDC = fixed-dose combination; M = number of patients entering double-blind down-titration period in the Safety Population; N = number of patients in the Safety Population; n = number of patients with the specific event; Neb = nebivolol; SAE = serious adverse event; TEAE = treatment-emergent adverse event; Val = valsartan.

9.1.3 Common Treatment-Emergent Adverse Events

There was a low incidence of TEAEs in Study NAC-MD-01, which led to a low number of common TEAEs (defined as occurring in ≥ 2% of patients in any treatment group). Most TEAEs were mild or moderate in intensity and were assessed by the Investigators to be not related to investigational product. All FDCs showed similar rates of TEAEs, with no clear dose-dependency.

The percentage of patients reporting at least 1 TEAE during the double-blind treatment period was numerically lower in the FDC groups compared to the placebo group and comparable to those seen in the monotherapy groups (Table 9.1.3–1). Only 2 of the TEAEs, fatigue and dizziness, occurred with an incidence of ≥ 2% in at least 1 of the FDC groups and at a higher rate than placebo. Of note, the rates and types of TEAEs that occurred during Weeks 0-4 of treatment (with a lower-dose FDC) were similar to the rates and types of TEAEs during Weeks 4-8 of treatment (with an up-titrated, higher-dose FDC) (Appendix 1, Table 14–5).

As described in Section 6.3, FDC 20/320 mg was evaluated for efficacy in comparison with nebivolol 40 mg and valsartan 320 mg to fulfill the regulatory requirements for approval of an FDC. In evaluating these same doses for safety, the rates of TEAEs in the FDC 20/320 mg group (34.1%) were lower than those in the high-dose monotherapy groups (nebivolol 40 mg [35.7%] and valsartan 320 mg [34.3%]) (Table 9.1.3–1). Similar safety findings were also observed when FDC 20/320 mg was compared to more commonly utilized doses of monotherapy, nebivolol 10 mg and valsartan 160 mg, with similar rates of TEAEs between FDC and these lower-dose monotherapy groups.

AEs typically associated with β-blockers, such as bradycardia, sinus bradycardia, and fatigue, occurred less frequently in all FDC groups than in the nebivolol 40 mg group. ARB-associated AEs such as dizziness occurred less frequently in all FDC groups as compared to valsartan 160 mg and 320 mg. Overall, all FDC doses had similar rates of AEs as compared to the nebivolol and valsartan monotherapy groups, and, in multiple instances, at similar or lower rates than observed in the placebo group.

Table 9.1.3–1. Preferred Terms in Which ≥ 2% of Patients in Any Treatment Group Had a Treatment-Emergent Adverse Event During the Double-blind Treatment Period of Study NAC-MD-01—Safety Population

Preferred Term	*Placebo (N = 277) n (%)*	*FDC 10/160 (N = 555) n (%)*	*FDC 10/320 (N = 555) n (%)*	*FDC 20/320 (N = 554) n (%)*	*NEB 10 (N = 555) n (%)*	*NEB 40 (N = 554) n (%)*	*VAL 160 (N = 555) n (%)*	*VAL 320 (N = 554) n (%)*
Patients with at least 1 TEAE during the double-blind treatment period	**100 (36.1)**	**193 (34.8)**	**185 (33.3)**	**189 (34.1)**	**196 (35.3)**	**198 (35.7)**	**165 (29.7)**	**190 (34.3)**
Headache	14 (5.1)	20 (3.6)	22 (4.0)	24 (4.3)	23 (4.1)	25 (4.5)	24 (4.3)	20 (3.6)
Fatigue	3 (1.1)	5 (0.9)	13 (2.3)	11 (2.0)	5 (0.9)	19 (3.4)	2 (0.4)	5 (0.9)
Dizziness	1 (0.4)	10 (1.8)	13 (2.3)	9 (1.6)	4 (0.7)	9 (1.6)	15 (2.7)	15 (2.7)
Nasopharyngitis	6 (2.2)	7 (1.3)	8 (1.4)	8 (1.4)	8 (1.4)	6 (1.1)	8 (1.4)	16 (2.9)
Sinus bradycardia	2 (0.7)	4 (0.7)	5 (0.9)	8 (1.4)	4 (0.7)	20 (3.6)	2 (0.4)	3 (0.5)
Bradycardia	0	8 (1.4)	8 (1.4)	6 (1.1)	7 (1.3)	14 (2.5)	3 (0.5)	0
Upper respiratory tract infection	6 (2.2)	11 (2.0)	7 (1.3)	6 (1.1)	8 (1.4)	12 (2.2)	7 (1.3)	8 (1.4)

Note: Patients were counted only once within each system organ class and preferred term. Preferred terms included in this table were based on Table 14.5.1.3A of the CSR, in which AE preferred terms were assessed categorically as having an incidence of < 2% or ≥ 2% utilizing no rounding of incidence values.

FDC = fixed-dose combination; N = number of patients in the Safety Population; n = number of patients who had the specified TEAE; Neb = nebivolol; TEAE = treatment-emergent adverse event; Val = valsartan.

9.1.4 Serious Adverse Events

A total of 80 SAEs were reported in 64 patients during Study NAC-MD-01, of which 27 SAEs occurred during the double-blind treatment period. There were no dose-related increases in SAEs in the FDC treatment groups. None of the SAEs were assessed by the Investigators to be related to investigational product. SAEs during the double-blind treatment period occurred at a low rate in all FDC treatment groups (range: 0.2% to 0.4%) and even at a numerically lower rate compared with the placebo group (1.4%) (Appendix 1, Table 14–6).

The number of SAEs during the double-blind treatment period in the FDC 20/320 mg group (0.2%) was lower than those in the high-dose monotherapy groups, nebivolol 40 mg (0.7%) and valsartan 320 mg (0.9%) (Appendix 1, Table 14–6). Similar rates of SAEs during the double-blind treatment period were also observed when FDC 20/320 mg was compared to more commonly utilized doses of monotherapy, nebivolol 10 mg (0.7%) and valsartan 160 mg (0.7%) (Appendix 1, Table 14–6).

9.1.5 Premature Discontinuations

9.1.5.1 Comparisons Among FDCs, Highest Dose Monotherapies, and Placebo Groups

A total of 446 patients prematurely discontinued during the double-blind treatment period from Study NAC-MD-01. There were no dose-related increases in discontinuations in the FDC treatment groups. The most common reason for discontinuation during the double-blind treatment period was withdrawal of consent, which occurred in 2.2% of patients on FDC 20/320 mg, 3.2% of patients on nebivolol 40 mg, and in 3.1% of patients on valsartan 320 mg.

Premature discontinuations due to any reason occurred at a low rate in all FDC treatment groups and even at a numerically lower rate compared with the placebo group (11.9%) (Appendix 1, Table 14–7). The number of discontinuations in the FDC 20/320 mg group (8.7%) was fewer than those in the highest-dose monotherapy groups, nebivolol 40 mg (13.7%) and valsartan 320 mg (10.5%) (Appendix 1, Table 14–7), meeting statistical significance in a post hoc analysis of FDC 20/320 mg vs nebivolol 40 mg (OR 0.598, $p = 0.008$) (Table 9.1.5.1–1). Moreover, the lower rate of discontinuations in the 20/320 mg FDC group relative to the highest-dose nebivolol group was clear throughout the duration of treatment, as shown in a Kaplan-Meier plot of discontinuations due to any reason (Figure 9.1.5.1–1).

Discontinuations specifically due to AEs were low in frequency for all treatment groups and were not dose-dependent in the FDC groups. A total of 1.6% of patients in the FDC 20/320 mg group experienced discontinuations due to AEs compared with 4.0% in the nebivolol 40 mg group and 1.8% in the valsartan 320 mg group (Appendix 1, Table 14–7), and statistical significance was met in a post hoc analysis of FDC 20/320 mg vs nebivolol 40 mg (OR 0.399, p = 0.018; Table 9.1.5.1–1). FDC 20/320 mg also demonstrated numerically lower rates of SAEs and severe TEAEs compared with nebivolol 40 mg, however these comparisons did not achieve statistical significance (Table 9.1.5.1–1).

Table 9.1.5.1–1. Tolerability and Safety Findings (Including Discontinuations and Adverse Events) of the FDC 20/320 mg and Nebivolol 40 mg Treatment Groups

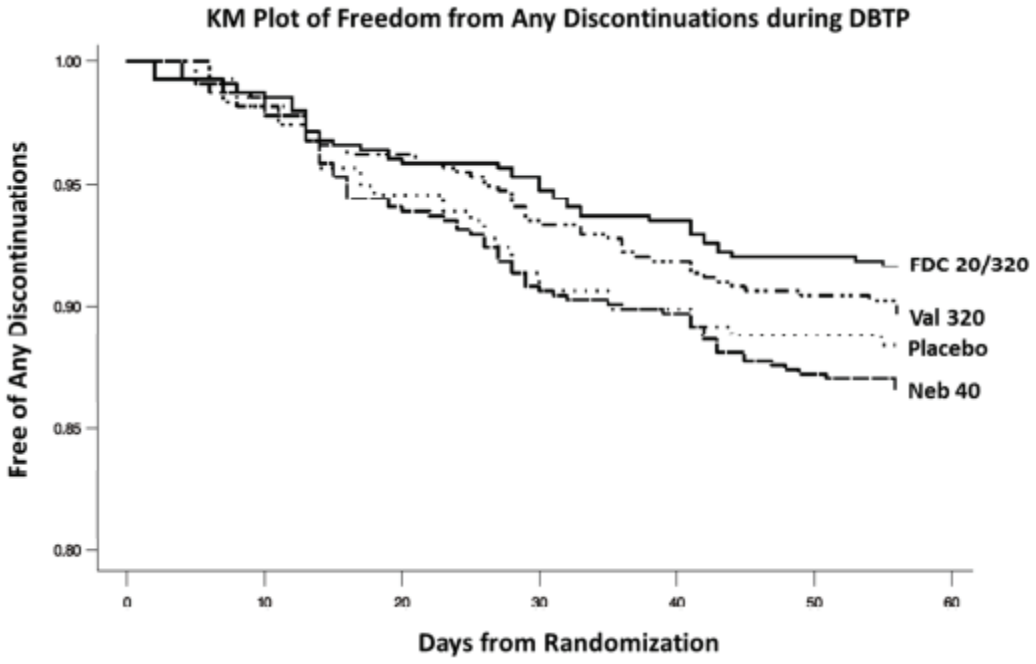
	FDC 20/320 mg (N=554) (%)	***Nebivolol 40 mg (N=554) (%)***	***Odds Ratio[a]***	***p-Value***
Discontinuation due to any reason	8.7%	13.7%	0.598	0.008
AEs leading to Discontinuation	1.6%	4.0%	0.399	0.018
SAEs	0.2%	0.7%	0.249	0.179
Severe TEAEs	0.9%	1.8%	0.495	0.194

Note: This table shows the percentage of patients experiencing a discontinuation due to any reason, an AE leading to discontinuation, an SAE, or a severe TEAE.

a Odds ratios were then calculated between the FDC and monotherapy group which generated the p-values displayed in the final column.

AE = adverse event; FDC = fixed-dose combination; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Figure 9.1.5.1–1. Kaplan-Meier Plot of Freedom From Discontinuations Due to Any Reason During the Double-blind Treatment Phase of Study NAC-MD-01: FDC 20/320 mg, Nebivolol 40 mg, Valsartan 320 mg, and Placebo



Note: This figure shows the rates of freedom from discontinuation due to any reason during Study NAC-MD-01 over 8 weeks of double-blinded treatment with FDC 20/320 mg, nebivolol 40 mg, valsartan 320 mg, or placebo.

Post hoc assessment of the difference between the plots discontinuations of the FDC 20/320 mg group vs the nebivolol 40 mg group showed an odds ratio 0.598, p = 0.008.

DBTP = double-blind treatment phase; FDC = fixed-dose combination; KM = Kaplan-Meier; Neb = nebivolol; Val = valsartan.

Table 9.1.5.1–2 summarizes tolerability and safety findings from Study NAC-MD-01 for patients treated with FDC 20/320 mg and those treated with the highest dose of valsartan (320 mg). Patients treated with FDC 20/320 mg, compared with those treated with valsartan 320 mg, demonstrated numerically lower rates of discontinuations due to any reason, AEs leading to discontinuation, SAEs, and severe TEAEs, however these comparisons did not meet statistical significance

Table 9.1.5.1–2. Tolerability and Safety Findings (Including Discontinuations and Adverse Events) of the FDC 20/320 mg and Valsartan 320 mg Treatment Groups

	FDC 20/320 mg (N=554) (%)	*Valsartan 320 mg (N=554) (%)*	*Odds Ratio*[a]	*p-Value*
Discontinuation due to any reason	8.7%	10.5%	0.813	0.312
AEs leading to Discontinuation	1.6%	1.8%	0.898	0.817
SAEs	0.2%	0.9%	0.199	0.102
Severe TEAEs	0.9%	2.2%	0.411	0.087

Note: This table shows the percentage of patients experiencing a discontinuation due to any reason, an AE leading to discontinuation, an SAE, or a severe TEAE.

a Odds ratios were then calculated between the FDC and monotherapy group which generated the p-values displayed in the final column.

AE = adverse event; FDC = fixed-dose combination; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

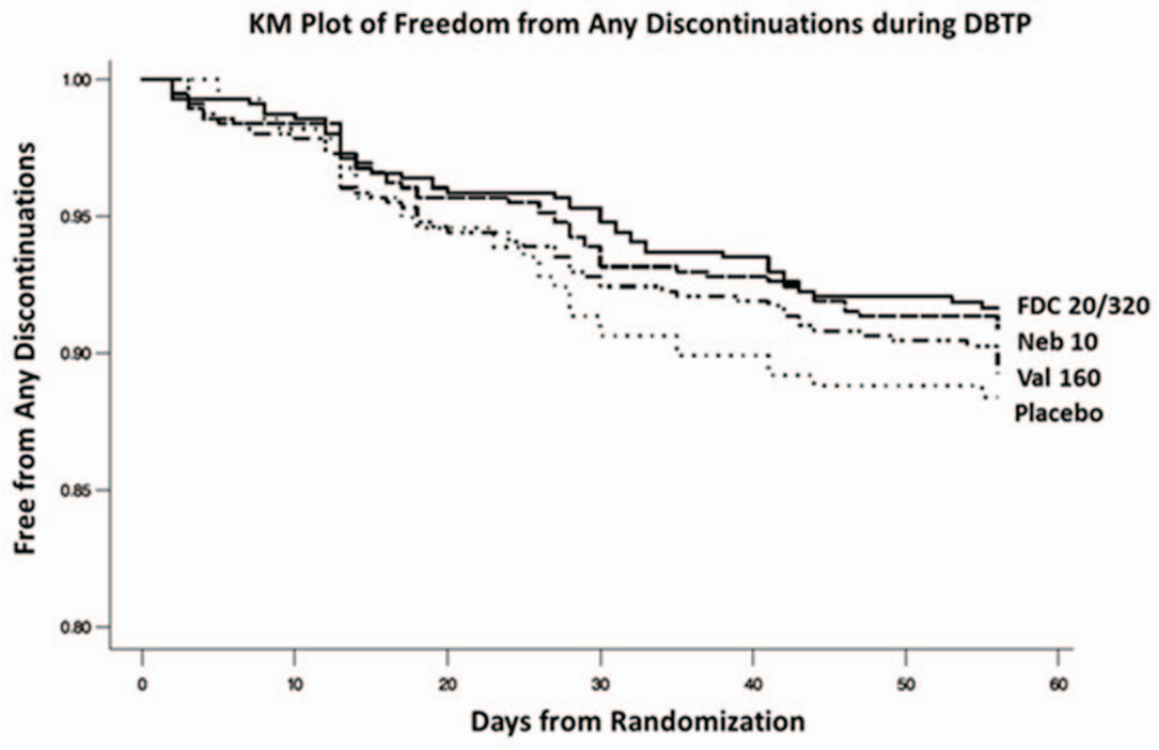
In terms of individual AEs leading to discontinuation, the most common event was bradycardia, which occurred in 0.5% of patients on FDC 20/320 mg, 0.9% of patients on nebivolol 40 mg, 0% of patients on valsartan 320 mg, and 0% of patients on placebo (Appendix 1, Table 14–7).

9.1.5.2 Comparisons Among Highest-Dose FDC (20/320 mg), Lower-Dose Monotherapy, and Placebo Groups

Similar rates of discontinuation were observed when FDC 20/320 mg (8.7%) was compared with even lower and more commonly utilized doses of monotherapy, nebivolol 10 mg (9.0%) and valsartan 160 mg (10.3%) (Appendix 1, Table 14–7). The findings demonstrate similar discontinuation rates between FDC 20/320 mg and even lower doses of monotherapy or placebo. Notably, FDC 20/320 mg showed similar rates of discontinuation due to bradycardia (0.5%) as compared with nebivolol 10 mg (0.5%) (Appendix 1, Table 14–7).

Moreover, these discontinuation findings in the FDC 20/320 mg group relative to the nebivolol 10 mg and valsartan 160 mg were clear throughout the duration of treatment, as shown in the Kaplan-Meier plots of discontinuations due to any reason in Figure 9.1.5.2–1.

Figure 9.1.5.2–1. Kaplan-Meier Plot of Freedom From Discontinuations Due to Any Reason During the Double-blind Treatment Phase of Study NAC-MD-01: FDC 20/320 mg, Nebivolol 10 mg, Valsartan 160 mg, and Placebo



Note: This figure shows the rates of freedom from discontinuation due to any reason during Study NAC-MD-01 over 8 weeks of double-blinded treatment with FDC 20/320 mg, nebivolol 10 mg, valsartan 160 mg, or placebo.
DBTP = double-blind treatment phase; FDC = fixed-dose combination; KM = Kaplan-Meier; Neb = nebivolol; Val = valsartan.

9.1.6 Deaths

No patients who received active treatment (ie, Safety Population, N = 4159) in Study NAC-MD-01 died. Two patients died during the single-blind placebo run-in period, prior to administration of investigational product (Table 9.1.6–1).

Table 9.1.6–1. Patients With Fatal Serious Adverse Events in Study NAC-MD-01—Screened Population

Age/Sex	*On Study Drug (Y/N)*	*Date of First/Last Dose of DB Treatment*	*Preferred Term/ Investigator Term*	*Related to Study Drug (Y/N)*	*Autopsy (Y/N)*
43/F	N	Not applicable	Road traffic accident/motor vehicle accident	N	N
69/M	N	Not applicable	Cerebrovascular accident/ cerebral vascular accident	N	N

Note: The 2 fatal SAEs reported in this study both occurred during the single-blind run-in period, before the patients were randomized to a treatment group. Neither patient took any double-blind investigational product.
DB = double-blind; F = female; M = male; N = no; SAE = serious adverse event; Y = yes.

9.1.7 Laboratory Values, Vital Signs, and Electrocardiogram Parameters

Mean changes in laboratory values, as well as the incidence of potentially clinically significant laboratory values, were low. In addition, there was a low incidence of potentially clinically significant values for laboratory evaluations that were potentially associated with TEAEs.

There were no clinically meaningful changes in vital signs during Study NAC-MD-01. There was no unexpected safety signal in pulse rate or unexpected magnitude of pulse-rate change.

There were no clinically meaningful changes in ECG findings during Study NAC-MD-01.

9.1.8 8-Week Placebo-Controlled Study (NAC-MD-01) Safety Conclusions

The Safety Population in this study consisted of 4159 patients, with a total of 1664 patients receiving nebivolol/valsartan FDC (273 patient-years of exposure). There was a low incidence of SAEs, AEs, any premature discontinuations, or discontinuations due to AEs in this study, as was expected; both monotherapy components are well-established, commonly used in practice, and have AE profiles comparable to placebo and favorable tolerability (Bystolic 2014; Diovan, 2014).

None of the SAEs were judged to be related to the investigational product, and the FDC 20/320 mg group had the lowest rate of SAEs during the study. There were no deaths during the double-blind treatment or down-titration periods. Moreover, there were no dose-related increases in SAEs among the FDC groups, and the rates of safety findings in FDC groups were similar, or numerically lower in some cases, compared with higher-dose monotherapy, lower-dose monotherapy, and placebo groups.

Lower rates of TEAEs, SAEs, any discontinuations, and AEs leading to discontinuations were observed between FDC 20/320 mg and the highest approved doses of monotherapy (nebivolol 40 mg and valsartan 320 mg), which were the doses used in the primary efficacy analysis to fulfill requirements for approval of an FDC. In an even more stringent comparison, FDC 20/320 mg was compared with more commonly utilized and lower doses of monotherapy, nebivolol 10 mg and valsartan 160 mg, and showed similar safety and tolerability findings.

In summary, all doses of FDC demonstrated safety and tolerability profiles similar to those of each monotherapy and even placebo.

10.0 OVERVIEW OF OPEN-LABEL, LONG-TERM SAFETY STUDY (NAC-MD-02)

The positive safety and tolerability findings in the placebo-controlled study NAC-MD-01 are supported by a robust dataset demonstrating long-term safety and tolerability of the free-tablet combination in the 52-week open-label long-term safety study NAC-MD-02. Studies NAC-MD-01 and NAC-MD-02 were conducted in parallel on separate hypertensive patients (ie, separate Safety Populations) with similar baseline characteristics.

There were no new common AEs seen in up to 1 year of treatment in patients taking the nebivolol and valsartan combination that were not already known to be associated with either monotherapy component. No increases in rates or magnitude of AEs were seen, as compared to prior clinical experience with either component agent.

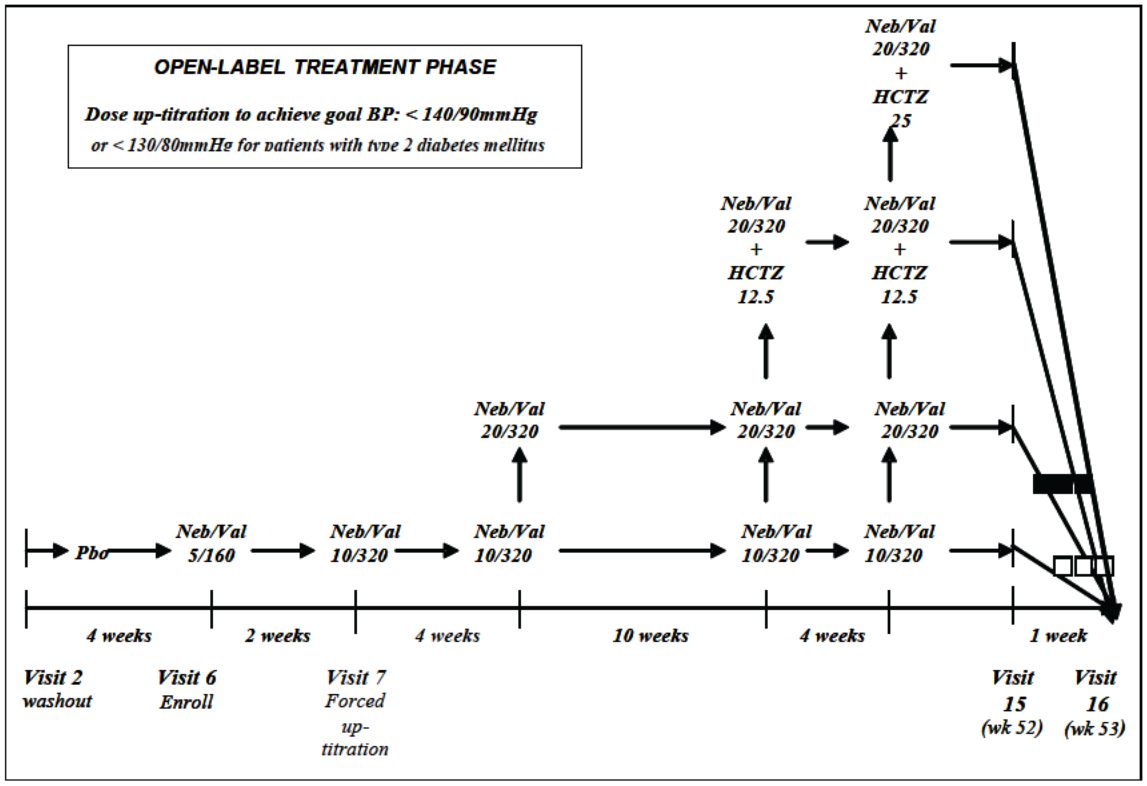
10.1 STUDY DESIGN

Study NAC-MD-02 enrolled patients 18 years or older with a diagnosis of stage 1 or stage 2 hypertension. The study was conducted in 133 centers in the United States. Because this long-term study was initiated prior to the availability of this FDC product, NAC-MD-02 utilized free-tablet combination of nebivolol and valsartan. Bioequivalence had been demonstrated between the 20/320 mg FDC and the coadministration of 20 mg nebivolol and 320 mg valsartan as free-tablet combination, demonstrating a valid bridge between the FDC and the approved monotherapy products (Study NAC-PK-05), and FDA agreed with the appropriateness of this approach.

Study NAC-MD-02 was designed to evaluate the long-term safety of the nebivolol and valsartan combination and to fulfill ICH safety exposure requirements of at least 300 patients exposed to the nebivolol and valsartan combination for 6 months and 100 patients exposed for 1 year (International Conference on Harmonisation, 1994). These ICH criteria were fully met and exceeded.

Study NAC-MD-02 consisted of 1 week of screening followed by a 4-week washout, single-blind placebo, run-in phase, followed by a 52-week open-label treatment phase and a 1-week down-titration phase. An overview is provided in Figure 10.1–1.

Figure 10.1–1. NAC-MD-02 Dose Titration Schematic



Numerals written underneath a drug's name are the dosage in mg.
BP = blood pressure; HCTZ = hydrochlorothiazide; Neb/Val = nebivolol/valsartan; Pbo = placebo.

The 4-week, single-blind placebo phase served as a washout phase for patients who were on antihypertensive drugs at the time of enrollment, and as an adjustment phase for patients to become familiar with study visits.

At the end of the washout/run-in phase, patients still meeting entry criteria were enrolled in the study and assigned to free-tablet combination of nebivolol 5 mg + valsartan 160 mg. After 2 weeks of treatment with this combination, the doses of nebivolol and valsartan were doubled for all patients to nebivolol 10 mg + valsartan 320 mg and continued for a minimum of 4 weeks. If the goal BP (< 140/90 mm Hg for nondiabetic or < 130/80 mm Hg for type 2 diabetic patients) was not met, patients were up-titrated and could have HCTZ added as described in Figure 10.1–1. If, after a total of 14 weeks of treatment with the addition of HCTZ, BP goal was not achieved, the patient was discontinued from the study.

If a patient experienced symptoms of hypotension or displayed intolerance to study medication at any time during the treatment phase, the dose was reduced to the previous lower dose at the Investigator's discretion. If HCTZ was started, the protocol instructed that it not be discontinued. After 52 weeks of treatment or at early termination, patients entered a 1-week down-titration treatment phase. During this phase, nebivolol doses were down-titrated while the dose of valsartan remained constant.

10.1.1 Inclusion/Exclusion Criteria in Study NAC-MD-02

The inclusion and exclusion criteria in Study NAC-MD-02 were similar to those in Study NAC-MD-01 (Section 8.1.1).

10.1.2 Endpoints

The purpose of this study was to evaluate the long-term safety of the combination of nebivolol and valsartan in patients with hypertension. Efficacy assessments were also conducted.

10.1.3 Statistical Methods for Study NAC-MD-02

Safety analyses were performed using the Safety Population and parameters included AEs, clinical laboratory parameters, vital sign measurements, physical examinations, and ECG measurements. For each safety parameter, the last assessment made before the first dose of open-label investigational product was used as the baseline value. Each safety analysis was performed based on 2 sets of data: 1) all measurements in the Safety Population, and 2) measurements before the potential initiation of HCTZ. Efficacy assessments were not grouped into primary, secondary, or additional categories, and descriptive statistics were used for summarizing data.

10.2 STUDY RESULTS

10.2.1 Patient Disposition

A total of 810 patients were enrolled; 807 patients received at least 1 dose of open-label investigational product (Safety Population); and 799 patients had at least 1 postbaseline assessment of trough seated DBP or trough seated SBP (ITT Population).

As shown in Table 10.2.1–1, 60.4% of the patients completed the study. The most frequent reasons for discontinuation during the open-label treatment phase were insufficient therapeutic response (did not meet BP goal) (8.4%), protocol deviation/violation (7.5%), and withdrawal of consent (6.9%).

Table 10.2.1–1. Number (%) of Patients Discontinued From the Study NAC-MD-0-2 During the Open-label Treatment Phase—Enrollment Population

Patient Status	*Free-Tablet Combination (N = 810) n (%)*
Open-label treatment phase	
Completed open-label treatment phase	489 (60.4)
Prematurely discontinued	321 (39.6)
Reason for premature discontinuation	
Insufficient therapeutic response[a]	68 (8.4)
Protocol violation[b]	61 (7.5)
Withdrawal of consent	56 (6.9)
Adverse event	53 (6.5)
Lost to follow-up	45 (5.6)
Other reasons	29 (3.6)
Study terminated by Sponsor[c]	5 (0.6)
Sitting pulse rate < 50 bpm	4 (0.5)

Note: In the open-label treatment phase, % = n/N × 100.

a Did not meet blood pressure goal.

b Deviation/violation.

c Refers to investigational sites that were closed by the Sponsor during the study.

bpm = beats per minute; N = number of patients in the Enrollment Population; n = number of patients within a specified category.

10.2.2 Key Demographic Characteristics

As shown in Appendix 1, Table 14–8, the mean age of patients in the Safety Population of Study NAC-MD-02 was 52.7 years; 65.8% of patients were white; and 55.5% of patients were male. The baseline seated mean trough BP was 158/100 mm Hg.

10.3 SAFETY RESULTS OF STUDY NAC-MD-02

10.3.1 Safety Population and Extent of Exposure

In Study NAC-MD-02, 807 patients were exposed to nebivolol/valsartan free-tablet combination for up to 52 weeks (Safety Population).

The overall mean treatment duration was 285.7 days. A total of 621 patients completed at least 180 days of therapy with the nebivolol/valsartan free-tablet combination, and 476 patients completed at least 360 days of therapy, exceeding the ICH-based requirements of exposure to an investigational product. The number of patient-years of exposure was 631.3.

10.3.2 Summary of Adverse Events

Table 10.3.2–1 is a summary of AEs that occurred during the open-label treatment phase and the open-label down-titration phase. The rates of death, SAEs, and AEs leading to study discontinuation were low in Study NAC-MD-02. Three deaths were reported, none judged to be related to investigational product (Section 10.3.6). During the open-label treatment phase, 19 patients reported SAEs (Section 10.3.4), and 53 patients discontinued from the study due to AEs (Section 10.3.5).

Table 10.3.2–1. Overall Summary of Adverse Events in Study NAC-MD-02—Safety Population

Event	***Free-Tablet Combination (N = 807, M = 609) n (%)***
Patients who died	3 (0.4)
Patients with SAEs	19 (2.4)
Patients with ADOs occurring during OLTP	53 (6.6)
Patients with ADOs occurring during OLDP	2 (0.3)
Patients with TEAEs	478 (59.2)

Note: Deaths, SAEs, and TEAEs were those that started on or after the date of the first dose of open-label investigational product and no more than 30 days after the date of the last dose of open-label investigational product.

Percentages were calculated as n/M if counting the number in the OLDP; otherwise percentages were calculated as n/N.

If a patient with an ADO during the OLDP had the same AE leading to discontinuation during the OLTP, this AE was only presented for the OLTP in all other AE tables and listings.

ADO = adverse event leading to dropout (ie, premature discontinuation); AE = adverse event; M = number of patients entering the OLDP in the Safety Population; N = number of patients in the Safety Population; n = number of patients who had the event; OLDP = open-label down-titration phase; OLTP = open-label treatment phase; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

10.3.3 Common Treatment-Emergent Adverse Events

Table 10.3.3–1 presents the most common TEAEs (reported by ≥ 2% of patients) that occurred during the 52-week open-label treatment phase. TEAEs were reported in 477 patients (59.1%). The most commonly reported TEAEs during the open-label treatment phase were headache (5.7%), nasopharyngitis (5.0%), and upper respiratory tract infection (4.6%). The percentages of TEAEs that occurred before the initiation of HCTZ, if it was initiated, were similar to the percentages observed in the entire Safety Population.

Most TEAEs during the open-label treatment phase were mild (280 [34.7% of the Safety Population]) or moderate (167 [20.7% of the Safety Population]) in intensity. A total of 30 patients in the study (3.7%) had TEAEs that were judged by the Investigator to be severe in intensity. In addition, most of the common TEAEs reported were assessed as not related to investigational product.

Table 10.3.3–1. Preferred Terms in Which ≥ 2% of Patients Had a Treatment-Emergent Adverse Event During the Open-label Treatment Phase of Study NAC-MD-02—Safety Population

Preferred Term	*Safety Population (N = 807) n (%)*	*Safety Population Before the Potential Initiation of HCTZ (N=807) n (%)*
Patients with at least 1 TEAE	477 (59.1)	410 (50.8)
Headache	46 (5.7)	39 (4.8)
Nasopharyngitis	40 (5.0)	35 (4.3)
Upper respiratory tract infection	37 (4.6)	27 (3.3)
Dizziness	35 (4.3)	26 (3.2)
Bronchitis	24 (3.0)	17 (2.1)
Cough	22 (2.7)	17 (2.1)
Fatigue	21 (2.6)	18 (2.2)
Back pain	20 (2.5)	16 (2.0)
Urinary tract infection	20 (2.5)	14 (1.7)
Bradycardia	19 (2.4)	15 (1.9)
Sinusitis	19 (2.4)	18 (2.2)
Oedema peripheral	18 (2.2)	14 (1.7)

Note: Version 15.1 of the *Medical Dictionary for Regulatory Activities* was used to code TEAEs. Patients were counted only once within each system organ class and each preferred term.

Percentages were calculated as n/N × 100.

Preferred terms included in this table were based on Table 14.5A.1.3A, in which AE preferred terms were assessed categorically as having an incidence of < 2% or ≥ 2% utilizing no rounding of incidence values.

AE = adverse event; HCTZ = hydrochlorothiazide; N = the number of patients in the Safety Population; n = number of patients with TEAE occurring on or after the date of the first dose of open-label investigational product and 1) within 30 days of the date of the last dose of open-label investigational product for patients who entered the open-label treatment phase and did not enter the open-label down-titration phase, 2) no later than the day of the early termination visit for patients who prematurely discontinued from the open-label treatment phase and entered the open-label down-titration phase, or 3) no later than the day of Visit 15 for patients who completed the open-label treatment phase and entered the open-label down-titration phase; TEAE = treatment-emergent adverse event.

10.3.4 Serious Adverse Events

A total of 39 SAEs were reported in 29 patients during Study NAC-MD-02. Appendix 1, Table 14–9 presents the incidence of on-therapy SAEs that occurred during the 52-week open-label treatment phase in the Safety Population and in patients before potential initiation of HCTZ therapy if it was started. On-therapy SAEs occurred at a low rate (2.1% during the open-label treatment phase and 0.3% during the open-label down-titration phase). The percentage of SAEs that occurred before the potential initiation of HCTZ was similar to those observed in the Safety Population. Only 1 SAE (bradycardia, a known effect of nebivolol) in the study was considered by the Investigator to be related to investigational product.

10.3.5 Premature Discontinuations

Table 10.2.1–1 describes the number and reasons for premature discontinuation during Study NAC-MD-02. The top 3 reasons for discontinuation were, in decreasing order, insufficient therapeutic response, protocol violations, and withdrawal of consent. There was a low incidence of discontinuations due to AEs in the open-label treatment phase of Study NAC-MD-02 as shown in Table 10.3.5–1.

Table 10.3.5–1. Incidence of Adverse Events Associated With Premature Discontinuation in > 1 Patient During the Open-label Treatment Phase in Study NAC-MD-02—Safety Population

Preferred Term	*Safety Population (N = 807) n (%)*	*Safety Population Before the Potential Initiation of HCTZ (N = 807) n (%)*
Overall discontinuation due to AEs	53 (6.6)	45 (5.6)
Bradycardia	11 (1.4)	8 (1.0)
Fatigue	4 (0.5)	4 (0.5)
Alanine aminotransferase increased	3 (0.4)	3 (0.4)
Glomerular filtration rate decreased	3 (0.4)	1 (0.1)
Acute myocardial infarction	2 (0.2)	2 (0.2)
Blood pressure increased	2 (0.2)	2 (0.2)
Dizziness	2 (0.2)	2 (0.2)
Headache	2 (0.2)	2 (0.2)
Hypotension	2 (0.2)	2 (0.2)
Non-cardiac chest pain	2 (0.2)	2 (0.2)

Note: Version 15.1 of the *Medical Dictionary for Regulatory Activities* was used to code TEAEs. Patients were counted only once within each system organ class and each preferred term.

Percentages were calculated as n/N × 100.

AEs = adverse events; HCTZ = hydrochlorothiazide; N = number of patients in the Safety Population; n = number of patients who prematurely discontinued due to an AE occurring during the period; TEAE = treatment-emergent adverse event.

10.3.6 Deaths

Three patients had SAEs that resulted in death during Study NAC-MD-02 (Table 10.3.6–1). Two of these deaths (gunshot wound and cardiac arrest) occurred while patients were on open-label treatment. The third (coronary artery occlusion) occurred 8 days after the patient completed the open-label down-titration phase. All deaths were assessed by Investigators to be not related to investigational product.

Table 10.3.6–1. Patients With Fatal Serious Adverse Events in Study NAC-MD-02—Screened Population

Age/Sex	*On Study Drug (Y/N)*	*Date of First/ Last Dose of OL Treatment*	*Preferred Term/ Investigator Term*	*Related to Study Drug (Y/N)*	*Autopsy (Y/N)*
56/M	Y	2011-09-29/ 2012-03-17	Gun shot wound/ gun shot wound	N	Y
59/M	N	2011-12-07/ 2012-12-13	Coronary artery occlusion/ occlusion of coronary artery	N	Y
67/M	Y	2011-10-24/ 2012-01-04	Cardiac arrest/ cardiac arrest	N	N

M = male; N = no; OL = open-label; Y = yes.

10.3.7 Laboratory Values, Vital Signs, and Electrocardiogram Parameters

Mean changes in laboratory values, vital signs, and ECG parameters, as well as the overall incidence of potentially clinically significant values for these safety parameters, were generally low. Small differences were seen in some laboratory values (potassium, blood urea nitrogen, creatinine, and uric acid) between patients receiving the nebivolol/valsartan combination alone versus patients receiving the nebivolol/valsartan combination plus HCTZ.

10.3.8 Open-label Long-term Safety Study (NAC-MD-02) Safety Conclusions

Study NAC-MD-02 demonstrated the long-term safety of the nebivolol and valsartan combination and met the ICH criteria for exposure, with 621 patients treated with nebivolol + valsartan free-tablet combination for at least 180 days, and 476 patients for at least 360 days. The Safety Population in this study consisted of 807 patients (631 patient-years of exposure).

No new AEs that had not been previously observed in the experiences of either monotherapy were detected in up to 52 weeks of treatment. The relatively low occurrence of β-blocker-associated AEs (bradycardia, erectile dysfunction, fatigue, and weight gain) in this study is consistent with the results of the 8-week placebo-controlled trial, Study NAC-MD-01. Overall, long-term treatment with nebivolol + valsartan free-tablet combination, with the potential initiation of HCTZ, was safe and well tolerated, further supporting the favorable safety profile observed in the placebo-controlled trial, Study NAC-MD-01.

10.4 SUMMARY OF SAFETY

Both nebivolol and valsartan are approved, safe, well tolerated, efficacious, and widely utilized antihypertensive agents, either alone or in combination. Along with extensive clinical experience, a total of 4966 patients were analyzed in the Phase 3 Safety Population, with 1664 patients exposed to the nebivolol/valsartan FDC in the 8-week, placebo-controlled Study NAC-MD-01 (Giles et al, 2014; Waeber and Feihl, 2014) and 807 patients exposed to the free-tablet combination of nebivolol and valsartan in the 52-week, open-label, safety Study NAC-MD-02.

Favorable safety and tolerability results of this combination were consistent across both studies, demonstrating low numbers of TEAEs, SAEs, AEs leading to discontinuations, and deaths. Overall, AEs were generally low in frequency, mild or moderate in intensity, and not related to investigational product.

Furthermore, in Study NAC-MD-01, rates of AEs, SAEs, any discontinuations, and AEs leading to discontinuation were 1) not elevated in the FDC groups, 2) not related to FDC dose, and 3) occurred at comparable or lower rates than rates observed in the monotherapy groups or even the placebo group. These safety and tolerability results were consistent when FDC 20/320 mg was compared to high-dose monotherapy (nebivolol 40 mg or valsartan 320 mg) or even, more stringently, to the more commonly utilized lower doses of monotherapy (nebivolol 10 mg or valsartan 160 mg).

Study NAC-MD-02 long-term data were supportive of the safety results in Study NAC-MD-01. In both studies, no new AEs were observed in up to 1 year of treatment in patients taking the nebivolol/valsartan FDC or free-tablet combination that were not already known to be associated with either drug monotherapy. No increases in rates or magnitude of AEs were seen, as compared to the extensive, prior clinical experience with either component agent.

Thus, the data from studies NAC-MD-01 and NAC-MD-02, the experience from extensive marketed use of both component drugs, and safety data from registration studies of both drugs (Bystolic, 2014; Diovan, 2014) indicate that the nebivolol/valsartan combination is well tolerated, with no excessive or unexpected safety signals, including during long-term exposure, in patients with stage 1 or 2 hypertension.

11.0 DOSING SCHEDULE RECOMMENDATIONS

As described in Section 6.3, the Sponsor is seeking approval of the FDC for the following indications: replacement therapy, add-on therapy, and initial therapy. The proposed clinical doses, investigated in the nebivolol/valsartan FDC program, are 5/80 mg, 5/160 mg, 10/160 mg, 10/320mg, and 20/320 mg per day.

Replacement Therapy: Practitioners are currently able to prescribe free tablets of nebivolol (Bystolic) and valsartan (Diovan). Based on a patient's current free-tablet combination of nebivolol and valsartan, 1 of the 5 FDCs could be substituted, as appropriate, as replacement therapy. With availability of each of the 5 FDCs, a patient could be switched, as appropriate, to an FDC with similar doses. As described in Section 5.1.1, an FDC of antihypertensive agents represents a therapeutic alternative to free-tablet combinations because an FDC provides greater convenience by reducing the number of dosage forms and simplifying treatment and possibly improving compliance (Burnier, 2006).

Add-on Therapy: In patients whose BP is not adequately controlled with nebivolol (or another β-blocker) alone, or valsartan (or another ARB) alone, treatment may be switched to the nebivolol/valsartan FDC. In this way, a single-tablet FDC provides both the original drug and a second drug in combination. Similar to replacement therapy, the availability of 5 different FDC doses would also be beneficial when used as add-on therapy and mimics real world clinical practice.

Initial Therapy: For patients who are likely to need multiple drugs to achieve their BP goals, the nebivolol/valsartan FDC may be used as initial therapy with a starting dose of either FDC 5/80 mg or FDC 10/160 mg. There is clinical trial experience with initial therapy with each of these doses. Moreover, titration by simple dose-doubling allows transition from FDC 5/80 mg to 10/160 mg; and, if needed, to the maximum FDC dose of 20/320 mg, which was the dose that demonstrated attainment of maximal BP control rates. Thus, these proposed dosing regimens are as follows:

- FDC 5/80 mg to FDC 10/160 mg to FDC 20/320 mg, or
- FDC 10/160 to FDC 20/320

These titrations were examined in Study NAC-MD-01 and reflect the timing of treatment initiation, BP re-assessment, and potential dose adjustment that occurs in customary medical practice. The dose doubling of each of the FDC doses within each treatment group (FDC 5/80 mg to FDC 10/160 mg; FDC 5/160 mg to FDC 10/320 mg; and FDC 10/160 mg to FDC 20/320 mg) led to further SBP/DBP reductions with further attainment of BP control.

Since hypertensive patients require individualized treatment options based on the severity of their disease, age, comorbidities, and experience on prior medications, the recommended regimen offers safe and effective treatment options that can be titrated to higher dosing options as appropriate.

The recommended dosing regimen is supported by the incremental efficacy observed after dose up-titration, the low rates of TEAEs, SAEs, and AEs leading to discontinuation, and the established safe and effective utilization of each of the approved, component drugs.

12.0 BENEFIT AND RISK

The nebivolol/valsartan FDC, studied in a development program of almost 5000 hypertensive patients, demonstrates a favorable benefit-risk profile of all doses of nebivolol and valsartan administered in combination. For patients with hypertension, this provides the first and only FDC of a β-blocker and an ARB in a number of combinations that will allow for flexible dosing to tailor therapy to the needs of the individual patient. The safety and efficacy profile of each of these individual therapies, nebivolol and valsartan, has been well defined by their extensive use in clinical practice. Building on that basis, this development program demonstrated the efficacy, safety, and tolerability of the nebivolol/valsartan FDC. Furthermore, based on well-accepted, published data on compliance and combination products, this FDC of 2 widely used antihypertensive agents is likely to contribute to improved compliance with the treatment regimen for a disease requiring long-term therapy, and will be a clinically useful addition to treatment options for patients with hypertension.

12.1 EFFICACY

The NAC-MD-01 study met the regulatory "combination rule" for a FDC, by demonstrating, with statistical significance, that nebivolol and valsartan each contributed to the effects of the FDC when compared to the highest approved monotherapy doses. Thus, this program met its regulatory goal by demonstrating that the nebivolol/valsartan FDC reduced BP to a greater and statistically significant extent compared to the highest-dose monotherapy.

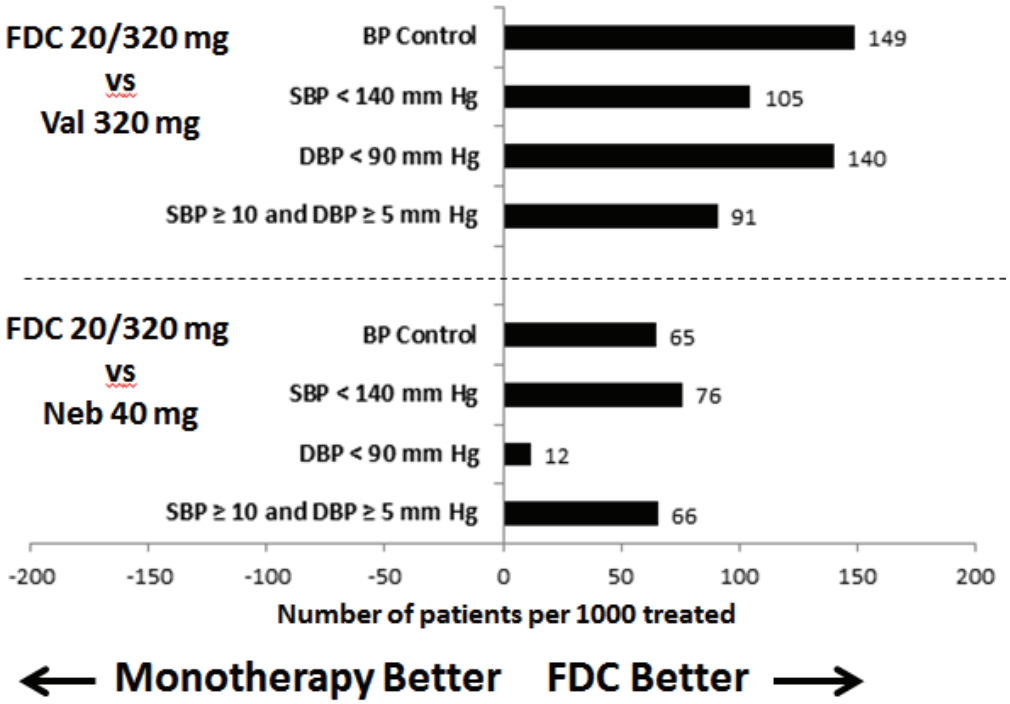
Study NAC-MD-01 also demonstrated that treatment with each of the 5 FDCs led to clinically meaningful reductions in both SBP and DBP compared with respective monotherapies. Because the main comparison in this study (FDC 20/320 vs highest-dose monotherapy) used a dose of nebivolol (40 mg) rarely utilized in clinical practice (< 1%), an analysis of FDC 20/320 vs nebivolol 20 mg was also performed and a higher, statistically significant treatment effect with FDC treatment was observed compared with monotherapy. Moreover, a greater percentage of patients achieved target BP control for each of the 5 FDC doses as compared with each component monotherapy, all of which met statistical significance. Over 50% of patients treated with FDC 20/320 mg achieved BP goal; this level of BP control was not observed with any dose of monotherapy, including the highest doses, and was approximately 2.5-fold the rate of placebo. These BP control data are robust, as shown by even stronger results when a more current definition of BP control is used as the target. These positive findings are supported by the consistency of efficacy observed in the maintenance of ambulatory BP reductions over the 24-hour dosing period and the comparable BP reductions observed in the long-term safety study, NAC-MD-02.

In order to illustrate the clinical benefit of the NAC-MD-01 efficacy results, analyses were performed to demonstrate the impact of FDC treatment versus the findings with the comparator monotherapy. These analyses assessed the number of patients with a favorable efficacy response in the FDC 20/320 mg group versus those with a favorable response in each high-dose monotherapy group, per 1000 patients treated. This was determined directly from Study NAC-MD-01 data ($N_{\text{ITT Population}} = 4118$), and the efficacy responses examined were: the achievement of BP control, achievement of SBP or DBP goal, and achievement of at least a SBP/DBP reduction of 10/5 mm Hg. The *higher* number of favorable responses with FDC treatment is graphed in Figure 12.1–1.

More patients, per 1000 patients treated, exhibited favorable responses to FDC 20/320 mg treatment versus the number of patients exhibiting a favorable response to high-dose monotherapy, for each type of achievement. For example, for every 1000 patients treated, 149 *more* patients would be expected to achieve BP control with FDC 20/320 mg compared with the number of patients achieving BP control with valsartan 320 mg; and 65 *more* patients with FDC 20/320 mg would be expected to achieve BP control compared with those in the nebivolol 40 mg group.

In sum, for each type of efficacy goal, more patients treated with FDC achieved a favorable response versus those treated with either high-dose monotherapy.

Figure 12.1–1. Patients Achieving BP Control, SBP Response, DBP Response, and BP Reductions per 1000 Patients Treated



Note: This figure shows the number of patients expected to achieve BP control (BP goals of < 140/90 mm Hg), SBP goals (< 140 mm Hg), DBP goals (< 90 mm Hg), or reductions in SBP/DBP of greater than or equal to 10/5 mm Hg per 1000 patients treated based on the results of Study NAC-MD-01. All bars are to the right of zero, indicating that treatment with FDC 20/320 mg will lead to *more* patients achieving BP goals than either highest-dose monotherapy.

BP = blood pressure; DBP = diastolic blood pressure; FDC = fixed-dose combination; Neb = nebivolol; SBP = systolic blood pressure; Val = valsartan.

12.2 SAFETY AND TOLERABILITY

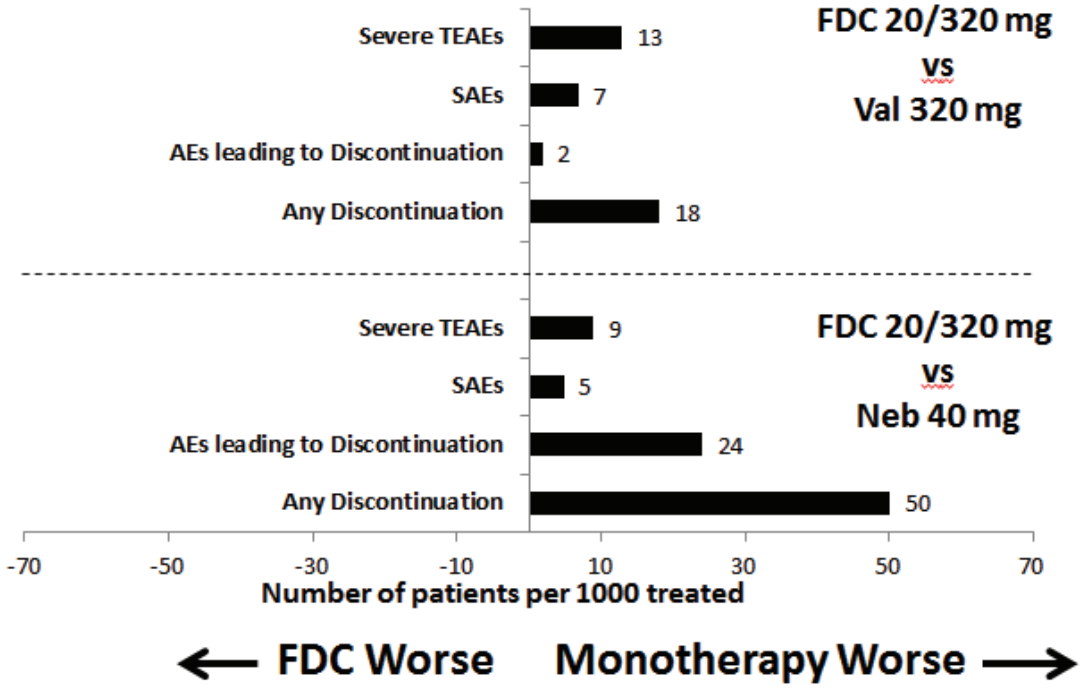
The nebivolol/valsartan program, with a systematic examination of approximately 5000 patients, demonstrates that this FDC is a safe and well-tolerated agent for the treatment of hypertension. The vast clinical-study and post-approval experience of each monotherapy component is further supportive of the current program's data. A favorable safety and tolerability profile was demonstrated by the nebivolol/valsartan FDC in Study NAC-MD-01, as rates of AEs, SAEs, discontinuations due to any reason, and discontinuations due to AEs were comparable to the profile of each component monotherapy and even to placebo, with no dose dependency among FDC doses. This favorable safety and tolerability profile is supported by the long-term data from Study NAC-MD-02.

In order to illustrate the projected clinical impact of the NAC-MD-01 safety results, analyses were performed to demonstrate the lower risk of FDC treatment versus that of monotherapy. These analyses determined the number of patients with a discrete safety finding in the FDC 20/320 mg group compared with those with a discrete safety finding in each highest-dose monotherapy group, per 1000 patients treated. This was determined directly from Study NAC-MD-01 data ($N_{\text{Safety Population}} = 4159$), and the safety findings examined were: severe TEAEs, SAEs, AEs leading to discontinuation, and discontinuations due to any reason. The *lower* number of discrete safety findings with FDC treatment is shown in Figure 12.2–1.

More patients, per 1000 patients treated, exhibited a safety finding with highest-dose monotherapy (valsartan 320 mg or nebivolol 40 mg) versus the number of patients exhibiting a safety finding with FDC 20/320 mg, for each type of safety event. For example, for every 1000 patients treated, 18 *more* patients would be expected to experience a discontinuation due to any reason with valsartan 320 mg compared with the number of patients experiencing a discontinuation due to any reason with FDC 20/320 mg treatment; and 50 *more* patients in the nebivolol 40 mg group would experience a discontinuation for any reason compared with the number of patients with a discontinuation due to any reason in the FDC 20/320 mg group.

In summary, for each type of discrete safety finding, representing risk, fewer patients treated with FDC experienced such a finding versus those treated with either high-dose monotherapy.

Figure 12.2–1. Number of Patients Experiencing Severe TEAEs, SAEs, AEs Leading to Discontinuation, and Any Discontinuation Per 1000 Patients Treated



Note: This figure shows the number of patients expected to experience a severe TEAE, SAE, AE leading to discontinuation, or a discontinuation due to any reason per 1000 patients treated based on the results of Study NAC-MD-01. All bars are to the right of zero, indicating that treatment with either highest-dose monotherapy will lead to more patients experiencing these safety events compared with FDC 20/320 mg.

AE = adverse event; FDC = fixed-dose combination; Neb = nebivolol; SAE = serious adverse event; TEAE= treatment-emergent adverse event; Val = valsartan.

Taken together, these data (Figure 12.1–1 and Figure 12.2–1) further emphasize the advantageous efficacy of FDC 20/320 mg treatment when compared to treatment with either highest-dose monotherapy, and without incurring a higher risk; in fact, a *lower* risk is shown by the lower number of safety events per 1000 patients treated with FDC treatment.

In addition, it is useful to consider that nebivolol at 40 mg is very rarely utilized, and thus safety and tolerability comparisons should also be made to more commonly used doses. Comparisons of FDC 20/320 mg versus nebivolol 10 mg and valsartan 160 mg, more stringent comparisons given the lower dosages of the monotherapies, showed similar safety profiles; specifically, SAEs, TEAEs, and discontinuations due to AEs in the FDC 20/320 mg group occurred at similar rates compared with those in the lower-dose monotherapy groups at Week 8.

The favorable safety findings in patients treated with nebivolol/valsartan FDC in Study NAC-MD-01 are supported by the demonstration of long-term safety in Study NAC-MD-02. Deaths, SAEs, AEs leading to discontinuation, and TEAEs occurred at a low incidence. There was also a low incidence of β-blocker–typical AEs (eg, bradycardia, erectile dysfunction, fatigue, weight gain), which is in line with prior monotherapy trials of nebivolol. The overall safety profile was as favorable, even more favorable with respect to some events, than the safety profile of each of the individual therapies. No new AEs were reported that were not already described in the nebivolol or valsartan package inserts.

12.3 BENEFITS AND RISKS CONCLUSIONS

The nebivolol/valsartan antihypertensive FDC is the first combination of a β-blocker and an ARB.

Benefits of the nebivolol/valsartan FDC include:

1. Efficacy, safety, and tolerability as demonstrated by the data of this Phase 3 program in approximately 5000 patients. The efficacy study met the key regulatory "combination rule," and greater BP reductions and rates of BP control were shown by all 5 FDCs compared with corresponding monotherapies

2. Both components are approved for the treatment of hypertension, are frequently utilized together currently, and have well-established safety and efficacy profiles. An FDC would allow for a single pill, offering benefits in convenience and compliance

3. The reliability of administering 2 medications that have now been systematically examined in combination

4. The flexibility of multiple available FDC dosages, which allow tailored dosing to the needs of the individual patient

Risks: There are no substantial risks. The safety profile of the FDC is similar to the profiles of each monotherapy, and is even similar to placebo. These findings are consistent with the extensive experience in the clinical studies and with post-approval administration of each agent.

The data from this program support the use of the nebivolol/valsartan FDC as initial, add-on, and replacement therapy for stage 1 and 2 hypertension. In conclusion, there is a favorable benefit:risk profile, extensive clinical study experience with this combination program of nebivolol and valsartan, and a high utilization of both drugs that would make this FDC significantly valuable to the prescribing physician.

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14.0 APPENDICES

APPENDIX I. TABLES AND FIGURES

Table 14–1. Tabular Listing of All Clinical Studies

Study Identifier	*Primary Objective of the Study*	*Study Design and Type of Control*	*Test Products; Dose Regimen; Route of Administration*[a]	*Number of Subjects (Randomized or Enrolled/ Safety)*[b]	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*
Phase 3 Pivotal Studies						
NAC-MD-01	Efficacy and safety	Phase 3, multicenter, randomized, short-term, placebo-controlled, parallel-group study	*Test product:* FDC 10/160 mg (titrated after 4 weeks of 5/80 mg), 10/320 mg (titrated after 4 weeks of 5/160 mg), 20/320 mg (titrated after 4 weeks of 10/160 mg). *Reference therapy:* Nebivolol 10 mg (titrated after 4 weeks of 5 mg) and 40 mg (titrated after 4 weeks of 20 mg), valsartan 160 mg (titrated after 4 weeks of 80 mg) and 320 mg (titrated after 4 weeks of 160 mg), placebo	4161/4159	Patients with stage 1 or stage 2 essential hypertension	8 weeks
NAC-MD-02	Safety	Phase 3, multicenter, open-label, long-term, single-arm study	Nebivolol/valsartan free-tablet combination 5/160 mg, 10/320 mg, and 20/320 mg; HCTZ 12.5 mg, 25 mg (rescue medication)	810/807	Patients with stage 1 or stage 2 essential hypertension	52 weeks

Table 14–1. Tabular Listing of All Clinical Studies

Study Identifier	*Primary Objective of the Study*	*Study Design and Type of Control*	*Test Products; Dose Regimen; Route of Administration*[a]	*Number of Subjects (Randomized or Enrolled/ Safety)*[b]	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*
Phase 1 Studies						
NAC-PK-01	Evaluate the PK interaction between nebivolol and valsartan to determine the safety and tolerability of concomitantly administered single doses of nebivolol and valsartan	Phase 1, single-center, open-label, single-dose, 3-way crossover study	Nebivolol 20-mg tablets, valsartan 320-mg tablets; **Treatment A:** nebivolol 20-mg tablet, single dose (fasted conditions); **Treatment B:** valsartan 320-mg tablet, single dose (fasted conditions); **Treatment C:** nebivolol 20-mg tablet and valsartan 320-mg tablet, single dose (fasted conditions)	24/24	Healthy subjects	3 dosing days separated by a 7-day washout period
NAC-PK-03	Evaluate the PK and PD interaction between nebivolol and valsartan at steady state and to determine the tolerability of concomitantly administered multiple doses of nebivolol and valsartan	Phase 1, single-center, open-label, 3-way crossover, drug-interaction study	Nebivolol 20-mg tablets, valsartan 320-mg tablets; **Treatment A:** nebivolol 20-mg tablet, once daily (fasted conditions); **Treatment B:** valsartan 320-mg tablet, once daily (fasted conditions); **Treatment C:** nebivolol 20-mg tablet and valsartan 320-mg tablet, once daily (fasted conditions)	30/30	Healthy subjects	7 days in each of 3 treatment periods, separated by a washout of 7 days

Table 14–1. Tabular Listing of All Clinical Studies

Study Identifier	*Primary Objective of the Study*	*Study Design and Type of Control*	*Test Products; Dose Regimen; Route of Administration*[a]	*Number of Subjects (Randomized or Enrolled/ Safety)*[b]	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*
NAC-PK-04	Evaluate the effect of food on the oral bioavailability of a FDC of nebivolol and valsartan	Phase 1, single-center, open-label, 2-way crossover, single-dose study	FDC 20/320 mg tablets; **Treatment A:** FDC 20/320 mg tablet, single dose (fasted conditions); **Treatment B:** FDC 20/320 mg tablet, single dose (fed conditions)	32/32	Healthy subjects	2 dosing days separated by a 7-day washout period
NAC-PK-05	Compare the systemic exposures following the administration of a FDC tablet of nebivolol and valsartan vs the co-administration of separate nebivolol and valsartan tablets	Phase 1, single-center, randomized, open-label, 2-way crossover, single-dose study	Nebivolol 20-mg tablets, valsartan 320-mg tablets, FDC 20/320 mg tablets; **Treatment A:** nebivolol 20-mg tablet and valsartan 320-mg tablet, single dose (fasted conditions); **Treatment B:** FDC 20/320 mg tablet, single dose (fasted conditions)	70/70	Healthy subjects	2 dosing days separated by a 7-day washout period
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	Phase 1, multicenter, randomized, open-label, parallel, multiple-dose study	FDC 5/80 mg, 10/160 mg, 20/320 mg; **Treatment A:** FDC 5/80 mg tablet, once daily (fasted conditions); **Treatment B:** FDC 10/160 mg tablet, once daily (fasted conditions); **Treatment C:** FDC 20/320 mg tablet, once daily (fasted conditions)	30/30	Healthy subjects	14 days in each of 3 treatment periods

Table 14–1. Tabular Listing of All Clinical Studies

Study Identifier	*Primary Objective of the Study*	*Study Design and Type of Control*	*Test Products; Dose Regimen; Route of Administration*[a]	*Number of Subjects (Randomized or Enrolled/ Safety)*[b]	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*
NAC-PK-07	Evaluate the bioequivalence of the current FDC formulation of nebivolol and valsartan and the new FDC formulation of nebivolol and valsartan	Phase 1, single-center, randomized, open-label, 2-way crossover, single-dose study	FDC 10/320 mg tablets (current formulation), FDC 10/320 mg tablets (new formulation); **Treatment A:** FDC 10/320 mg tablet, single dose (current formulation); **Treatment B:** FDC 10/320 mg tablet, single dose (new formulation)	70/70	Healthy subjects	2 dosing days separated by a 7-day washout period

Note: FDC is the combination of nebivolol and valsartan, with the dose of each shown as nebivolol/valsartan.

a All doses given orally.

b Population of subjects. Randomized or Enrolled Population/Safety Population.

FDC = fixed-dose combination; HCTZ = hydrochlorothiazide; PD = pharmacodynamic; PK = pharmacokinetic.

Table 14–2. Number (%) of Patients Discontinued From Study NAC-MD-01 During the Double-blind Treatment Period—Randomized Population

Patient Status	*Placebo (N = 277) n (%)*	*FDC 10/160 (N = 555) n (%)*	*FDC 10/320 (N = 555) n (%)*	*FDC 20/320 (N = 554) n (%)*	*NEB 10 (N = 555) n (%)*	*NEB 40 (N = 555) n (%)*	*VAL 160 (N = 555) n (%)*	*VAL 320 (N = 555) n (%)*	*Total (N = 4161) n (%)*
Completed DBTP	244 (88.1)	490 (88.3)	496 (89.4)	506 (91.3)	505 (91.0)	479 (86.3)	498 (89.7)	497 (89.5)	3715 (89.3)
Prematurely discontinued from DBTP	33 (11.9)	65 (11.7)	59 (10.6)	48 (8.7)	50 (9.0)	76 (13.7)	57 (10.3)	58 (10.5)	446 (10.7)
Reason for premature discontinuation									
Withdrawal of consent	5 (1.8)	22 (4.0)	20 (3.6)	12 (2.2)	12 (2.2)	18 (3.2)	13 (2.3)	17 (3.1)	119 (2.9)
AE	10 (3.6)	15 (2.7)	9 (1.6)	9 (1.6)	12 (2.2)	22 (4.0)	10 (1.8)	10 (1.8)	97 (2.3)
Lost to follow-up	5 (1.8)	5 (0.9)	13 (2.3)	9 (1.6)	9 (1.6)	11 (2.0)	9 (1.6)	9 (1.6)	70 (1.7)
Protocol deviation/ violation	2 (0.7)	12 (2.2)	4 (0.7)	6 (1.1)	4 (0.7)	11 (2.0)	6 (1.1)	11 (2.0)	56 (1.3)
Insufficient therapeutic response	9 (3.2)	6 (1.1)	5 (0.9)	3 (0.5)	6 (1.1)	1 (0.2)	12 (2.2)	7 (1.3)	49 (1.2)
Seated pulse < 50 bpm	0	0	1 (0.2)	3 (0.5)	0	7 (1.3)	0	0	11 (0.3)
Low blood pressure (seated SBP < 100 or DBP < 60)	0	0	1 (0.2)	0	0	0	0	0	1 (0.0)
Other reasons	2 (0.7)	5 (0.9)	6 (1.1)	6 (1.1)	7 (1.3)	6 (1.1)	7 (1.3)	4 (0.7)	43 (1.0)

In the double-blind treatment period, % = n/N × 100.

AE = adverse event; bpm = beats per minute; DBP = diastolic blood pressure; DBTP = double-blind treatment period; FDC = fixed dose combination; N = number of patients in the Randomized Population in each treatment group; n = number of patients within a specified category; Neb = nebivolol; SBP = systolic blood pressure; Val = valsartan.

Table 14–3. Demographic and Physical Characteristics in Study NAC-MD-01—Safety Population

Parameter	*Placebo (N = 277)*	*FDC 10/160 (N = 555)*	*FDC 10/320 (N = 555)*	*FDC 20/320 (N = 554)*	*NEB 10 (N = 555)*	*NEB 40 (N = 554)*	*VAL 160 (N = 555)*	*VAL 320 (N = 554)*	*Total (N = 4159)*
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	51.7 ± 9.9	51.1 ± 10.7	51.3 ± 10.2
n	277	555	555	554	555	554	555	554	4159
Age group, years, n (%)									
< 65	250 (90.3)	511 (92.1)	510 (91.9)	513 (92.6)	500 (90.1)	500 (90.3)	505 (91.0)	500 (90.3)	3789 (91.1)
≥ 65	27 (9.7)	44 (7.9)	45 (8.1)	41 (7.4)	55 (9.9)	54 (9.7)	50 (9.0)	54 (9.7)	370 (8.9)
Sex, n (%)									
Male	148 (53.4)	300 (54.1)	315 (56.8)	313 (56.5)	307 (55.3)	297 (53.6)	333 (60.0)	295 (53.2)	2308 (55.5)
Female	129 (46.6)	255 (45.9)	240 (43.2)	241 (43.5)	248 (44.7)	257 (46.4)	222 (40.0)	259 (46.8)	1851 (44.5)
Diabetic, n (%)									
Yes	40 (14.4)	81 (14.6)	88 (15.9)	89 (16.1)	82 (14.8)	86 (15.5)	84 (15.1)	88 (15.9)	638 (15.3)
No	237 (85.6)	474 (85.4)	467 (84.1)	465 (83.9)	473 (85.2)	468 (84.5)	471 (84.9)	466 (84.1)	3521 (84.7)
Race, n (%)									
White	231 (83.4)	464 (83.6)	475 (85.6)	474 (85.6)	452 (81.4)	471 (85.0)	481 (86.7)	475 (85.7)	3523 (84.7)
All other races	46 (16.6)	91 (16.4)	80 (14.4)	80 (14.4)	103 (18.6)	83 (15.0)	74 (13.3)	79 (14.3)	636 (15.3)
Black or African American	30 (10.8)	56 (10.1)	56 (10.1)	52 (9.4)	69 (12.4)	54 (9.7)	43 (7.7)	51 (9.2)	411 (9.9)
Asian	12 (4.3)	25 (4.5)	11 (2.0)	18 (3.2)	22 (4.0)	19 (3.4)	24 (4.3)	18 (3.2)	149 (3.6)
American Indian or Alaska native	2 (0.7)	7 (1.3)	6 (1.1)	2 (0.4)	4 (0.7)	3 (0.5)	3 (0.5)	3 (0.5)	30 (0.7)
Native Hawaiian or other Pacific Islander	0	0	3 (0.5)	3 (0.5)	1 (0.2)	3 (0.5)	1 (0.2)	2 (0.4)	13 (0.3)
Other	2 (0.7)	3 (0.5)	4 (0.7)	5 (0.9)	7 (1.3)	4 (0.7)	3 (0.5)	5 (0.9)	33 (0.8)

Table 14–3. Demographic and Physical Characteristics in Study NAC-MD-01—Safety Population

Parameter	*Placebo (N = 277)*	*FDC 10/160 (N = 555)*	*FDC 10/320 (N = 555)*	*FDC 20/320 (N = 554)*	*NEB 10 (N = 555)*	*NEB 40 (N = 554)*	*VAL 160 (N = 555)*	*VAL 320 (N = 554)*	*Total (N = 4159)*
Ethnicity, n (%)									
Hispanic or Latino	113 (40.8)	252 (45.4)	239 (43.1)	231 (41.7)	206 (37.1)	220 (39.7)	207 (37.3)	216 (39.0)	1684 (40.5)
Non-Hispanic or Latino	164 (59.2)	303 (54.6)	316 (56.9)	323 (58.3)	349 (62.9)	334 (60.3)	348 (62.7)	338 (61.0)	2475 (59.5)
Weight, kg									
Mean ± SD	93.55 ± 20.65	91.06 ± 20.43	92.20 ± 20.03	92.17 ± 20.82	92.42 ± 21.18	91.33 ± 21.25	92.32 ± 20.85	92.11 ± 20.79	92.05 ± 20.75
n	277	555	555	554	555	554	555	554	4159
Height, cm									
Mean ± SD	169.11 ± 9.84	168.66 ± 10.19	169.34 ± 10.79	169.48 ± 10.27	169.32 ± 10.79	168.56 ± 10.18	170.20 ± 10.33	169.25 ± 10.48	169.25 ± 10.40
n	277	555	554	554	555	554	555	554	4158
Body mass index, kg/m^2									
Mean ± SD	32.57 ± 6.05	31.93 ± 6.27	32.04 ± 5.95	32.03 ± 6.46	32.12 ± 6.30	32.04 ± 6.33	31.75 ± 6.02	32.05 ± 6.05	32.03 ± 6.19
n	277	555	554	554	555	554	555	554	4158
Participation in substudy, n (%)									
Yes	52 (18.8)	108 (19.5)	109 (19.6)	110 (19.9)	106 (19.1)	109 (19.7)	104 (18.7)	107 (19.3)	805 (19.4)
No	225 (81.2)	447 (80.5)	446 (80.4)	444 (80.1)	449 (80.9)	445 (80.3)	451 (81.3)	447 (80.7)	3354 (80.6)

Note: Age was as of the informed consent date.

cm = centimeter; FDC = fixed-dose combination; N = number of patients in the Safety Population; n = number of patients in the specified category; Neb = nebivolol; SD = standard deviation; Val = valsartan.

Table 14–4. Study NAC-MD-01: Blood Pressure Findings at Week 4 and at Week 8—Intent-to-Treat Population

Treatment (Weeks 0-4 → Weeks 4-8)	*Blood Pressure, mm Hg*		
	Week 4, mm Hg	*Week 8, mm Hg*	*Difference Upon Up-titration, mm Hg (p-Value)*
Diastolic Blood Pressure			
Placebo → placebo	93.7	92.9	–0.8 (p = 0.0914)
FDC 5/80 mg → FDC 10/160 mg	86.4	84.8	–1.6 (p < 0.0001)
FDC 5/160 mg → FDC 10/320 mg	86.1	84.7	–1.4 (p < 0.0001)
FDC 10/160 mg → FDC 20/320 mg	85.8	84.2	–1.6 (p < 0.0001)
Systolic Blood Pressure			
Placebo → placebo	148.3	147.2	–1.1 (p = 0.1760)
FDC 5/80 mg → FDC 10/160 mg	139.5	137.0	–2.5 (p < 0.0001)
FDC 5/160 mg → FDC 10/320 mg	139.5	137.5	–2.0 (p = 0.0011)
FDC 10/160 mg → FDC 20/320 mg	138.8	136.8	–2.0 (p = 0.0004)

Note: This table shows the observed mean DBP and SBP for each FDC treatment arm at Week 4 (at the end of Weeks 0-4 of treatment with FDC 5/80 mg, 5/160 mg, and 10/160 mg) and at Week 8 (at the end of Weeks 4-8 of treatment with the up-titrated FDC, FDC 10/160 mg, 10/320 mg, and 20/320 mg). The differences in DBP and SBP resulting from the up-titration between the 2 dosing periods are shown.

DBP = diastolic blood pressure; FDC = fixed-dose combination; SBP = systolic blood pressure.

Table 14–5. Patients With Any Common (≥ 2% Incidence) Treatment-Emergent Adverse Events by Preferred Term by Time During the Double-blind Treatment Period in Study NAC-MD-01—Safety Population

TEAE Before Week 4								
Preferred Term	***Placebo (N = 277) n (%)***	***FDC 10/160 (N = 555) n (%)***	***FDC 10/320 (N = 555) n (%)***	***FDC 20/320 (N = 554) n (%)***	***NEB 10 (N = 555) n (%)***	***NEB 40 (N = 554) n (%)***	***VAL 160 (N = 555) n (%)***	***VAL 320 (N = 554) n (%)***
Patients with at least 1 TEAE[a]	**59 (21.3)**	**116 (20.9)**	**112 (20.2)**	**110 (19.9)**	**116 (20.9)**	**116 (20.9)**	**105 (18.9)**	**121 (21.8)**
Headache	7 (2.5)	11 (2.0)	16 (2.9)	20 (3.6)	13 (2.3)	14 (2.5)	21 (3.8)	10 (1.8)
Fatigue	2 (0.7)	1 (0.2)	8 (1.4)	5 (0.9)	2 (0.4)	12 (2.2)	2 (0.4)	4 (0.7)
Dizziness	1 (0.4)	8 (1.4)	4 (0.7)	3 (0.5)	4 (0.7)	5 (0.9)	10 (1.8)	11 (2.0)
Nasopharyngitis	4 (1.4)	4 (0.7)	4 (0.7)	4 (0.7)	7 (1.3)	5 (0.9)	4 (0.7)	9 (1.6)
Sinus bradycardia	2 (0.7)	0	1 (0.2)	1 (0.2)	0	2 (0.4)	1 (0.2)	2 (0.4)
Bradycardia	0	3 (0.5)	3 (0.5)	2 (0.4)	3 (0.5)	4 (0.7)	0	0
Upper respiratory tract infection	5 (1.8)	5 (0.9)	5 (0.9)	1 (0.2)	6 (1.1)	5 (0.9)	5 (0.9)	5 (0.9)
TEAE Between Week 4 and Week 8								
Preferred Term	***Placebo (N = 264) n (%)***	***FDC 10/160 (N = 530) n (%)***	***FDC 10/320 (N = 529) n (%)***	***FDC 20/320 (N = 532) n (%)***	***NEB 10 (N = 534) n (%)***	***NEB 40 (N = 521) n (%)***	***VAL 160 (N = 529) n (%)***	***VAL 320 (N = 526) n (%)***
Patients with at least 1 TEAE[a]	**58 (22.0)**	**108 (20.4)**	**97 (18.3)**	**114 (21.4)**	**111 (20.8)**	**123 (23.6)**	**96 (18.1)**	**111 (21.1)**
Headache	8 (3.0)	9 (1.7)	7 (1.3)	5 (0.9)	10 (1.9)	12 (2.3)	6 (1.1)	11 (2.1)
Fatigue	2 (0.8)	4 (0.8)	5 (0.9)	6 (1.1)	3 (0.6)	7 (1.3)	0	1 (0.2)
Dizziness	0	2 (0.4)	9 (1.7)	6 (1.1)	0	5 (1.0)	5 (0.9)	4 (0.8)
Nasopharyngitis	2 (0.8)	3 (0.6)	4 (0.8)	4 (0.8)	2 (0.4)	1 (0.2)	4 (0.8)	7 (1.3)
Sinus bradycardia	0	4 (0.8)	4 (0.8)	7 (1.3)	4 (0.7)	18 (3.5)	1 (0.2)	2 (0.4)
Bradycardia	0	5 (0.9)	5 (0.9)	4 (0.8)	4 (0.7)	11 (2.1)	3 (0.6)	0
Upper respiratory tract infection	1 (0.4)	7 (1.3)	2 (0.4)	5 (0.9)	2 (0.4)	7 (1.3)	2 (0.4)	3 (0.6)

Note: Version 15.1 of the *Medical Dictionary for Regulatory Activities* was used to code TEAEs.

Preferred terms included in this table were based on NAC-MD-01 Table 14.5.1.3A, in which AE preferred terms were assessed categorically as having an incidence of < 2% or ≥ 2% utilizing no rounding of incidence values.

a The number of patients with any TEAE, not just the TEAEs that occurred in ≥ 2% of patients.

FDC = fixed-dose combination; N = number of patients in the Safety Population who were randomized into the specified double-blind treatment group; n = number of TEAEs occurring on or after the date of the first dose of double-blind investigational product and before Week 4 (ie, during Weeks 0-4) or after Week 4 and before Week 8 (ie, during Weeks 4-8); Neb = nebivolol; TEAE = treatment-emergent adverse event; Val = valsartan.

Table 14–6. Incidence of On-Therapy Serious Adverse Events During the Double-blind Treatment Period of Study NAC-MD-01—Safety Population

Preferred Term	*Placebo (N = 277, M = 244) n (%) [Related]*	*FDC 10/160 (N = 555, M = 505) n (%) [Related]*	*FDC 10/320 (N = 555, M = 495) n (%) [Related]*	*FDC 20/320 (N = 554, M = 520) n (%) [Related]*	*NEB 10 (N = 555, M = 515) n (%) [Related]*	*NEB 40 (N = 554, M = 501) n (%) [Related]*	*VAL 160 (N = 555, M = 508) n (%) [Related]*	*VAL 320 (N = 554, M = 507) n (%) [Related]*
Double-blind Treatment Period								
Patients with at least 1 on-therapy SAE	**3 (1.1) [0]**	**2 (0.4) [0]**	**2 (0.4) [0]**	**1 (0.2) [0]**	**2 (0.4) [0]**	**4 (0.7) [0]**	**4 (0.7) [0]**	**5 (0.9) [0]**
Diverticulitis	0	0	0	1 (0.2) [0]	0	0	0	0
Acute myocardial infarction	0	0	1 (0.2) [0]	0	0	0	0	1 (0.2) [0]
Appendicitis	0	0	1 (0.2) [0]	0	0	0	0	1 (0.2) [0]
Cerebrovascular accident	1 (0.4) [0]	1 (0.2) [0]	0	0	0	0	0	0
Ankle fracture	0	1 (0.2) [0]	0	0	0	0	0	0
Abortion spontaneous	1 (0.4) [0]	0	0	0	0	0	0	0
Transient ischaemic attack	1 (0.4) [0]	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	1 (0.2) [0]	0	0
Pancreatitis	0	0	0	0	0	1 (0.2) [0]	0	0
Small intestinal obstruction	0	0	0	0	0	1 (0.2) [0]	0	0
Thyroid cancer	0	0	0	0	0	1 (0.2) [0]	0	0
Pyelonephritis acute	0	0	0	0	1 (0.2) [0]	0	0	0
Syncope	0	0	0	0	1 (0.2) [0]	0	0	0
Atrial fibrillation	0	0	0	0	0	0	0	1 (0.2) [0]
Facial bones fracture	0	0	0	0	0	0	0	1 (0.2) [0]
Gastrointestinal haemorrhage	0	0	0	0	0	0	0	1 (0.2) [0]

Table 14–6. Incidence of On-Therapy Serious Adverse Events During the Double-blind Treatment Period of Study NAC-MD-01—Safety Population

Preferred Term	*Placebo (N = 277, M = 244) n (%) [Related]*	*FDC 10/160 (N = 555, M = 505) n (%) [Related]*	*FDC 10/320 (N = 555, M = 495) n (%) [Related]*	*FDC 20/320 (N = 554, M = 520) n (%) [Related]*	*NEB 10 (N = 555, M = 515) n (%) [Related]*	*NEB 40 (N = 554, M = 501) n (%) [Related]*	*VAL 160 (N = 555, M = 508) n (%) [Related]*	*VAL 320 (N = 554, M = 507) n (%) [Related]*
Pneumonia	0	0	0	0	0	0	0	1 (0.2) [0]
Acute respiratory failure	0	0	0	0	0	0	1 (0.2) [0]	0
Carbon dioxide increased	0	0	0	0	0	0	1 (0.2) [0]	0
Cerebral infarction	0	0	0	0	0	0	1 (0.2) [0]	0
Intracranial aneurysm	0	0	0	0	0	0	1 (0.2) [0]	0
Mental status changes	0	0	0	0	0	0	1 (0.2) [0]	0
Substance abuse	0	0	0	0	0	0	1 (0.2) [0]	0
Suicide attempt	0	0	0	0	0	0	1 (0.2) [0]	0

Note: Patients were counted only once within each preferred term; For the double-blind treatment period, % = 100 × n/N; For the double-blind down-titration period, % = 100 × n/M.

FDC = fixed-dose combination; M = number of patients in the Safety Population who entered the double-blind down-titration period; N = number of patients in the Safety Population; n = number of patients who had the specified SAE; Neb = nebivolol; Related = number of patients with SAEs that were related to investigational product as recorded by the Investigator; SAE = serious adverse event; Val = valsartan.

Table 14–7. Incidence of Adverse Events Associated With Premature Discontinuation During the Double-blind Treatment Period of Study NAC-MD-01—Safety Population

Preferred Term	*Placebo (N = 277) n (%)*	*FDC 10/160 (N = 555) n (%)*	*FDC 10/320 (N = 555) n (%)*	*FDC 20/320 (N = 554) n (%)*	*NEB 10 (N = 555) n (%)*	*NEB 40 (N = 554) n (%)*	*VAL 160 (N = 555) n (%)*	*VAL 320 (N = 554) n (%)*
Prematurely discontinued from double-blind treatment period for any reason[a]	**33 (11.9)**	**65 (11.7)**	**59 (10.6)**	**48 (8.7)**	**50 (9.0)**	**76 (13.7)**	**57 (10.3)**	**58 (10.5)**
Patients with at least 1 AE leading to discontinuation during the double-blind treatment period	**10 (3.6)**	**15 (2.7)**	**9 (1.6)**	**9 (1.6)**	**12 (2.2)**	**22 (4.0)**	**10 (1.8)**	**10 (1.8)**
Bradycardia	0	2 (0.4)	2 (0.4)	3 (0.5)	3 (0.5)	5 (0.9)	0	0
Fatigue	0	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.5)
Blood pressure increased	1 (0.4)	0	0	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Dyspnoea	0	0	0	1 (0.2)	0	1 (0.2)	0	2 (0.4)
Electrocardiogram QT prolonged	0	0	0	1 (0.2)	0	1 (0.2)	0	0
Liver function test abnormal	0	0	0	1 (0.2)	0	1 (0.2)	0	0
Cardiac failure congestive	0	0	0	1 (0.2)	0	0	0	0
Chest discomfort	0	0	0	1 (0.2)	0	0	0	0
Fluid overload	0	0	0	1 (0.2)	0	0	0	0
Headache	1 (0.4)	0	1 (0.2)	0	1 (0.2)	3 (0.5)	4 (0.7)	2 (0.4)
Alanine aminotransferase increased	1 (0.4)	0	1 (0.2)	0	2 (0.4)	1 (0.2)	0	0
Acute myocardial infarction	0	0	1 (0.2)	0	0	0	0	1 (0.2)
Diarrhoea	0	0	1 (0.2)	0	0	0	0	0
Glomerular filtration rate decreased	0	0	1 (0.2)	0	0	0	0	0
Transaminases increased	0	0	1 (0.2)	0	0	0	0	0
Dizziness	1 (0.4)	1 (0.2)	0	0	0	0	1 (0.2)	1 (0.2)

Table 14–7. Incidence of Adverse Events Associated With Premature Discontinuation During the Double-blind Treatment Period of Study NAC-MD-01—Safety Population

Preferred Term	*Placebo (N = 277) n (%)*	*FDC 10/160 (N = 555) n (%)*	*FDC 10/320 (N = 555) n (%)*	*FDC 20/320 (N = 554) n (%)*	*NEB 10 (N = 555) n (%)*	*NEB 40 (N = 554) n (%)*	*VAL 160 (N = 555) n (%)*	*VAL 320 (N = 554) n (%)*
Oedema peripheral	0	2 (0.4)	0	0	0	2 (0.4)	0	0
Cerebrovascular accident	1 (0.4)	1 (0.2)	0	0	0	0	0	0
Hypotension	0	1 (0.2)	0	0	0	1 (0.2)	0	0
Non-cardiac chest pain	0	2 (0.4)	0	0	0	0	0	0
Angina pectoris	0	1 (0.2)	0	0	0	0	0	0
Blood glucose increased	0	1 (0.2)	0	0	0	0	0	0
Electrocardiogram abnormal	0	1 (0.2)	0	0	0	0	0	0
Migraine	0	1 (0.2)	0	0	0	0	0	0
Ventricular extrasystoles	0	1 (0.2)	0	0	0	0	0	0
Vertigo	0	1 (0.2)	0	0	0	0	0	0
Hypertension	2 (0.7)	0	0	0	0	1 (0.2)	1 (0.2)	1 (0.2)
Rash	0	0	0	0	0	1 (0.2)	0	1 (0.2)
Sinus bradycardia	0	0	0	0	0	2 (0.4)	0	0
Abnormal weight gain	0	0	0	0	0	1 (0.2)	0	0
Blood potassium increased	0	0	0	0	0	1 (0.2)	0	0
Bronchial hyperreactivity	0	0	0	0	0	1 (0.2)	0	0
Bronchospasm	0	0	0	0	0	1 (0.2)	0	0
Heart rate decreased	0	0	0	0	0	1 (0.2)	0	0
Hypertriglyceridaemia	0	0	0	0	0	1 (0.2)	0	0
Small intestinal obstruction	0	0	0	0	0	1 (0.2)	0	0

Table 14–7. Incidence of Adverse Events Associated With Premature Discontinuation During the Double-blind Treatment Period of Study NAC-MD-01—Safety Population

Preferred Term	***Placebo (N = 277) n (%)***	***FDC 10/160 (N = 555) n (%)***	***FDC 10/320 (N = 555) n (%)***	***FDC 20/320 (N = 554) n (%)***	***NEB 10 (N = 555) n (%)***	***NEB 40 (N = 554) n (%)***	***VAL 160 (N = 555) n (%)***	***VAL 320 (N = 554) n (%)***
Aspartate aminotransferase increased	1 (0.4)	0	0	0	1 (0.2)	0	0	0
Alcohol abuse	0	0	0	0	1 (0.2)	0	0	0
Hyperkalaemia	0	0	0	0	1 (0.2)	0	0	0
Pruritus	0	0	0	0	1 (0.2)	0	0	0
Pyelonephritis acute	0	0	0	0	1 (0.2)	0	0	0
Urticaria	0	0	0	0	1 (0.2)	0	0	0
Insomnia	1 (0.4)	0	0	0	0	0	0	1 (0.2)
Apathy	0	0	0	0	0	0	0	1 (0.2)
Gastrointestinal haemorrhage	0	0	0	0	0	0	0	1 (0.2)
Hepatic enzyme increased	0	0	0	0	0	0	0	1 (0.2)
Oedema	0	0	0	0	0	0	0	1 (0.2)
Palpitations	0	0	0	0	0	0	0	1 (0.2)
Pneumonia	0	0	0	0	0	0	0	1 (0.2)
Somnolence	0	0	0	0	0	0	0	1 (0.2)
Tachycardia	0	0	0	0	0	0	0	1 (0.2)
Abdominal pain	0	0	0	0	0	0	1 (0.2)	0
Acute respiratory failure	0	0	0	0	0	0	1 (0.2)	0
Carbon dioxide increased	0	0	0	0	0	0	1 (0.2)	0
Cerebral infarction	0	0	0	0	0	0	1 (0.2)	0
Erythema	0	0	0	0	0	0	1 (0.2)	0

Table 14–7. Incidence of Adverse Events Associated With Premature Discontinuation During the Double-blind Treatment Period of Study NAC-MD-01—Safety Population

Preferred Term	*Placebo (N = 277) n (%)*	*FDC 10/160 (N = 555) n (%)*	*FDC 10/320 (N = 555) n (%)*	*FDC 20/320 (N = 554) n (%)*	*NEB 10 (N = 555) n (%)*	*NEB 40 (N = 554) n (%)*	*VAL 160 (N = 555) n (%)*	*VAL 320 (N = 554) n (%)*
Mental status changes	0	0	0	0	0	0	1 (0.2)	0
Presyncope	0	0	0	0	0	0	1 (0.2)	0
Renal failure acute	0	0	0	0	0	0	1 (0.2)	0
Substance abuse	0	0	0	0	0	0	1 (0.2)	0
Suicide attempt	0	0	0	0	0	0	1 (0.2)	0
Thrombocytopenia	0	0	0	0	0	0	1 (0.2)	0
Agitation	1 (0.4)	0	0	0	0	0	0	0
Attention deficit/hyperactivity disorder	1 (0.4)	0	0	0	0	0	0	0
Disorientation	1 (0.4)	0	0	0	0	0	0	0
Heart sounds abnormal	1 (0.4)	0	0	0	0	0	0	0
Upper respiratory tract infection	1 (0.4)	0	0	0	0	0	0	0

Note: Patients were counted only once within each preferred term; For the double-blind treatment period, % = 100 × n/N.

a The study population for this row was based on the Randomized Population and was the same as the Safety Population except for the nebivolol 40 mg group (N = 555) and the valsartan 320 mg group (N = 555).

AE = adverse event; FDC = fixed-dose combination; N = number of patients in the Safety Population; n = number of patients who discontinued due to the specified AE; Neb = nebivolol; Val = valsartan.

Table 14–8. Demographic and Other Baseline Characteristics in Study NAC-MD-02—Safety Population

Characteristic	*Free-Tablet Combination (N = 807)*
Age, years	
Mean	52.7
SD	9.5
n	807
Sex, n (%)	
Male	448 (55.5)
Female	359 (44.5)
Race, n (%)	
Caucasian (White)	531 (65.8)
All Other Races	276 (34.2)
Black or African American	245 (30.4)
Asian	21 (2.6)
American Indian or Alaska Native	3 (0.4)
Native Hawaiian or Other Pacific Islander	2 (0.2)
Other	5 (0.6)
Ethnicity, n (%)	
Hispanic or Latino	197 (24.4)
Not Hispanic or Latino	610 (75.6)
Weight, kg	
Mean	94.06
SD	20.89
n	807
Height, cm	
Mean	170.00
SD	10.18
n	807
BMI, kg/m^2	
Mean	32.49
SD	6.40
n	807
Type 2 diabetes status, n (%)	
Type 2 diabetes	138 (17.1)
Non-type 2 diabetes[a]	669 (82.9)

Note: Age was based on the informed consent date.

a Patients without type 2 diabetes.

BMI = body mass index; N = number of patients in the Safety Population; n = number of patients in the specified category; SD = standard deviation.

Table 14–9. Incidence of On-Therapy Serious Adverse Events During the Open-label Treatment Phase in Study NAC-MD-02—Safety Population

Preferred Term	***Safety Population (N = 807) n (%)***	***Safety Population Before the Potential Initiation of HCTZ (N = 807) n (%)***
Patients with at least 1 on-therapy SAE	17 (2.1)	13 (1.6)
Non-cardiac chest pain	3 (0.4)	2 (0.2)
Acute myocardial infarction	2 (0.2)	2 (0.2)
Ankle fracture	1 (0.1)	0
Anxiety	1 (0.1)	1 (0.1)
Bradycardia	1 (0.1)	1 (0.1)
Bronchitis	1 (0.1)	1 (0.1)
Cardiac arrest	1 (0.1)	1 (0.1)
Cellulitis	1 (0.1)	0
Cerebrovascular accident	1 (0.1)	1 (0.1)
Chronic obstructive pulmonary disease	1 (0.1)	1 (0.1)
Gunshot wound	1 (0.1)	0
Hydronephrosis	1 (0.1)	1 (0.1)
Impetigo	1 (0.1)	0
Inguinal hernia	1 (0.1)	1 (0.1)
Ischaemic stroke	1 (0.1)	1 (0.1)
Lower gastrointestinal haemorrhage	1 (0.1)	1 (0.1)
Myocardial infarction	1 (0.1)	0
Renal failure acute	1 (0.1)	1 (0.1)
Road traffic accident	1 (0.1)	1 (0.1)

Note: Version 15.1 of the *Medical Dictionary for Regulatory Activities* was used to code TEAEs. Patients were counted only once within each system organ class and each preferred term.

Percentages were calculated as n/N × 100.

HCTZ = hydrochlorothiazide; N = the number of patients in the Safety Population; n = number of patients with SAE occurring on or after the date of the first dose of open-label investigational product and 1) within 30 days of the date of the last dose of open-label investigational product for patients who entered the open-label treatment phase and did not enter the open-label down-titration phase, 2) no later than the day of the early termination visit for patients who prematurely discontinued from the open-label treatment phase and entered the open-label down-titration phase, or 3) no later than the day of Visit 15 for patients who completed the open-label treatment phase and entered the open-label down-titration phase; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Figure 14–1. Mean (± SD) Steady-State *d,l*-Nebivolol Plasma Concentration Versus Time Profiles Following 7 Days Dosing of Once Daily 20 mg Nebivolol Alone (Treatment A) or Concomitant 20 mg Nebivolol and 320 mg Valsartan (Treatment C)—Semilogarithmic Scale

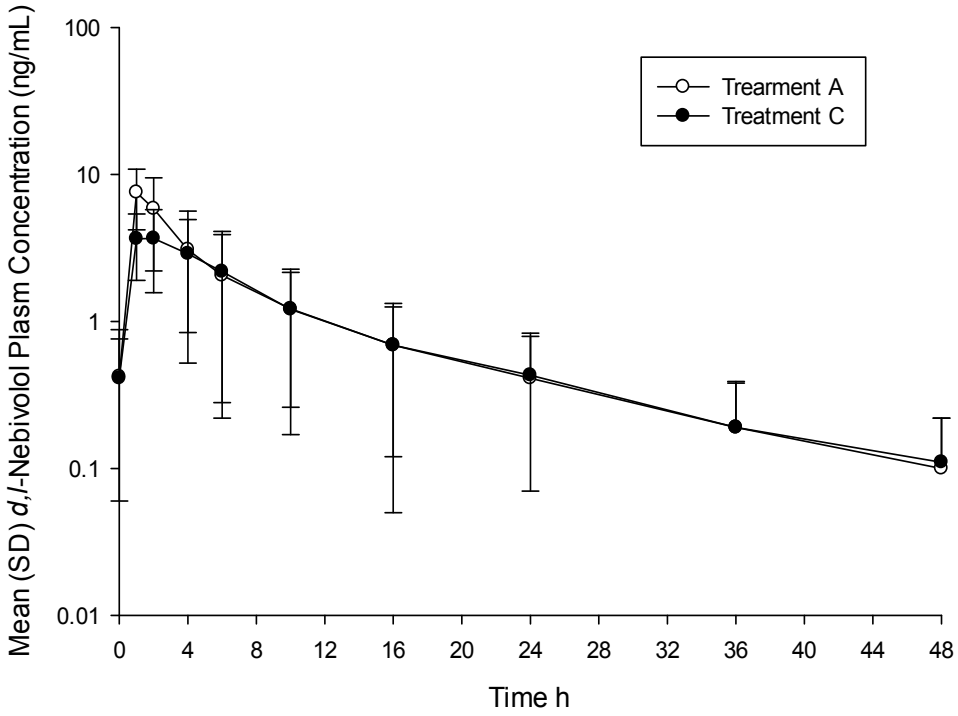


Figure 14–2. Mean (± SD) Steady-State Valsartan Plasma Concentration Versus Time Profiles Following 7 Days Dosing of Once Daily 20 mg Nebivolol Alone (Treatment B) or Concomitant 20 mg Nebivolol and 320 mg Valsartan (Treatment C)—Semilogarithmic Scale

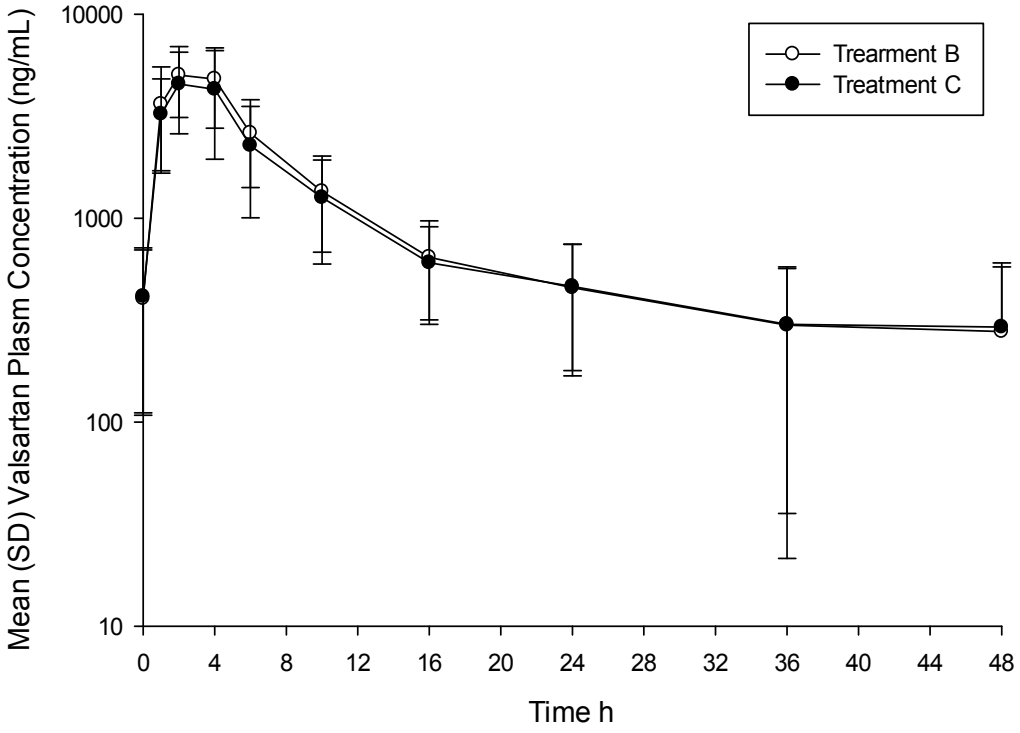
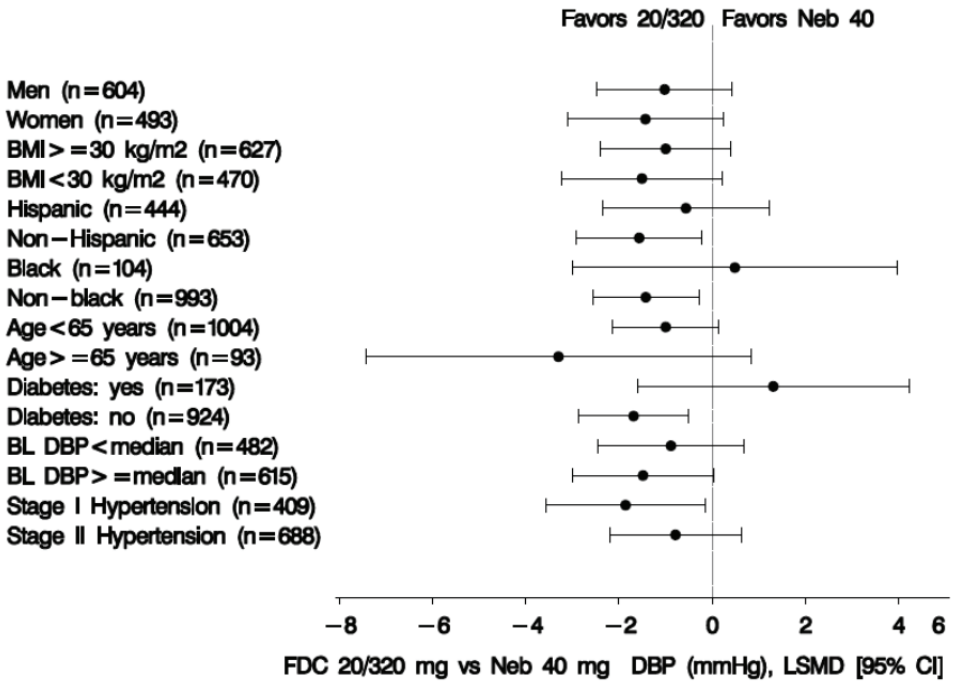
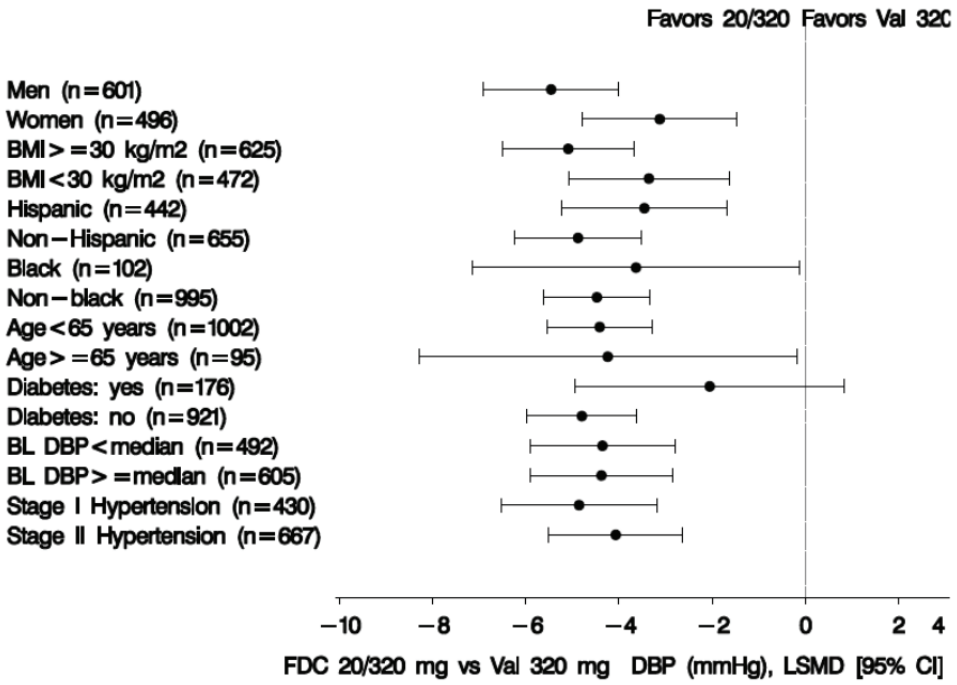


Figure 14–3. DBP Analysis for the Comparison of FDC 20/320 mg Versus Nebivolol 40 mg in Subgroups of Study NAC-MD-01—Intent-to-Treat Population



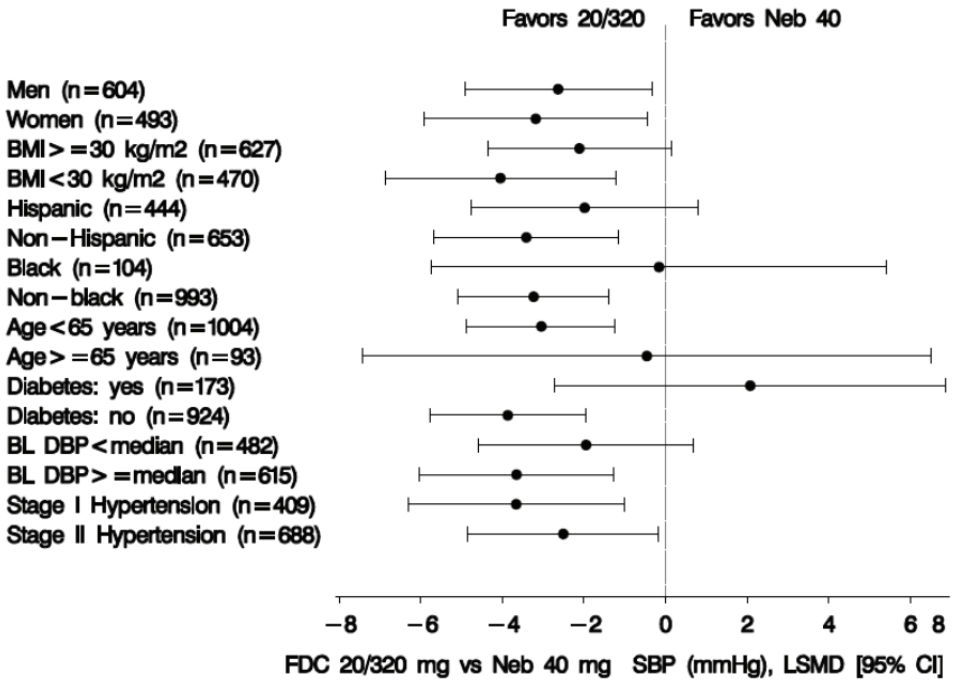
BL = baseline; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; FDC = fixed-dose combination; LSMD = least squares mean difference; Neb = nebivolol.

Figure 14–4. DBP Analysis for the Comparison of FDC 20/320 mg Versus Valsartan 320 mg in Subgroups of Study NAC-MD-01—Intent-to-Treat Population



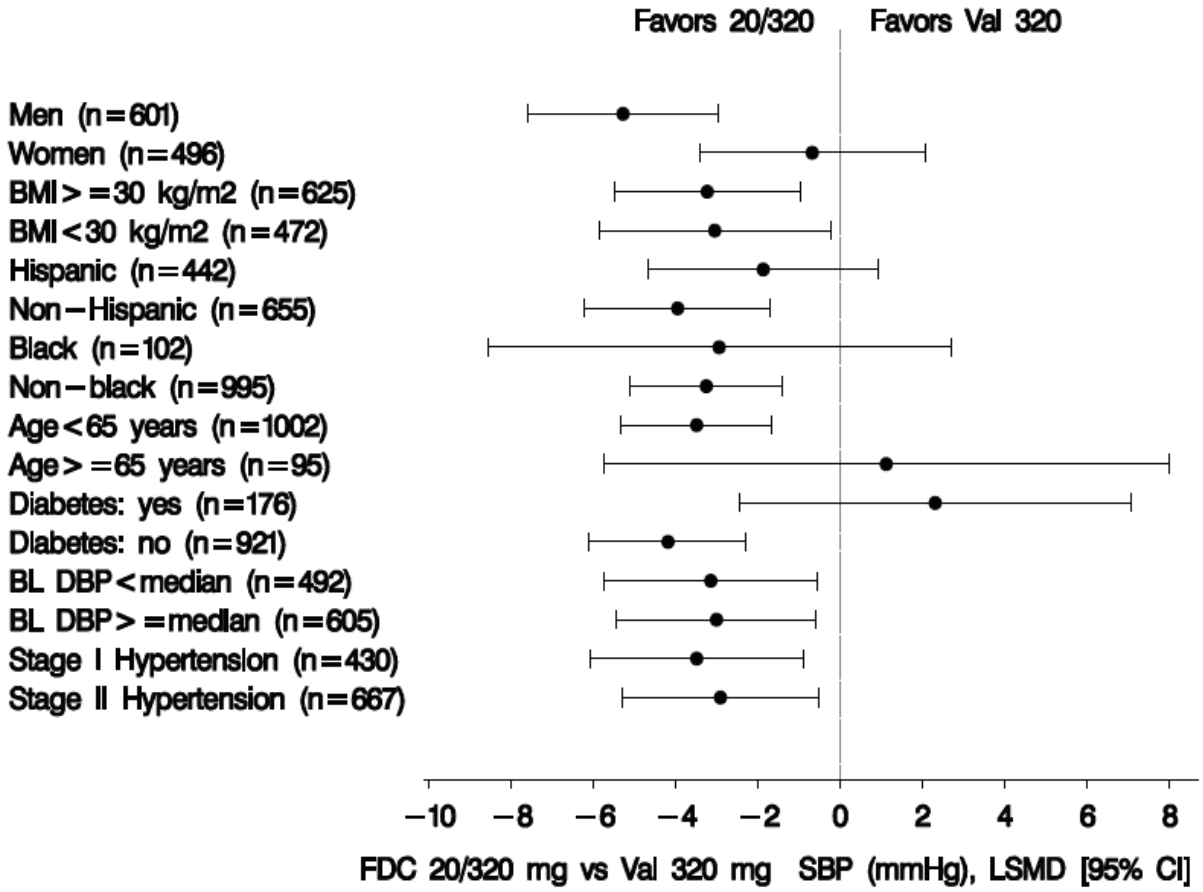
BL = baseline; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; FDC = fixed-dose combination; LSMD = least squares mean difference; Val = valsartan.

Figure 14–5. SBP Analysis for the Comparison of FDC 20/320 mg Versus Nebivolol 40 mg in Subgroups of Study NAC-MD-01—Intent-to-Treat Population



BL = baseline; BMI = body mass index; CI = confidence interval; FDC = fixed-dose combination; LSMD = least squares mean difference; Neb = nebivolol; SBP = systolic blood pressure.

Figure 14–6. SBP Analysis for the Comparison of FDC 20/320 mg Versus Valsartan 320 mg in Subgroups of Study NAC-MD-01—Intent-to-Treat Population



BL = baseline; BMI = body mass index; CI = confidence interval; FDC = fixed-dose combination; LSMD = least squares mean difference; SBP = systolic blood pressure; Val = valsartan.