1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Nebivolol is approvable for the treatment of _____ hypertension, pending the following results:

1. Within the next two months, the sponsor plans to perform mechanistic studies in mice and rats to explain the development of Leydig cell tumors (LCT). If the sponsor proves nebivolol is not potentially carcinogenic in humans, the application is approvable.
2, Through consultative review, the Division of Reproductive and Urologic Drug Products will assist the Cardio-Renal Division in identifying the most sensitive markers for drug-related estrogenic effects in humans and in determining whether or not these markers predict the development of subsequent malignancies.

Nebivolol may be carcinogenic in humans. In a 21 lunar month study in Swiss mice performed by Janssen in 1989, 42% (21/50) of the male mice receiving nebivolol 40 mg/kg developed Leydig cell tumors (LCT) and 28% (14/50) developed testicular hyperplasia. On August 24th, 2004, the Agency Executive Carcinogenicity Assessment Committee (CAC) found the Leydig cell tumors in mice to be drug-related.[1]

Recently, Bertek Pharmaceuticals, Inc. sponsored an independent review of the original mouse carcinogenicity slides by Henry Wall, DVM, John Vanderberghe, DVM, W. Ray Brown, DVM, Ph.D, and Charles Capen, DVM, Ph.D. Although there were reclassifications in both directions, the overall impression was unchanged. A total of 17/50 (34%) male mice "had neoplastic lesions."[2]

Although the exact mechanism of LCT development is unknown, Elizabeth Hausner, DVM, of the Cardio-Renal Division, suspects an estrogenic effect. From preclinical studies in various species, Dr. Hausner found evidence of endocrine disruption manifested by histologic effects on male and female reproductive organs, increased serum potassium, increased adrenal weights, and decreased total cholesterol and triglycerides (Hausner E, Executive Summary, 2004, Pharmacology/Toxicology Review, Cardio-Renal Division, NDA 21,742).

Based on the mouse carcinogenicity findings, I am concerned nebivolol may be carcinogenic in humans. Although there is some nebivolol safety data covering approximately two years, in my opinion, this limited time period does not adequately evaluate nor predict the malignant potential of this antihypertensive which would be taken chronically. Furthermore, it is unlikely post-marketing surveillance in Europe, where nebivolol has already been approved, would adequately record all malignancies in patients taking nebivolol.

The sponsor performed 6 pivotal trials in 2,800 patients to evaluate the efficacy of nebivolol in patients with mild to moderate hypertension. A total of 2,464 of these patients received

[1] **Executive CAC Minutes, August 24, 2004, page 2.**
[2] **E-mail communication with Elizabeth Hausner, DVM, dated December 20, 2004.**

nebivolol. Of these 6 pivotal trials, three were randomized, double-blind, multi-center, placebo-controlled monotherapy trials, NEB-302, NEB-305, and NEB-202. In addition to the three monotherapy trials, the sponsor performed NEB-203, a phase II, randomized double-blind, active-controlled pilot study to assess methodology for comparing the effect of nebivolol and atenolol on exercise capacity as well as NEB-321, a phase III, randomized, double-blind placebo-controlled trial to evaluate the efficacy of nebivolol as add-on therapy to patients already receiving one or two antihypertensives from the angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and/or diuretic class. Lastly, the sponsor performed NEB-306, a phase III, uncontrolled nine-month extension study with an optional four-week placebo-controlled randomized withdrawal study to evaluate the long-term safety and efficacy of nebivolol and to determine whether or not abrupt withdrawal of nebivolol resulted in rebound hypertension.

In the monotherapy trials (NEB-302, NEB-305, and NEB-202), nebivolol significantly reduced sitting diastolic blood pressure (DBP) at trough in Blacks and Non-Blacks with mild to moderate hypertension. In these studies, 2,016 intent-to-treat (ITT) patients received 12 weeks of daily placebo or nebivolol. Of these 2,016 ITT patients, 1,811 patients received nebivolol in doses ranging from 1.25 mg to 40 mg daily, depending on the study. NEB-302 and NEB-305 evaluated nebivolol in 1,716 ITT patients in the general hypertensive population, and NEB-202 evaluated nebivolol in 300 ITT patients in the Black population. In all treatment arms, patients were stratified in decreasing priority by metabolism of nebivolol (poor metabolizer (PM) versus extensive metabolizer (EM), diabetes status (history of diabetes mellitus versus no history of diabetes mellitus), ethnicity (Black versus Non-Black in NEB-302 and NEB-305 only), age (< 65 and ≥ 65 years), and gender.

The primary efficacy endpoint was the change in the mean trough sitting diastolic blood pressure at the end of treatment compared to baseline. Using an Analysis of Covariance (ANCOVA) model with treatment as factor and baseline sitting DBP, metabolism of nebivolol, diabetes status, ethnicity, age, and gender as covariates, the sponsor and the Agency confirmed the statistical significance of nebivolol 1.25 mg through 40 mg in NEB-302, nebivolol 5 mg, 10 mg, and 20 mg in NEB-305, and nebivolol 5 mg through 40 mg in NEB-202.

Table 1 shows the results of the primary analyses.

Table 1. Primary Analysis Results of Pivotal Studies (NEB-302, NEB-305, and NEB-202)

Treatment	N	Baseline Mean	Mean at the End of Study	LS Mean Change from Baseline (SE)	Step-Down trend Test p-value
NEB-302					
Placebo	81	100.3	97.1	-2.9 (1.1)	-
1.25 mg	83	98.9	90.8	-8.0 (1.1)	<0.0001
2.5 mg	82	99.8	91.1	-8.5 (1.1)	<0.0001
5 mg	165	99.6	91.0	-8.4 (1.0)	<0.0001
10 mg	166	99.5	90.2	-9.2 (0.9)	<0.0001
20 mg	166	99.4	89.5	-9.8 (0.9)	<0.0001
30/40 mg	166	99.3	88.0	-11.2 (0.9)	<0.0001

(continued)

Treatment	N	Baseline Mean	Mean at the End of Study	LS Mean Change from Baseline (SE)	Step-Down trend Test p-value
NEB-305					
Placebo	75	98.7	91.4	-4.6 (1.3)	-
5 mg	244	99.1	88.5	-7.8 (1.0)	0.0015
10 mg	244	98.9	87.7	-8.5 (1.0)	0.0009
20 mg	244	99.2	87.2	-9.1 (1.0)	0.0002
NEB-202					
Placebo	49	100.8	96.4	-2.8 (2.1)	-
2.5 mg	49	99.5	92.8	-5.7 (2.1)	0.14
5 mg	50	100.5	91.4	-7.7 (2.1)	0.0187
10 mg	51	100.3	90.0	-8.9 (2.0)	0.0032
20 mg	50	101.5	90.9	-8.9 (2.1)	0.0019
40 mg	51	98.7	89.6	-8.3 (2.0)	0.0014

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 4)

Nebivolol also had a statistically significant effect on most of the secondary efficacy endpoints. In NEB-302, trough systolic blood pressure (SBP) parameters responded significantly to nebivolol 1.25 mg through 40 mg. For peak systolic blood pressure parameters, nebivolol 2.5 mg through 40 mg was statistically significant. For sitting systolic blood pressure at peak, nebivolol 1.25 mg was also statistically significant.

In NEB-305, nebivolol 20 mg significantly reduced trough systolic blood pressure parameters. For reduction of peak systolic blood pressure parameters, generally, nebivolol 5.0 mg and above was statistically significant, with the exception of sitting systolic blood pressure at peak, which required nebivolol 10 mg.

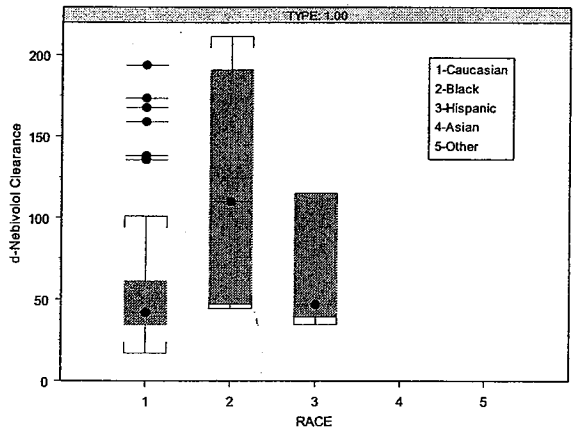
In NEB-202, Black hypertensive patients generally required nebivolol 40 mg for statistical significance in reducing trough systolic blood pressure parameters, although nebivolol 10 mg and 20 mg significantly reduced sitting SBP at trough. At 40 mg daily, however, nebivolol did not significantly reduce supine systolic blood pressure at trough. For peak systolic blood pressure parameters, nebivolol 5 mg through 40 mg was statistically significant.

Although efficacy results differed somewhat between NEB-302 and NEB-305 for the general hypertensive population, NEB-202 suggested Blacks required higher doses of nebivolol for statistically significant reductions in most diastolic as well as systolic parameters at peak and trough.

In NEB-202, the placebo-subtracted trough to peak ratios for sitting diastolic blood pressure reduction from baseline to end of treatment ranged from 0.6 to 0.8, with most doses being 0.7. In NEB-302, the trough to peak ratios ranged from 0.9 to 1.4. In NEB-305, the trough to peak ratio was 0.9 for nebivolol 5 mg and 20 mg and 0.8 for nebivolol 10 mg. These ratios suggest some Blacks may benefit from twice daily dosing with nebivolol.

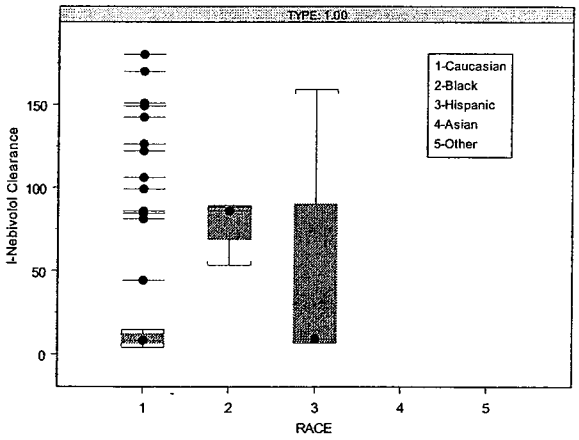
In NEB-302, Elena Mishina, Ph.D., a Biopharmacologist in the Cardio-Renal Division, found Black poor metabolizers had a 30% increased clearance of *d*-nebivolol and *l*-nebivolol, compared with other ethnicities, as seen in Figure 1 and Figure 2. Although there were only two Black poor metabolizers studied and further investigation is needed, the data suggest Black poor metabolizers may require higher doses of nebivolol for efficacy in the treatment of mild to moderate hypertension. If nebivolol is carcinogenic in humans, Black poor metabolizers would be at greatest risk because there would be no safety margin.

Figure 1. d-Nebivolol Clearance (L/hr) in Poor Metabolizers by Race (NEB-302)



(Reproduced from Mishina E, Review of NEB-302, NDA 21,742

Figure 2. l-Nebivolol Clearance (L/hr) in Poor Metabolizers by Race (NEB-302)



(Reproduced from Mishina E, Review of NEB-302, NDA 21,742

In NEB-203, nebivolol 5 mg increased exercise duration by 7.1%, but nebivolol 10 mg and 20 mg decreased exercise duration by 10.4% and 8.9%, respectively. Although 38% of patients in the atenolol 100 mg group did not complete the final submaximal exercise treadmill test (ETT), patients in the atenolol 50 mg and 100 mg treatment groups increased exercise duration by 3.7% and 9.2%, respectively.

In NEB-321, nebivolol 5 mg, 10 mg, and 20 mg significantly reduced trough sitting diastolic blood pressure in patients on background antihypertensive therapy.

Finally, in NEB-306, nebivolol as monotherapy or in combination with diuretics or amlodipine significantly reduced trough sitting diastolic blood pressure from baseline to end of study. Although the randomized withdrawal study consisted of only 28 patients, there did not appear to be rebound hypertension in the 18 patients assigned to placebo during that four-week period.

From an efficacy standpoint, nebivolol is not significantly different from other β_1 selective blockers currently on the market, except nebivolol is potentially carcinogenic in humans. Blacks require higher doses of nebivolol for efficacy as they do with other beta blockers. Although *in vitro* experiments using human umbilical vein preparations and forearm blood flow studies in small numbers of humans suggest nebivolol may have some effect on nitric oxide release, the exact mechanism is unknown. Metoprolol, another β_1 selective adrenoceptor blocking agent, also increases nitric oxide release. Many of these studies were not placebo-controlled and were performed up to seventeen years ago. With technological improvements, it is unclear whether or not these results are reproducible today.

In Dr. Salma Lemtouni's safety review of the pivotal studies, nebivolol did not cause deaths or malignancies in excess of those seen in the carvedilol hypertension program (Lemtouni S, 2004, Executive Summary, Safety Review, Cardio-Renal Division, NDA 21,742). Nebivolol decreased HDL cholesterol, increased uric acid, and significantly increased triglycerides. Additionally, individuals on nebivolol had a 3 fold increase in hs-C-reactive protein, a 20 fold increase in chest pain, and a 4 fold increase in bradycardia and insomnia, compared with placebo. Bradycardia occurred in 1.3% of patients on nebivolol compared with 0.3% of patients on placebo. The highest incidence of bradycardia occurred in patients taking nebivolol 20 mg (2.4%) and was statistically significant. Adverse events leading to withdrawal from nebivolol included cardiovascular disorders in 23 patients (9.3%), with 10 patients withdrawing due to bradycardia. Other adverse events leading to withdrawal included general disorders in17 patients (6.9%), nervous system disorders in14 patients (5.7%), and gastrointestinal disorders in 11 patients (4.5%)). General disorders consisted of fatigue in 8 patients (3.2%), edema in 4 patients (1.6%), and chest pain in 3 patients (1.2%).

In NEB-122, the electrocardiographic study in 281 healthy volunteers, there were no consistent increases in QTcF[3] or QTcP[4] related to nebivolol.

In my opinion, the benefits of nebivolol do not exceed the possible carcinogenicity risk. I consider nebivolol approvable only if the sponsor can clearly demonstrate nebivolol is not carcinogenic in humans.

[3]**QTcF is the QT correction using Fridericia's formula ($QT/RR^{1/3}$).**
[4]**QTcP is the QT correction using the Population correction factor (0.329).**

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk management activity will depend on the findings of the mechanistic studies which the sponsor plans to perform as well as the recommendations from the Division of Reproductive and Urologic Drug Products.

1.2.2 Required Phase 4 Commitments

Required Phase 4 commitments will depend on the mechanistic study results and consultation.

1.2.3 Other Phase 4 Requests

Other Phase 4 requests will depend on the mechanistic study results and consultation.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Janssen Pharmaceutica Products, LP, Bertek Pharmaceuticals, Inc., and A. Menarini LTD developed nebivolol. In the late 1980s and early 1990s, Janssen performed approximately 65 clinical trials in 2874 patients in the United States and Europe. According to the sponsor, 2,570 of these 2,874 patients received nebivolol for the treatment of hypertension. Additionally, 144 patients received nebivolol for the treatment of congestive heart failure, and 144 patients received nebivolol for the treatment of ischemic heart disease. For the 16 remaining patients, the sponsor did not specify their disease process. Most of the nebivolol doses studied were less than 10 mg; however, Janssen also studied does up to 30 mg in short-term dose-finding studies. Approximately 400 patients received nebivolol for 12 months or longer at doses of approximately 5 mg.

As part of the 65 clinical trials, Janssen performed 5 "Legacy Trials" in the United States (US), conducted under IND 33,060. These Legacy Trials included INT-1, USA-1, USA-3, USA-4, and USA-6. INT-1 was a Phase III trial, and the other trials were Phase II. In the Legacy Trials, Janssen randomized 516 patients out of the 2874 patients described above. Most of the patients in INT-1, USA-1, USA-3, and USA-4 had hypertension. In USA-6, however, investigators studied nebivolol in 38 randomized subjects with congestive heart failure.

On August 4, 1994, Janssen placed IND 33,060 on inactive status and suspended US development of nebivolol. According to the sponsor, Janssen inactivated the IND because "of the wish to invest in the development of other non-cardiovascular opportunities."[5] Janssen Research Foundation in Belgium continued to develop nebivolol internationally, outside of the US. For marketing in the United States and Europe, Janssen licensed nebivolol to Bertek Pharmaceuticals, Inc. and to A. Menarini LTD, respectively.

[5] **Janssen Statement submitted to Bertek Pharmaceuticals, Inc., and forwarded to FDA in e-mail dated October 14, 2004.**

In October 1995, the Netherlands approved nebivolol for the treatment of hypertension, with a recommended starting dose of 5 mg. On April 3, 1996, the other European Union Member States accepted this approval as part of the Mutual Recognition Procedure. According to the sponsor, since 1995, nebivolol has been registered in 65 countries in Europe, Latin America, Eastern Europe, the Middle East, and South Africa.

In 1997, A. Menarini LTD first marketed nebivolol in Germany and the Netherlands. Currently, Menarini markets nebivolol in 53 countries under multiple trademarks as a 5 mg tablet and has approximately 3.5 million person-years of post-marketing nebivolol use in data on file

On May 1, 1998,[6] Bertek Pharmaceuticals, Inc., a subsidiary of Mylan, assumed ownership of IND 33,060 and subsequently performed six pivotal studies with nebivolol in patients with mild to moderate hypertension in the United States, the United Kingdom, the Netherlands, and Belgium from May 2002 until present. The pivotal studies, comprised of NEB-302, NEB-305, NEB-202, NEB-321, NEB-306, and NEB-203, evaluated 2,800 patients with hypertension. A total of 2,464 out of these 2,800 patients received nebivolol in doses ranging from 1.25 mg to 40 mg. Additionally, NEB-122 studied electrocardiographic changes in 281 healthy subjects.

Due to licensing agreements with Janssen, Bertek considers the Janssen studies to be supportive, but not pivotal. Full case report form (CRF) documentation is lacking for some Janssen studies, and many of the studies were performed in the late 1980s prior to the publication of the ICH Good Clinical Practice guidance.

NEB-323, performed by the sponsor, is a study assessing the safety and efficacy of long-term nebivolol exposure (up to 24 months) in patients with mild to moderate hypertension and is ongoing at the time of this NDA. Safety information from this study is incorporated in Dr. Lemtouni's safety review of nebivolol.

A. Menarini LTD performed a study with nebivolol in patients with stable angina pectoris (NAP 01). Although the Agency requested the efficacy and safety data for NAP 01, we have not yet received the results. Currently, A. Menarini LTD is performing a study with nebivolol in seniors with heart failure (MR/01-99/01-Nhf). The Agency received some preliminary safety results for MR/01-99/01-Nhf, but because the sponsor is seeking an indication for the use of nebivolol in the treatment of hypertension, this data will not be incorporated in the safety review.

For NDA 21,742, Bertek Pharmaceuticals, Inc. performed and submitted 94 primary safety and efficacy studies, including 6 pivotal trials, and submitted 62 supportive studies performed by Janssen.

[6] **According to AO Williams, M.D., in his review of the Protocol Amendment, Serial No 055, for IND 33,060, dated June 8, 2002, the transfer of ownership for IND 33,060 became effective on May 1, 1998. On page 85 of the Integrated Summary of Safety, however, the sponsor indicates the date of transfer was September 17, 1998.**

1.3.2 Efficacy

There were six pivotal studies, including NEB-302, NEB-305, NEB-202, NEB-203, NEB-306, and NEB-321. Although the Statistical Review and Evaluation, Pharmacology/Toxicology Review, Biopharmacology Review, and Safety Review were submitted individually, I incorporated pertinent data and information from these reviews into my Efficacy Review.

1.3.3 Safety

I reviewed NEB-122, the safety evaluation of electrocardiographic intervals. Dr. Salma Lemtouni of the Cardio-Renal Division reviewed the remaining safety data from the Bertek program. Please see her review for full details.

1.3.4 Dosing Regimen and Administration

The pivotal studies used once daily oral doses of nebivolol ranging from 1.25 mg to 40 mg. Bertek plans to market the 2.5, 5.0, and 10.0 mg tablets.

1.3.5 Drug-Drug Interactions

Drugs inhibiting CYP2D6 and CYP3A4 may increase plasma levels of nebivolol. Fluoxetine, a known inhibitor of CYP2D6, increases peak plasma concentrations of *d*-nebivolol by 3-fold and peak plasma concentrations of *l*-nebivolol by 2-fold (Mishina E, 2005, Clinical Pharmacology Review, Cardio-Renal Division, NDA 21,742). With fluoxetine administration, area under the curve for *d*-nebivolol increases 8-fold and for *l*-nebivolol increases 5-fold. Other CYP2D6 inhibitors, such as quinidine and paroxetine, may also increase the plasma concentration of nebivolol. Additionally, cimetidine, a non-specific cytochrome P450 enzyme inhibitor, increases the plasma concentration of nebivolol by 23%.

There were no significant pharmacokinetic interactions between 10 mg of oral nebivolol and digoxin, warfarin, furosemide, hydrochlorothiazide, spironolactone, ramipril, and losartan.

Concomitant use of nebivolol with medications known to cause myocardial depression or inhibit AV conduction, such as verapamil, diltiazem, or antiarrhythmics such as disopyramide, requires caution.

Use of nebivolol with other beta-blockers is contraindicated. Additionally, patients taking catecholamine-depleting drugs, such as reserpine or guanethidine, require close monitoring when nebivolol is coadministered because excessive reduction of sympathetic activity can occur. Lastly, if patients are receiving nebivolol and clonidine, nebivolol should be discontinued for several days before the clonidine taper is initiated.

Activated charcoal administration may decrease the plasma concentration of nebivolol.

There are two cases of nebivolol overdose cited by either European post-marketing pharmacovigilance or the literature (Integrated Summary of Safety, item 8.9, page 99). From European post-marketing pharmacovigilance, a 61-year old female attempted suicide by consuming nebivolol 200 mg along with cisapride, acetylsalicylic acid, diclofenac, and gallo sanol®. The patient became hypotensive, dizzy, and tired. The hospital physicians performed

gastic lavage with the administration of charcoal, and the patient subsequently recovered. It was not known whether or not this patient was taking nebivolol or cisapride prior to the suicide attempt.

In the literature, Heinroth reported a suicide attempt by a 17 year old German diabetic woman (Heinroth 1999). The patient ingested 80-100 tablets of nebivolol 5 mg, several tablets of acetylsalicylic acid 100 mg, 9 IUs of Actrapid® (short-acting soluble human insulin), and 2 IUs Actraphane® (insulin human recombinant). Eight hours following ingestion, the patient had a blood pressure of 105/55, a heart rate of 55 bpm, and a nebivolol plasma level of 480 ng/mL. According to the sponsor, "the maximum plasma concentration 2 to 4 hours after a therapeutic [nebivolol] dose is 88-195 ng/mL." The acetylsalicylic acid level was nontoxic at 8.8 mcg/mL. The patient demonstrated reduced vigilance, slow motor function, pale skin, and diaphoresis. Serum potassium and glucose were low at 3.5 mEq/L and 2.1 mmol/L, respectively, and leukocytes were elevated at 12,200/mcL. An arterial blood gas was remarkable for a respiratory acidosis. Urinalysis revealed ketone bodies and protein. Physicians treated this patient with warm-water gastric lavage with charcoal and sodium sulphate every 6 hours for 24 hours, supplemental oxygen, a temporary pacemaker, arterial blood pressure monitoring, and intravenous potassium with insulin and glucagon (for 14 hours). At 18, 26, and 48 hours, nebivolol plasma concentration decreased from 480 ng/mL to 240 ng/mL, 84 ng/mL, and 25 ng/mL, respectively. The patient recovered and was discharged after 48 hours.

1.3.6 Special Populations

Hepatic: "In patients with moderate hepatic impairment, *d*- and *l*-nebivolol peak plasma concentration increased 3 and 2 times, exposure (AUC) increased 10 and 5 times, and the apparent clearance decreased by 86 and 7%, respectively (Mishina E, 2005, Executive Summary, Labeling Recommendations, Clinical Pharmacology Review, NDA 21,742)." The recommended starting dose is 2.5 mg in patients with mild and moderate hepatic impairment, and dose increments require caution. The sponsor has not performed studies in patients with severe hepatic impairment, and for this reason, nebivolol is contraindicated in this population.

Renal: The European Summary states the starting dose of "Nebilet®" (nebivolol) for patients with renal insufficiency is 2.5 mg daily, although the dose may be increased to 5.0 mg, if needed. With mild renal impairment (ClCr = 50 to 80 mL/min), there is no change in the clearance of nebivolol. With moderate (ClCr = 30 to 50 mL/min) and severe (ClCr $\leq$ 30 mL/min) renal impairment, however, there is a 17% and 53% reduction in clearance, respectively. The Agency recommends dose adjustment in patients with severe renal impairment. The sponsor has not performed studies in hemodialysis patients; therefore, the Agency recommends cautious use of nebivolol in this population.

There is little evidence to support an effect of age, race, gender, body weight, smoking status, and diabetic status on the safety of nebivolol. The starting dose in patients over 65 years of age, however, is 2.5 mg/day.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Janssen Pharmaceutica Products, LP developed nebivolol tablets and licensed the formulation and process for the 5 mg tablet to Bertek Pharmaceuticals, Inc. on February 21, 2001. Upon review of the Janssen formulation, Bertek made two excipient changes [redacted] Pregelatinized Starch and [redacted] Magnesium Stearate/Sodium Lauryl Sulfate. Bertek subsequently developed additional strengths and currently manufactures the [redacted] 2.5 mg, 5 mg, 10 mg, [redacted] doses. All nebivolol tablets are manufactured by Mylan Pharmaceuticals, Inc. in Morgantown, West Virginia. Nebivolol tablets have the following ingredients:

Figure 3. Quantitative Composition of Nebivolol Tablets

Ingredients	2.5mg mg/tab	5mg mg/tab	10mg mg/tab
Nebivolol Hydrochloride[1]			
Hypromellose, USP			
Polysorbate 80, NF			
Lactose Monohydrate, NF			
Pregelatinized Starch, NF			
Croscarmellose Sodium, NF			
Microcrystalline Cellulose, NF			
FD&C Blue #2			
D&C Red #27			
FD&C Yellow #6			
Colloidal Silicon Dioxide, NF			
Magnesium Stearate/Sodium Lauryl Sulfate			
Total Theoretical Weight	115	230	230

(Reproduced from Sponsor, Summary, Section 3.4.3, Drug Product, Table 3.4-03, Page 76)

2.2 Currently Available Treatment for Indications

Nebivolol, 5 mg, is approved in over 45 countries in Europe, South America, and the Caribbean for the treatment of essential hypertension. Marketed trade names of Nebivolol vary by country and include Nebilet®, Lobivon, Nebilox, Nobiten, and Silostar.

2.3 Availability of Proposed Active Ingredient in the United States

Final drug product will be manufactured in Morgantown, West Virginia.

2.4 Important Issues With Pharmacologically Related Products

Concomitant use of nebivolol with other beta blockers or calcium channel blockers (verapamil, diltiazem) could exacerbate bradycardia.

2.5 Presubmission Regulatory Activity

On August 4, 1994, Janssen Pharmaceutica Products, LP ceased US development of nebivolol and inactivated IND 33,060. In October 1995, the Netherlands approved nebivolol for the treatment of hypertension, with a recommended starting dose of 5 mg. In April 1996, the other European Union Member States accepted this approval as part of the Mutual Recognition Procedure.

On September 17, 1998, Janssen transferred IND 33,060 to Bertek Pharmaceuticals, Inc., a subsidiary of Mylan. On February 21, 2001, Janssen licensed the nebivolol formulation and process for the 5 mg tablet to Bertek Pharmaceuticals, Inc.. Bertek subsequently performed six pivotal studies with nebivolol in patients with mild to moderate hypertension in the United States, the United Kingdom, the Netherlands, and Belgium from May 2002 until present. A. Menarini LTD, an Italian firm, currently owns nebivolol marketing rights for Europe.

2.6 Other Relevant Background Information

According to Ram Mittal, Ph.D., Chemistry, Cardio-Renal Division, chemistry reviews from the 1989 to 1991 time frame described a nebivolol formulation with [redacted]. The nebivolol formulation used in the pivotal studies for NDA 21,742, however, is completely free of [redacted].

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

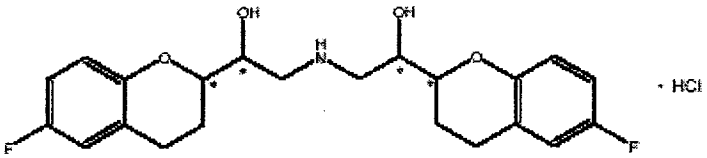
3.1 CMC (and Product Microbiology, if Applicable)

Nebivolol is a racemic mixture of *d*- and *l*-isomers and was developed by the sponsor for the treatment of [redacted] hypertension. Nebivolol has a dual mechanism of action and is a selective β_1-receptor antagonist as well as a vasodilator. According to the sponsor, the *l*-isomer is a weak β_1-receptor antagonist; however, the *d*-isomer causes the predominant effect and has over a 1750 fold higher affinity for β_1-adrenergic receptors, compared with *l*-nebivolol. The exact ß1 selectivity of nebivolol is controversial. Studies performed in Bristow's laboratory (Bristow 2004a) demonstrated a β_1/β_2 selectivity of approximately 320 fold for nebivolol, while studies performed in Bohm's laboratory (Bohm 2001) and in Schwinger's laboratory (Schwinger 2001) demonstrated a $\beta_1\beta_2$ selectivity of 3-4 fold and 41 fold, respectively. The sponsor states

vasodilatation is related to the activation of the L-arginine-nitric oxide system which is mediated primarily through the *l*-isomer. After reviewing the nitric oxide and pharmacodynamic studies, however, I think the exact mechanism involved with vasodilatation and nitric oxide release is unknown. In the supportive studies, I found the the *d*-isomer to have between 53% and 92% of the activity of *l*-nebivolol to release nitric oxide. In most cases, the *d*-isomer had over 75% the activity of *l*-nebivolol, suggesting it was more than just a weak contributer. According to the sponsor, the ratio of β_1/α_1 selectivity for nebivolol is greater than 400 (Bristow 2004). Nebivolol is free of intrinsic sympathomimetic activity and is a hepatically metabolized lipophilic compound capable of crossing the blood brain barrier.

The chemical name for nebivolol is (±)[2R*[R*[R*(S*)]]]-α,α' - [iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol] hydrochloride. Nebivolol's molecular formula is ($C_{22}H_{25}F_2NO_4$·HCL) and the structural formula is as follows:

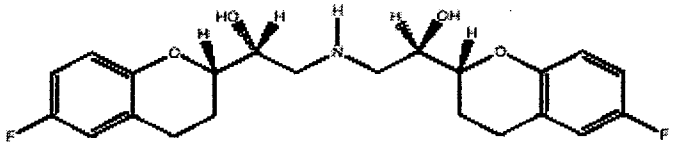
Chemical Structure of Nebivolol



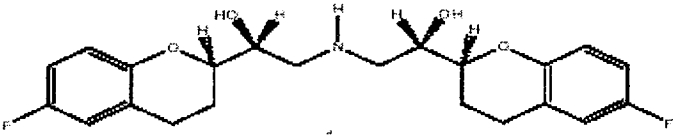
* = stereogenic centers

(Source: Sponsor, Summary, Section 3.4.2.1.1 Description of the Drug Substance, page 70)

Nebivolol is a 1:1 racemic mixture of mirror image d- and l-isomers, with stereochemical designations of [SRRR]-nebivolol and [RSSS]-nevibolol, respectively. Because of its four stereogenic carbon centers, also known as asymmetric or chiral carbon atoms, however, sixteen theoretical stereoisomers of nebivolol are possible, although only ten isomers exist, with the N-atom serving as the internal plane of symmetry.



SRRR- or *d*-nebivolol



RSSS- or *l*-nebivolol

(Source: Sponsor, Summary, Section 3.4.2.1.1 Description of the Drug Substance, page 71)

According to the sponsor, nebivolol has a β_1 adrenergic receptor binding affinity (Ki) of 0.7 nM (Bristow 2004b). Four nebivolol metabolites, including 4-hydroxy nebivolol, 5-hydroxy nebivolol, 8-hydroxy nebivolol, and 4-hydroxy-5-phenol nebivolol bind to the ß1 adrenergic receptor with affinities approaching that of the parent racemate.

3.2 Animal Pharmacology/Toxicology

Findings from the preclinical studies in rats, dogs, mice, and rabbits include

- hemolytic anemia in the rat and dog
- increased spleen size and weight in the rat and dog as well as increased red blood cells in the red pulp
- increased serum potassium in rodents
- decreased total protein, albumin, cholesterol, triglycerides, phospholipids, and inorganic phosphorus in rodents
- increased lung, liver, spleen, heart, and adrenal gland weight in males and females
- decreased pancreas, kidney, and "gonad" weight
- foamy macrophages in the alveolar lumina and inflammatory thickening of the alveolar septae
- increased prostate weight in rats following one month of oral nebivolol
- urolithiasis and prostatitis in dogs following three months of nebivolol

Nonclinical issues possibly relevant to clinical use include poor characterization of active metabolites, QTc prolongation, carcinogenicity, endocrine disruption, and reproductive and developmental toxicity (Hausner E, 2004, Executive Summary, Pharmacology/Toxicology Review, Cardio-Renal Division, NDA 21,742, page 2).

In the HERG assay, nebivolol inhibited IKr with an IC_{50} of $3x10^{-7}$M, compared with astemizole which had an IC_{50} of $2x10^{-8}$M. In the dog studies, only the Bazett's formula was used for QT correction. According to Dr. Hausner, the acute cardiovascular safety study and 2 week repeat dose study had no QTc effects. After one month of oral nebivolol, QTc increased in treatment and control groups. After one month of intravenous nebivolol, QTc decreased. In a 3 month study at nebivolol doses $\geq$ 10 mg/kg, there were inconsistent increases in QTc at 4 weeks onward. If humans received nebivolol 10 mg, the safety margin between the dose in dogs which had a QTc effect and the human dose would be 8.7 fold (Hausner E, 2004, Executive Summary, Pharmacology/Toxicology Review, Cardio-Renal Division, NDA 21,742, page 2). Obviously, if humans received nebivolol doses up to 40 mg, there would be no significant safety margin.

Regarding carcinogenicity, Janssen initially submitted nebivolol under IND 33,060 in April 1989. On October 20, 1989, Janssen Research Foundation initiated Experiment 1967, a 19-20 calendar month study (~ 21 lunar months) in 500 SPF albino Swiss mice [redacted]. Investigators divided the mice into 5 groups of 50 males and 50 females. In the report dated December 9, 1994, the test article was Nebivolol R67444, batch # ZR067555 PFA091, and the Cyclodextrin batch numbers were FG25182 and FG24222. ß-cyclodextrin was used in the

nebivolol formulation at that time to improve bioavailability. As seen in Table 2, mice were divided into the following 5 dosage groups:

Table 2. Summary of Dietary Dosage Groups (Experiment 1967)

Group	Target Amount of nebivolol (mg/kg/day)	ß-cyclodextrin (mg/kg/day)
Control (C)	0	0
Vehicle (V)	0	440
Low (LD)	2.5	27.5
Medium (MD)	10	110
High (HD)	40	440

(Source: Elizabeth A. Hausner, D.V.M., October 17, 2002, Review and Evaluation of Toxicology Data, IND 33,060, Submission 059, Nebivolol hydrochloride (R67,555), page 3)

The histopathology was significant for unequivocal neoplastic changes in the male mice, as seen in Table 3.

Table 3. Neoplastic Changes in Male Swiss Mice (Experiment 1967)

	Dose group (mg/kg)				
	0	V	2.5	10	40
Testes: Leydig cell tumor	1/50 (2%)	2/50 (4%)	0/50	1/50	21/50 (42%)
Testicular hyperplasia	5/50 (10%)	6/50	4/50	4/50	14/50 (28%)

(Source: Elizabeth A. Hausner, D.V.M., October 17, 2002, Review and Evaluation of Toxicology Data, IND 33,060, Submission 059, Nebivolol hydrochloride (R67,555), page 15)

As stated in Dr. Elizabeth Hausner's review dated October 17, 2002, Leydig cell tumors (LCT) are the most frequent neoplasm seen in the testes of mice and rats. These tumors are often strain-dependent, and their incidence is much less in mice than rats. According to Dr. Hausner, some sources suggest the incidence of LCT in Swiss mice is $\leq 1\%$. Although there are many proposed mechanisms for the development of LCT, Dr. Hausner states the "only mechanism that causes LCT in mice but not rats, is estrogen receptor agonism/antagonism" which may present as endocrine disruption (Hausner E, October 17, 2002, Review and Evaluation of Toxicology Data, IND 33,060, Submission 059, page 41). Although Leydig cell hyperplasia and tumors in rats are not necessarily associated with tumors in humans, the human relevance of these findings in mice is uncertain.

On August 24th, 2004, the Executive Carcinogenicity Assessment Committee (CAC) of the Agency found these Leydig cell tumors in mice from Experiment 1967 to be drug-related.

In a telephone conference with Bertek Pharmaceuticals, Inc. on September 2, 2004, Dr. Hausner informed the sponsor about the CAC conclusions and asked the sponsor to "make a case to show that this finding was not clinically relevant."[7] Several weeks later, the sponsor informed Dr. Hausner of their plans to reevaluate the mouse carcinogenicity slides. Despite the Cardio-Renal Division's request for the sponsor to submit a protocol outlining the rationale and method for this reevaluation, the sponsor did not provide this information.

[7]**Teleconference Minutes, September 2, 2004, page 2.**

Bertek Pharmaceuticals, Inc. had the slides reviewed in a blinded fashion and then created a Pathology Working Group (PWG) comprised of Henry Wall, DVM, John Vanderberghe, DVM, W. Ray Brown, DVM, PhD, and Charles Capen, DVM, PhD. The PWG reviewed the 62 slides originally found to have an interstitial cell proliferative lesion as well as randomly selected slides from the 30 mice originally found to have no proliferative lesion. The written report from the PWG reclassified one adenoma as a Leydig cell carcinoma. According to Dr. Hausner, there were reclassifications in both directions, but "the overall interpretation did not change (Hausner E, November 23, 2004, Pharmacology/Toxicology Review, NDA 21,742, page 2)." A total of 17/50 (34%) male mice "had neoplastic lesions."[8]

The summary of preclinical endocrine findings, as quoted from page 43 of Dr. Hausner's 2002 review and page 3 of the 2004 Pharmacology/Toxicology Executive Summary, is listed below:

- "testicular degeneration in the 6 month rat study
- decreased weight of the testes in the vehicle control and at all dosage levels in the 12 month dog study
- Leydig cell tumors in mice
- decreased absolute and normalized "gonad" weight in the MD[9] and HD[10] female mice
- decreased female fertility in the MD and HD groups, with only 1 HD female becoming pregnant
- dystocia and cannibalism with decreased survival of the pups at all dosage levels in the Seg III review
- doses of 10 and 40 mg/kg, which were previously nontoxic and minimally toxic, respectively, were toxic in both the fertility study and the Seg III study
- 'testicular atrophy due to delayed maturation' in the 3 month study in Swiss mice (160 mg/kg dosing group)
- enlarged adrenal glands in rodents
- decreased total cholesterol and HDL
- increased serum potassium in rats and dogs"

Dr. Hausner also found evidence of significant reproductive and developmental toxicity:

- "decreased food consumption and weight loss in pregnant animals, with maternal toxicity noted at $\geq$ 20 mg/kg
- dystocia and cannibalism in the nebivolol-treated dams
- decreased pup birth weight with no NOAEL identified in several Seg III studies
- decreased fertility and decreased numbers of corpora lutea with no NOAEL identified
- teratogenicity manifested by ureteral dilatation, split center of thoracic vertebrae, and rudimentary sternal bones
- bronchoconstriction and decrease in coronary blood flow
- infiltration of foamy macrophages in pulmonary alveoli

[8]E-mail communication with Elizabeth Hausner, DVM, December 20, 2004.
[9]MD = Medium dose
[10]HD = High dose

- increased polyploidy and endoreduplication in the chromosome aberration assay performed in cultured human lymphocytes
- possible bone marrow toxicity, as seen in the micronucleus test in mice"

Although no transmission electron microscopy was performed of the foamy macrophages in the pulmonary alveoli for a definitive diagnosis, in my opinion, these findings may be consistent with phospholipidosis.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Nebivolol has been studied in approximately 160 clinical trials spanning two and a half decades and involving more than 5,700 subjects in whom the drug was administered via the oral and intravenous routes. Data for the clinical efficacy and safety reviews came from clinical trials performed in the United States and Europe. As part of this NDA, Bertek performed and submitted a total of 94 primary safety and efficacy studies, including 6 pivotal trials, and submitted 62 supportive studies performed by Janssen. Bertek plans to market the 2.5, 5.0, and 10.0 mg tablets.

4.2 Tables of Clinical Studies

The sponsor performed six pivotal studies for efficacy, including NEB-302, NEB-305, NEB-202, NEB-306, NEB-321, and NEB-203. I discuss the studies individually in the Appendix and summarize the pooled data in Section 6, the Integrated Review of Efficacy. The 6 pivotal studies used the oral formulation of nebivolol, and the doses are further described in Table 4. Study NEB-323 is ongoing and is a multi-center, open extension study to assess the safety and efficacy of long-term nebivolol exposure in patients with mild to moderate hypertension. The estimated study duration for NEB-323 is up to 24 months.

Integrated Review of Efficacy

Table 4. Description of Studies in Patients with Hypertension

Study Number of Sites Region	Study Design Phase Date	Primary Efficacy Study Objectives Entry Criteria	Study Treatments Regimen and Duration	# Subjects by Arm ITT/ Completed Study Total ITT/Total Completed	Gender (%) Median Age (Range) Blacks Age ≥ 65	Primary Endpoint Statistical Test/P-value
NEB 302 68 Sites USA	Double-blind, Multi-Center, Randomized, Placebo-Controlled, Seven Parallel Group Phase III September 19, 2001 – March 21, 2003	Change in average sitting DBP taken at trough drug plasma level (24 ± 2 hrs post-previous morning's dose) at the end of treatment (Day 84) c/w baseline. Study Objectives: · Efficacy · Dose Finding · Peak and Trough Effects · Safety · Population PK · Response Rates Entry Criteria Entry SDBP ≥ 95 mm Hg and ≤ 109 mm Hg at randomization HR ≥ 50 bpm	Placebo Nebivolol 1.25 mg 2.5 mg 5 mg 10 mg 20 mg 30/40 mg* Up to 126 days (28-42 day placebo run-in followed by 84 days of double-blind tx)	81/ 67 83/68 82/68 165/148 166/133 166/144 166/149 Total: 909/777	M/F 518/391 (57.0% M; 43.0 % F) Median Age: 54 years (22-84) Blacks: 132 (14.5%) Age ≥ 65: 193 (21.2%)	LS mean change from baseline to end of treatment for sitting DBP at trough (ITT LOCF) 1. Step-down trend test significant for all nebivolol doses ($p < 0.001$) 2. Step-up trend test did not detect statistically significant incremental increases in efficacy over the dose range from nebivolol 1.25 mg to 20 mg (30/40 mg evaluated only for safety). Increased blood pressure reduction seen with higher doses.

*** Patients randomized to the nebivolol 40 mg group initiated treatment with nebivolol 30 mg. The dose was increased to 40 mg at the Day 14 visit if the patient tolerated the 30 mg dose (sitting heart rate > 55 bpm). Nineteen patients received nebivolol 30 mg throughout the study; 147 patients were up-titrated to 40 mg.**

USA = United States, DB = Double-blind, ITT = Intent-to-Treat Population, M = Male, F = Female, DBP = Diastolic blood pressure, bpm = Beats per minute, LOCF = Last observation carried forward, LS = Least squares, qd = once daily, SDBP = Sitting diastolic blood pressure

(Adapted from Sponsor, Integrated Review of Efficacy, page 39)

(continued)

Table 4. Description of Studies in Patients with Hypertension (continued)

Study Number of Sites Region	Study Design Phase Date	Primary Efficacy Study Objectives Entry Criteria	Study Treatments Regimen and Duration	# Subjects by Arm ITT/Completed Study Total ITT/Total Completed	Gender (%) Median Age (Range) Blacks Age ≥ 65	Primary Endpoint Statistical Test/P-value
NEB 305 82 Sites 59 USA 23 Europe	Double-blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group, Multi-National Phase III September 17, 2001 – March 21, 2003	Change in average sitting DBP (24 ± 2 hours post-previous morning's dose) taken at trough at the end of treatment (Day 84) compared to baseline. Study Objectives: · Efficacy · Peak and Trough Effects · Safety · Response Rates Entry Criteria: Entry SDBP ≥ 95mm Hg and ≤ 109 mm Hg at randomization HR ≥ 50	Placebo Nebivolol 5 mg 10 mg 20 mg Up to 126 days (28–42 day placebo run-in followed by 84 days of double-blind tx)	75/61 244/218 244/206 244/217 Total: 807/702	M/F 432/375 (53.5% M; 46.5% F) Median Age: 53 years (22-82) Blacks: 105 (13.0%) Age ≥ 65: 147 (18.2%)	LS mean change from baseline to end of treatment for sitting DBP at trough (ITT, LOCF) 1. Step-down trend test significant for all nebivolol doses ($p \leq 0.002$) 2. Step-up trend test did not detect statistically significant incremental increases in efficacy over the dose range from nebivolol 5 mg to 20 mg. Increased blood pressure reduction seen with higher doses.

US = United States, DB = Double-blind, ITT = Intent-to-Treat population, M = Male, F = Female, DBP = Diastolic blood pressure, bpm = Beats per minute, LOCF = Last observation carried forward, LS = Least squares, qd = once daily, SDBP = Sitting diastolic blood pressure

(Adapted from Sponsor, Integrated Review of Efficacy, page 40)

(continued)

Integrated Review of Efficacy

Table 4. Description of Studies in Patients with Hypertension (continued)

Study Number of Sites Region	Study Design Phase Date	Primary Efficacy Study Objectives Entry Criteria	Study Treatments Regimen and Duration	# Subjects by Arm ITT/ Completed Study Total ITT/Total Completed	Gender (%) Median Age (Range) Blacks Age ≥ 65	Primary Endpoint Statistical Test/P-value
NEB 202 38 Sites USA	Double-blind, Multi-Center, Randomized, Placebo-Controlled, Six Parallel Group Phase III November 1, 2001 – August 5, 2003	Change in average sitting DBP taken at trough (24 ± 2 hours post-previous morning's dose) at the end of treatment compared with baseline. Study Objectives: · Black patients only · Efficacy · Dose Response · Peak and Trough Effects · Safety · Response Rates Entry Criteria: Entry SDBP ≥ 95 mm Hg and ≤ 109 mm Hg at randomization HR ≥ 50 bpm	Placebo Nebivolol 2.5 mg 5 mg 10 mg 20 mg 40 mg Up to 126 days (14-42 day placebo run-in followed by 84 days of double-blind tx)	49/41 49/42 50/41 51/47 50/45 51/43 Total: 300/259	M/F 136/164 (45.3% M; 54.7% F) Median Age: 50 years (26-79) Blacks: 300/300 (100%) Age ≥ 65: 35 (11.7%)	LS mean change from baseline to end of treatment for sitting DBP at trough (ITT LOCF) 1. Step-down trend test significant for nebivolol 5 mg through 40 mg ($p \leq 0.004$) 2. Step-up trend test did not detect statistically significant incremental increases in efficacy over the dose range from nebivolol 5 mg to 20 mg

US = United States, DB = Double-blind, ITT = Intent-to-Treat population, M = Male, F = Female, DBP = Diastolic blood pressure, bpm = Beats per minute, LOCF = Last observation carried forward, LS = Least squares, qd = once daily, SDBP = Sitting diastolic blood pressure

(Adapted from Sponsor, Integrated Review of Efficacy, page 41)

(continued)

Table 4. Description of Studies in Patients with Hypertension (continued)

Study Number of Sites Region	Study Design Phase Date	Primary Efficacy Study Objectives Entry Criteria	Study Treatments Regimen and Duration	# Subjects by Arm ITT/ Completed Study Total ITT/ Completed	Gender (%) Median Age (Range) Blacks Age ≥ 65	Primary Endpoint Statistical Test/P-value
NEB 306 123 Sites 105 USA 18 Europe	Double-blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Multi-National Randomized Withdrawal Phase III March 8, 2002 – September 25, 2003 Feeder Studies: NEB 202, NEB 302, or NEB 305	Change in average sitting DBP (24 ± 2 hours post-previous morning's dose) taken at trough at the end of treatment (Day 84) compared to feeder baseline. Study Objectives: · Long-term Safety · Long-term Efficacy Entry Criteria: Successful completion of NEB 202, 302, or 305.	Nebivolol 5 mg 10 mg 20 mg or Nebivolol and Diuretic or Nebivolol and Amlodipine 5 mg 10 mg qd up to 9 months Up to 10 months (9 months extension plus optional 4-week follow-up) Optional 28-day, double-blind, placebo-controlled follow-up (randomized withdrawal): 28 pts completed phase (18 pts were withdrawn from Nebivolol)	Nebivolol alone: 607/268 Nebivolol + diuretic 206/110 Nebivolol + CCB 21/7 Other* 11/8 Total: 845/393 * Includes patients who received a regimen other than nebivolol alone (e.g., nebivolol + diuretic + calcium channel blocker)	M/F 451/394 (53.4% M; 46.6% F) Median Age: 53 years (23-82) Blacks: 197 (23.3%) Age ≥ 65: 143 (16.9%)	LS mean change from baseline (of feeder study) to end of nebivolol treatment (NEB-306) in trough sitting DBP (ITT, OC) 1. Nebivolol, alone or in combination with diuretics or calcium channel blockers, decreased trough sitting diastolic blood pressure from baseline to end of study. 2. The nebivolol monotherapy treatment group appeared to have the greatest reduction in sitting diastolic blood pressure at trough (-15.0 mm Hg), compared with nebivolol + diuretic (-12.0 mm Hg), or nebivolol + calcium channel blocker (-6.7 mm Hg) 3. No rebound hypertension with nebivolol.

US = United States, DB = Double-blind, ITT = Intent-to-Treat population, M = Male, F = Female, DBP = Diastolic blood pressure, bpm = Beats per minute, LOCF = Last observation carried forward, LS = Least squares, EU = European Union, qd = once daily, CCB = Calcium channel blocker, OC = Observed case
***Includes patients who received a regimen other than nebivolol alone, nebivolol + diuretic or nebivolol + CCB. For example, a patient who received nebivolol + diuretic + CCB would be included in the Other regimen category for receiving two adjunct therapies rather than one as specified in the protocol**

(Adapted from Sponsor, Integrated Review of Efficacy, page 42)

Table 4. Description of Studies in Patients with Hypertension (continued)

Study Number of Sites Region	Study Design Phase Date	Primary Efficacy Study Objectives Entry Criteria	Study Treatments Regimen and Duration	# Subjects by Arm ITT/ Completed Study Total ITT/ Completed	Gender (%) Median Age (Range) Blacks Age ≥ 65	Primary Endpoint Statistical Test/P-value
NEB 321 80 USA	Double-blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Phase III October 22, 2002 – October 18, 2003	Change in average sitting DBP taken at trough (24 ± 2 hours post-previous morning's dose) at the end of treatment (Day 84) compared with baseline (Day 1). Study Objectives: · Efficacy and Safety of 3 dose levels of nebivolol vs. placebo, when added to a patient's existing antihypertensive medication for 3 months Entry Criteria: **Entry SDBP ≥ 90 mm Hg** and ≤ 109 mm Hg at screening and baseline, in patients on background antihypertensive therapy. Supine HR ≥ 50 bpm	Placebo Nebivolol 5 mg 10 mg 20 mg Up to 108 days (14 ± 3 days screening/ beta-blocker wash-out; 84 ± 7 days double-blind treatment).	167/146 168/152 168/150 166/150 Total: 669/598	M/F 368/301 (55.0% M; 45.0% F) Median Age: 53 years (19-86) Blacks: 197 (29.4%) Age ≥ 65: 103 (15.4%)	Change from baseline to end of treatment in trough sitting DBP (ITT, LOCF) 1. Nebivolol 5 mg, 10 mg, and 20 mg significantly reduced trough sitting diastolic blood pressure in patients on background antihypertensive therapy. 2. Hochberg adjusted p-value < 0.001 for nebivolol 5 mg, 10 mg, and 20 mg for primary efficacy endpoint.

US = United States, DB = Double-blind, ITT = Intent-to-Treat population, M = Male, F = Female, DBP = Diastolic blood pressure, bpm = Beats per minute, LOCF = Last observation carried forward, qd = once daily, ACEI = Angiotensin converting enzyme inhibitor, ARB = Angiotensin receptor blocker, SDBP = Sitting diastolic blood pressure

(Adapted from Sponsor, Integrated Review of Efficacy, page 43)

(continued)

Integrated Review of Efficacy

Table 4. Description of Studies in Patients with Hypertension (continued)

Study Number of Sites Region	Study Design Phase Date	Primary Efficacy Study Objectives Entry Criteria	Study Treatments Regimen and Duration	# Subjects by Arm ITT/ Completed Study/ Completed ETT Total/Total Completed	Gender (%) Median Age (Range) Blacks Age ≥ 65	Primary Endpoint Statistical Test/P-value
NEB 203 27 USA	Double-blind, Multi-Center, Randomized, Active Comparator, Five Treatment Phase II (Pilot Study) 29 May 29, 2002 – August 13, 2003	Percent Change in Sub-Maximal Exercise Duration By Cycle Ergometer at Peak at End of Treatment Compared to Baseline Study Objectives: · Dose-response effects on exercise capacity · Efficacy · Dose-response effects on left ventricular systolic and diastolic performance · To prepare for Phase III Trial Entry Criteria: SDBP ≥ 95 mm Hg and ≤ 109 mm Hg at randomization HR ≥ 50 bpm	Atenolol 50 mg 100 mg Nebivolol 5 mg 10 mg 20 mg 42 day single-blind placebo run-in followed by 28 days of double-blind therapy	24/24/23 21/15/13 23/23/22 23/22/21 24/24/24 Total: 115/108	M/F 85/30 (73.9% M; 26.1% F) Median Age: 50 years (21-79) Blacks: 17 (14.8%) Age ≥ 65: 14 (12.2%)	Percent change in sub-maximal exercise duration by cycle ergometer at peak drug effect at end of treatment (ITT, OC): 1. Exercise duration increased 3.7%, 9.2%, and 7.1% in atenolol 50 mg, atenolol 100 mg, and nebivolol 5 mg, respectively. Nebivolol 10 mg and 20 mg decreased exercise duration by 10.4% and 8.9%, respectively. 2. Atenolol and nebivolol reduced trough sitting DBP and SBP at all doses

US = United States, DB = Double-blind, ITT = Intent-to-Treat population, M= Male, F = Female, ETT = Exercise Tolerance Test, DBP = Diastolic blood pressure, bpm = Beats per minute, qd = once daily, OC = Observed case, SDBP = Sitting diastolic blood pressure

(Adapted from Sponsor, Integrated Review of Efficacy, page 44)

4.3 Review Strategy

Efficacy of oral nebivolol in patients with mild to moderate hypertension is based on six clinical trials.

4.4 Data Quality and Integrity

Acceptable from a statistical and efficacy standpoint.

4.5 Compliance with Good Clinical Practices (GCP)

All six pivotal trials were conducted in the United States and Europe under GCP and the Declaration of Helsinki.

4.6 Financial Disclosures

Attached are the Financial Certifications (Form FDA 3454) for the investigator's participating in the primary clinical studies NEB-302, NEB-305, NEB-202, NEB-306, NEB-203 and NEB-321.

No investigator or sub-investigator had a financial interest as described in 21 CFR 54 that required disclosure. Accordingly, this section does not provide a Financial Disclosure (Form FDA 3455) since it is not necessary.

NEB305; NEB306; NEB321
NEB202; NEB203; NEB302

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	------SEE ATTACHED LIST -------	

(Reproduced from Sponsor, Item 19 (Financial Information) of NDA 21,742, pages 1 and 2)

5 CLINICAL PHARMACOLOGY

I reviewed the following 17 pharmacokinetic studies listed in Table 5. I summarize the study results and the comments from the Clinical Pharmacology Executive Summary for NDA 21,742, written by Elena Mishina, Ph.D., of the Cardio-Renal Division, in Sections 1.3.4, 1.3.5, 1.3.6, 5.1, 5.2. 5.3, 8.1, 8.2, and 8.3.

Table 5. Pharmacokinetic Studies (all reviewed)

Study ID	Title	Study Category/ Type/Design
NEBI-0126	Single-Dose, Dose-Proportionality Pharmacokinetic Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status	Pharmacokinetic, ADME Open-label
NEBI-0127	Single-Dose, Relative Bioavailability and Food Effect Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status	Pharmacokinetic, ADME Open-label
NEBI-0136	Absorption, Metabolism, and Excretion of Nebivolol in Healthy Male Volunteers after a Single Oral Dose of 15 mg ^{14}C-Nebivolol HCl	Pharmacokinetic, ADME Open-label
NEBI-0142	Metabolism of [^{14}C]-Nebivolol in Human: Mass Balance and Metabolite Profiling/Identification in Plasma and Excreta	Pharmacokinetic, ADME Open-label
NEBI-0223	A Phase I Open-Label Single-Dose Study Assessing the Pharmacokinetics of Nebivolol HCL and the Formation of Metabolites in Healthy Volunteers	Pharmacokinetic, ADME Open-label
NEBI-0270	A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetics of Nebivolol HCl in Healthy Volunteers	Pharmacokinetic, ADME Open-label
NEBI-0128	A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction of Hydrochlorothiazide and Nebivolol HCl in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label
NEBI-0174	A Phase I Open-Label Study Comparing the Interaction of Nebivolol HCl on the Pharmacokinetics of Digoxin in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label
NEBI-0181	A Phase I Open-Label Study Comparing the Interaction of Steady-State Nebivolol HCl on the Pharmacokinetics and Pharmacodynamics of Warfarin Sodium in Healthy Volunteers	Pharmacokinetic Drug interaction Open-label
NEBI-0184	A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction of Fluoxetine Hydrochloride and Nebivolol HCl in Healthy Volunteers	Pharmacokinetic Drug interaction Open-label
NEBI-0213	A Phase I Open-Label Study of the Pharmacokinetic Interaction between Furosemide and Nebivolol HCl in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label
NEBI-0214	A Phase I Open-Label Multiple-Dose Study of the Pharmacokinetic Interaction between Nebivolol HCl and Spironolactone in Healthy Volunteers	Pharmacokinetic, Drug-interaction Open-label
NEBI-0220	A Phase I Open-Label Multiple-Dose Study of the Pharmacokinetic Interaction between Ramipril and Nebivolol HCl in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label
NEBI-02104	A Phase I Open-Label Single-Dose Study of the Pharmacokinetic Interaction between Nebivolol HCl and Losartan Potassium in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label
NEBI-02118	A Phase I Open-Label Study of the Effect of Repeated-Dose Activated Charcoal on the Pharmacokinetics of Nebivolol HCl in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label
NEBI-0124	A Phase I, Open-Label Study Investigating the Effects of Hepatic Impairment on the Single-Dose Pharmacokinetics of Nebivolol Hydrochloride	Pharmacokinetic, Special populations Open-label

Study ID	Title	Study Category/ Type/Design
NEBI-0125	A Phase I, Open-Label Study Investigating the Effects of Renal Impairment on the Single-dose Pharmacokinetics of Nebivolol Hydrochloride	Pharmacokinetic, Special populations Open-label

5.1 Pharmacokinetics

Nebivolol, a weak base with a pKa of 8.5, is slightly water soluble and highly lipophilic. As stated on page 46 of the Integrated Summary of Efficacy, "after oral administration, nebivolol undergoes extensive first-pass metabolism following a debrisoquine-like metabolic pathway regulated by cytochrome P450-2D6 (CYP2D6)." Because of genetic polymorphisms, CYP2D6 has variable activity, and subjects are known as either extensive metabolizers (EMs) or poor metabolizers (PMs). In the United States, approximately 7% of Caucasians, 2% of African Americans, and 2% of Asians are poor metabolizers.

When healthy subjects ingest racemic nebivolol, *d*- and *l*-nebivolol have different pharmacokinetic profiles. Following oral administration in EMs under steady-state conditions, the mean elimination half-life of *d*- and *l*-nebivolol is 13 and 17 hours, respectively, and the clearance is 960 and 500 L/hr, respectively (Mishina E, Executive Summary, 2005, Clinical Pharmacology Review, Cardio-Renal Division, NDA 21,742). In PMs, the mean elimination half-life of *d*- nebivolol is 22 hours, and the clearance is 50 L/hr. According to Dr. Mishina, the half-life of *l*-nebivolol, estimated at greater than 70 hours by the sponsor, is inaccurate. The clearance of *l*-nebivolol in poor metabolizers is approximately 9 L/hr. Compared to *d*-nebivolol, the exposure (AUCI) to *l*-nebivolol is 2-fold larger in EMs and 2 to 5 fold larger in PMs. With once daily administration, nebivolol does not accumulate in plasma.

Regarding absorption, EMs achieve peak concentration of *d*- and *l*-nebivolol in 1.5-2 hours, compared with 4 hours in PMs. Nebivolol tablets have a relative bioavailability of 87% in EMs and 111% in PMs. There is no food effect on bioavailability.

The plasma protein binding of *d*-nebivolol is 98.13% and of *l*-nebivolol is 97.85%, with human serum albumin (HSA) being the predominant protein (Mishina E, Executive Summary, 2005, Clinical Pharmacology Review, Cardio-Renal Division, NDA 21,742). According to Dr. Mishina, in healthy EMs, the mean volume of distribution is 15000 L and 11000 for *d*- and *l*-nebivolol, respectively. In healthy PMs, the mean volume of distribution is 1300 and 950 L for *d*- and *l*-nebivolol, respectively. Because of limited data from the Pivotal trials, the sponsor was unable to calculate the mean volume of distribution for these hypertensive patients.

In *vitro* studies with human microsomes show the CYP2D6 isoenzyme primarily and, to a lesser extent, the CYP3A4 isoenzyme metabolize nebivolol.

Study NEBI-142 found the major metabolic pathways in healthy subjects to include "formation of glucuronides of unchanged drug, mono- to multiple hydroxylations on alicyclic and/or aromatic rings followed by glucuronidation, and formation of N-dealkylated derivatives."

Glucuronidation of *d*-nebivolol "occurred much more rapidly than on *l*-nebivolol," and "the ratio of *d*-nebivolol glucuronide/*l*-nebivolol glucuronide in urine was 80:20." In urine, investigators recovered 38.4% and 66.5% of the nebivolol dose in EMs and PMs, respectively. According to Dr. Mishina in her review of NEBI-142, EM urine was remarkable for glucuronide conjugates of unchanged drug or hydroxylated and N-dealkylated metabolites. PM urine was remarkable for glucuronides of unchanged nebivolol primarily and small amounts of conjugates of monohydroxy-nebivolol and non-conjugated metabolites. In fecal extract, investigators recovered 43.6% and 13.1% of the nebivolol dose in EMs and PMs, respectively. The fecal extract of PMs had more unchanged nebivolol than EMs.

According to Dr. Mishina, the sponsor did not assess the pharmacokinetic profiles of the active metabolites of nebivolol in healthy and hypertensive patients. Although the pharmacokinetics of nebivolol in extensive and poor metabolizers are significantly different, the sponsor was unable to show any difference in drug effect.

5.2 Pharmacodynamics

In NEB-203 and the supportive studies, nebivolol appeared to have a dose-related effect on blood pressure and heart rate, even in the setting of exercise-induced increases in heart rate and blood pressure. Please see the Appendix for complete reviews of the following supportive studies and reports. Most of these studies were open-label and non-randomized, and some studies did not have placebo controls. Additionally, many of these studies contain only study reports and no actual protocols.

In Report Number 1270_01_00, investigators examined nitric oxide release from human umbilical vein endothelial cells (HUVEC) after acute treatment with nebivolol, nebivolol enantiomers, and several other beta blockers. Following acute treatment with nebivolol and its enantiomers at concentrations ranging from 0.01 μM to 100 μM, nitric oxide release from HUVEC was greatest for *l*-nebivolol and least for *d*-nebivolol. In general, the magnitude of nitric oxide release following *d*-nebivolol was 75-80% of that seen following *l*-nebivolol. Compared to carvedilol and metoprolol, acute treatment with nebivolol at concentrations ranging from 0.01 μM to 100 μM, resulted in greater nitric oxide release. In the setting of acute nebivolol administration, nitric oxide release from HUVEC occurred gradually over 15 seconds, plateaued for an additional 15 seconds, and subsequently declined over 30 seconds. Compared with nebivolol, the nitric oxide release characteristics of carvedilol and metoprolol demonstrated a rapid onset and shorter plateau phase.

In Report Number 1273_01_00, peak nitric oxide release from HUVEC following acute treatment with 5 μM of acetylcholine, nebivolol, and nebivolol metabolites was greatest in the acetylcholine treatment group, followed closely by 4-hydroxy nebivolol. Peak nitric oxide release then decreased in the following order: *l*-nebivolol, *d,l*-nebivolol, *d*-nebivolol, 5-hydroxy nebivolol, and 8-hydroxy nebivolol.

In Report Number 1332_00_00, acute treatment with nebivolol metabolites showed 4-hydroxy nebivolol, 4,5' dihyroxy nebivolol, and 4,8' dihydroxy nebivolol resulted in the greatest release of

nitric oxide from HUVEC. These studies suggest nebivolol and its enantiomers have physiologic effects on HUVEC, although the exact mechanism is unknown.

In Report Number 1333_00_00, investigators examined peak nitric oxide release from HUVEC following chronic treatment with nebivolol or atenolol (10 μM), after stimulation with calcium ionophore at 1 μM. Nebivolol produced an increase in NO release of approximately 120 nM, compared to untreated controls. Atenolol, at the dose tested, had a slightly negative effect. Increasing doses of atenolol were not studied. It is unclear to this reviewer whether or not atenolol would increase nitric oxide release if given at a higher dose. Additionally, in Report Number 1334_00_00, atenolol (10 μM) increased nitric oxide release in caucasian and black HUVEC following stimulation with acetylcholine (1 μM). Because atenolol, a selective β_1 inhibitor, can increase peak nitric oxide release from HUVEC, I do not feel the mechanism of nitric oxide release is completely independent of β_1 inhibition.

In Study GBR-29, *l*-nebivolol and *d*-nebivolol both significantly increased forearm blood flow, compared with a saline infusion, although both isomer formulations had cyclodextrin, which could have affected the results. Studies GBR-29 and GBR-28 demonstrated L-NMMA (4 μmol/min) inhibited the nebivolol vasodilator response of increased forearm blood flow. Additionally, in GBR-28, the administration of L-arginine (10 mg/min) almost completely counteracted the inhibitory effect of L-NMMA. These studies suggest the L-arginine/nitric oxide pathway may contribute to the hemodynamic effects.

Study GBR-27 in 8 healthy volunteers suggested an atenolol infusion at increasing doses from 10 to 200 μg/min did not have a significant effect on forearm blood flow. The nebivolol infusion at doses ranging from 18 to 354 μg/min significantly affected forearm blood flow at doses above 177 μg/min. It is unclear to this reviewer why higher doses of atenolol were not evaluated in this study.

Study GBR-31 evaluated absolute forearm blood flow in 8 healthy male volunteers receiving infusions of *l*-nebivolol, *d*-nebivolol, or *d,l*-nebivolol. Absolute blood flow was highest in subjects receiving *d,l*-nebivolol (5.5 ml/min/100 ml), followed closely by *l*-nebivolol (5.4 ml/min/100 ml). Subjects receiving *d*-nebivolol experienced some increase in forearm blood flow (4.7 ml/min/100 ml), compared with control, but it was not to the extent seen with the *l*-isomer or racemate.

In LMD No. 59987, invasive hemodynamics were obtained in 8 healthy volunteers at baseline, after a single dose of IV nebivolol 5 mg, or after one week of oral nebivolol 5 mg. IV nebivolol significantly decreased heart rate and cardiac index and significantly increased total peripheral resistance index (TPRI). Oral nebivolol significantly decreased heart rate and mean arterial pressure (MAP).

5.3 Exposure-Response Relationships

Although the sponsor attempted to describe the effect of *d*- and *l*-nebivolol on reduction of diastolic blood pressure and heart rate in hypertensive patients in NEB-302, Dr. Mishina found

the Emax model proposed by the sponsor to be unacceptable. The Emax model used an "unreasonably low EC50 value of 0.068 ng/mL" to reflect the effect of nebivolol on diastolic blood pressure. According to Dr. Mishina, this low EC50 value was "220 fold higher than the in *vitro* affinity of nebivolol to β_1-adrenoceptors in human myocardium (Ki 5-15 ng/mL)." In NEB-302, the average *d*-nebivolol plasma concentration associated with diastolic blood pressure reduction was 6 ng/mL, similar in magnitude to the Ki value. For heart rate reduction, the sponsor used an EC50 value of 0.0017 ng/mL. For both diastolic blood pressure and heart rate reduction, the "EC50 values estimated by the sponsor [did] not reflect the physiologic parameters for ß-adrenoceptor activity of nebivolol" (Mishina E, Executive Summary, 2005, Clinical Pharmacology Review, Cardio-Renal Division, NDA 21,742). As such, Dr. Mishina found the pharmacokinetic/pharmacodynamic (PK/PD) population models proposed by the sponsor to be unacceptable.

In summary, Dr. Mishina identified four significant deficiencies in the sponsor's application:

- inadequate assessment of the pharmacokinetics of the active metabolites of nebivolol
- inadequate determination of the relationship between pharmacokinetics and pharmacodynamics of nebivolol
- inadequate evaluation of pharmacokinetics and pharmacodynamics in African-American hypertensive patients
- inadequate assessment of the potential role of transporters on nebivolol pharmacokinetics

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Treatment of [redacted] hypertension

6.1.1 Methods

The sponsor performed 6 pivotal trials in 2,800 patients to evaluate the efficacy of nebivolol in the treatment of mild to moderate hypertension. The pivotal trials included Studies NEB-302, NEB-305, NEB-202, NEB-306, NEB-321, and NEB-203. A total of 2,464 of these 2,800 patients received nebivolol either as monotherapy or in combination with other antihypertensive agents. The sponsor summarizes the Intent-to-Treat Population for the Pivotal trials in Table 6. All but Study NEB-203, the Phase II Pilot study, were placebo-controlled. The three individual primary, placebo-controlled monotherapy studies (NEB-302, NEB-305, and NEB-202) had similar designs and endpoints and will be discussed together in this integrated review. The main difference between the three placebo-controlled monotherapy studies was that NEB-202 included only Blacks, and NEB-305 included non-US patients.

NEB-306 was a long-term safety and efficacy study up to 10 months in patients who were also on background antihypertensive therapy. For enrollment into NEB-306, patients had to successfully complete NEB-302, NEB-305, or NEB-202. NEB-321 used ambulatory blood pressure monitoring to evaluate the safety and efficacy of nebivolol as add-on therapy to patients already receiving one or two antihypertensives of the angiotensin converting enzyme inhibitor

(ACEI), angiotensin receptor blocker (ARB), and/or diuretic class. NEB-203 compared the effects of nebivolol versus atenolol on exercise capacity.

In the pivotal trials, the sponsor studied 157 poor metabolizers, divided amongst the respective treatment groups. Studies NEB-302, 305, 202, 321, and 203 had 59, 50, 7, 36, and 5 poor metabolizers. In Study NEB-306, 61 poor metabolizers from the feeder studies participated in the extension phase and one of these poor metabolizers participated in the follow-up phase. In NEB-122, the sponsor studied 6 poor metabolizers with 3 patients each in the atenolol and nebivolol treatment groups.

Table 6. Summary of Intent-to-Treat Populations for Bertek-Sponsored Clinical Studies and Analyses of Pooled Studies

Study Numbers	Placebo N	Nebivolol 1.25 mg N	Nebivolol 2.5 mg N	Nebivolol 5 mg N	Nebivolol 10 mg N	Nebivolol 20 mg N	Nebivolol 30/40 mg N	Total N
Double-Blind, Placebo-Controlled Monotherapy								
All Patients								
302	81	83	82	165	166	166	166[a]	909
305	75	N/A	N/A	244	244	244	N/A	807
302/305[b]	156	83	82	409	410	410	166	1716
202	49	N/A	49	50	51	50	51	300
202/302/305[c]	205	83	131	459	461	460	217	2016
Black Patients								
202	49	N/A	49	50	51	50	51	300
302B	11	12	13	23	23	25	25	132
305B	11	N/A	N/A	31	33	30	N/A	105
302B/305B[d]	22	12	13	54	56	55	25	237
202/302B/305B[e]	71	12	62	104	107	105	76	537
Long-Term Therapy	**Nebivolol**	**Nebivolol & Diuretic**		**Nebivolol & CCB**		**Other**		**Total**
306 (All Patients)	607	206		21		11		845
306 (Black Patients)	133	54		8		2		197
Double-Blind, Placebo-Controlled Combination Therapy								
321 (All Patients)	167	N/A	N/A	168	168	166	N/A	669
321 (Black Patients)	48	N/A	N/A	50	51	48	N/A	197
Exploratory Study of Exercise Tolerance			**Atenolol 50 mg**	**Atenolol 100 mg**	**Nebivolol 5 mg**	**Nebivolol 10 mg**	**Nebivolol 20 mg**	**Total**
203			24	21	23	23	24	115

Data Source: Study 202, Table 1.1.1; Study 302, Table 1.1.1; Study 305, Table 1.1.1; ISE Table 1.1.1; ISE Table 1.1.2; ISE Table 1.1.3; Study 321, Table 4; Study 306, Table 1.1.1; Study 203, Table 1.1.1.
CCB=calcium channel blocker
[a]Includes 19 patients who received nebivolol 30 mg for the duration of the study and 147 patients who were up-titrated to 40 mg.
[b]General Hypertensive Population
[c]Total Placebo-Controlled Population
[d]General Hypertensive Population, Black Patients
[e]Total Placebo-Controlled Population, Black Patients

(Reproduced from Sponsor, Integrated Summary of Efficacy, Table 7.1-01, page 56)

6.1.2 General Discussion of Endpoints

For Studies NEB-302, NEB-305, NEB-202, NEB-306, and NEB-321, the primary efficacy endpoint was change of the average sitting diastolic blood pressure taken at trough drug plasma level (24 ± 2 hours post-previous morning's dose) at the end of treatment (Day 84) compared to baseline.

For Study NEB-203, the primary efficacy endpoint was the percent change in sub-maximal exercise duration by cycle ergometer at peak drug effect at end of treatment compared to baseline.

The sponsor defined a responder as "a patient whose average sitting diastolic blood pressure at trough at end of study was either < 90 mm Hg or had decreased by ≥ 10 mm Hg from baseline."[11]

For the primary efficacy endpoint in Studies NEB-302, NEB-305, and NEB-202, NEB-306, and NEB-321, each patient was classified as a responder or a non-responder. The sponsor analyzed the response rates of treatment groups using logistic regression. In Studies NEB-302, NEB-305, NEB-202, and NEB-321, the primary population for the evaluation of efficacy was the intent-to-treat (ITT) population, last observation carried forward (LOCF). The secondary population for the evaluation of efficacy was the Per-Protocol (PP) population, consisting of all ITT patients who did not have any major protocol violations.

In Studies NEB-203 and NEB-306, the primary population for the evaluation of efficacy was the intent-to-treat (ITT) population, observed cases (OC).

In addition to using the LOCF, the sponsor used an observed cases (OC) analysis as well as a "worst case" method to handle missing data. The OC analysis did not carry forward any data from prior visits. The "worst case" method replaced missing data with the worst value from either baseline or the last time point.

For the primary and secondary efficacy endpoints in the individual primary, placebo-controlled monotherapy trials (Studies NEB-302, NEB-305, and NEB-202), the primary statistical method of treatment comparison was a step-down dose response test[12] utilizing a linear contrast in the ANCOVA model. For sitting diastolic blood pressure (DBP) and systolic blood pressure (SBP) at trough only, the sponsor also performed a secondary dose-response step-up trend test[13] using a

[11] **Sponsor, Study NEB-302, page 100.**

[12] **As described by the sponsor on page 47 of NEB-302, the step-down dose response test utilized "linear contrast in an ANCOVA model up to and including the 20 mg dose group. If this contrast was statistically significant, another linear contrast was performed to include all treatment groups up to and including the 10 mg dose. Testing continued in this manner until a linear contrast was found to be non-significant." In NEB-302, the 30/40 mg dose group was studied for safety purposes only; thus, the contrast coefficient for the 30/40 mg dose group was zero for all contrasts." In NEB-202, doses up to 40 mg were studied for efficacy.**

[13] **As stated on page 48 of NEB-302, the sponsor performed the step-up trend test (parametric trend test) to "better determine the range of effective doses for sitting diastolic blood pressure and systolic blood pressure at trough. This was a step-up dose response test using a linear contrast in ANCOVA. If the first contrast, with all treatments from placebo up to 20 mg, was found to be statistically significant, another linear contrast was tested with all nebivolol treatment groups from 1.25 mg up to and including the 20 mg dose. If this contrast was found to be statistically significant, another linear contrast was tested with all treatment groups from 2.5 up to and including the 20 mg dose. Testing continued until a linear contrast was found to be non-significant." In NEB-302, the 30/40 mg dose was studied only for safety; thus, "the contrast coefficient for the 30/40 mg dose group was zero for all contrasts." In NEB-202, doses up to 40 mg were studied for efficacy.**

linear contrast in an ANCOVA. Overall treatment effect was assessed after adjustment for baseline differences and treatment-by-center interaction as well as exclusion of sites with potential good clinical practice (GCP) issues. Patients were stratified across all treatment arms by the following factors in decreasing priority: metabolism of nebivolol (poor metabolizer (PM) versus extensive metabolizer (EM), diabetes status (history of diabetes mellitus vs. no history of diabetes mellitus), ethnicity (Black vs. Non-Black), age (< 65 and ≥ 65), and gender. The sponsor used the equality of linear trends to compare the placebo-subtracted results for each subgroup.

In study NEB-302, the nebivolol 30/40 mg group was not used for the step-down or step-up test because it was included primarily for the evaluation of safety. In study NEB-202, however, nebivolol 40 mg was used for all analyses.

For study NEB-203, however, the primary analysis was the Observed Case (OC) analysis. The OC analysis prevented baseline data from being carried forward, since there was only one post-baseline assessment for the primary efficacy endpoint, change in submaximal exercise duration.

In a post-hoc analysis, the sponsor calculated trough-to-peak ratios for sitting DBP and SBP measurements using placebo-subtracted LS mean change from baseline blood pressure value at trough on Day 84 relative to the corresponding value at peak for all treatment groups. The sponsor performed additional analyses using non-placebo-subtracted LS mean values as well as placebo-subtracted and non-placebo subtracted raw means.

Secondary efficacy endpoints for studies NEB-302, NEB-305, and NEB-202 included the following parameters, which were reproduced from the sponsor on page 44 of Study NEB-302:

- Change of average **sitting systolic** blood pressure taken at **trough** drug plasma level (24 ± 2 hours post-previous morning's dose) at end of treatment (Day 84) compared to baseline
- Change of average **sitting systolic and diastolic** blood pressures taken at **peak** drug plasma level (two to three hours post-dose) at end of treatment (Day 84) compared to baseline
- Change of average **supine systolic and diastolic** blood pressures taken at **trough** drug plasma level (24 ± 2 hours post-previous morning's dose) at end of treatment (Day 84)
- Change of average **supine systolic and diastolic** blood pressures taken at **peak** drug plasma level (two to three hours post-dose) at end of treatment (Day 84) compared to baseline
- Change of average **standing systolic and diastolic** blood pressures taken at **trough** drug plasma level (24 ± 2 hours post-previous morning's dose) at end of treatment (Day 84) compared to baseline
- Change of average **standing systolic and diastolic** blood pressures taken at **peak** drug plasma level (two to three hours post-dose) at end of treatment (Day 84) compared to baseline
- Response rates of treatment groups

- Correlation between plasma levels (at trough and peak) and change of average sitting diastolic blood pressure **(only for Study NEB-302)**

As listed on page 8 of the Integrated Summary of Efficacy, common secondary efficacy endpoints for studies NEB-302, NEB-305, NEB-202, NEB-306, and NEB-321 included the following parameters:

- Change from baseline to end of treatment in trough sitting systolic blood pressure (SBP)
- Change from baseline to end of treatment in trough standing DBP and SBP
- Change from baseline to end of treatment in peak sitting and standing DBP and SBP
- Proportion of responders to treatment (sitting DBP at trough < 90 mm Hg at end of treatment or decreased by ≥ 10 mm hg from baseline)

For the integrated analyses of studies NEB-302, NEB-305, and NEB-202, the sponsor also examined average sitting heart rate at trough as a key secondary efficacy endpoint.

6.1.3 Study Design

Studies NEB-302, NEB-305, and NEB-202 were double-blind, multi-center, randomized, placebo-controlled, monotherapy, parallel group studies which had two phases. Phase I consisted of screening, followed by washout/single-blind placebo run-in (28-42 days). Phase II consisted of double-blind therapy with patients randomized to either placebo or nebivolol for 84 days. Nebivolol doses for the various studies are further described in Table 7 under Section 6.1.4, Efficacy Findings. Nebivolol doses ranged from 1.25 mg through 40 mg. There was no dose titration in Studies NEB-305 and NEB-202. For Study NEB-302, patients assigned to nebivolol 40 mg were first initiated on 30 mg. At two weeks, if patients had a sitting heart rate at trough exceeding 55 bpm, the nebivolol dose was increased to 40 mg.

Basis of Review

The description of the study protocol is based on the original protocol and all of the amendments for Studies NEB-302, NEB-305, and NEB-202.

Objectives

The objectives of Studies NEB-302, NEB-305, and NEB-202 were to determine if nebivolol was superior to placebo for the treatment of elevated blood pressure in patients with mild to moderate hypertension, to determine the dose-response relationship of nebivolol, and to compare the safety and efficacy of nebivolol in poor and extensive metabolizers.

Randomization

The patients were assigned to treatment groups by central telephone randomization (TeleTrial®) and prospectively stratified by nebivolol metabolism, diabetes status, ethnicity, age, and gender.

Patients were to be assessed during 7 scheduled follow-up visits, in addition to the optional Visit 2a. Visit 2a was incorporated for patients who were not over 90% compliant during the placebo run-in or needed extra time to satisfy the inclusion criteria. Visit 1 occurred between Day -28 and Day -42, Visit 2 occurred between Day -14 and Day -28, and Visit 2a occurred 14 days after Visit 2. Visits 3, 4, 5, 6, and 7 occurred on Study Days 0, 14, 28, 56, and 84, respectively.

For Study NEB-202, if patients were not currently taking an antihypertensive, the sponsor required 6 follow-up visits. If patients were on prior antihypertensive therapy, however, the sponsor required 7 follow-up visits.

Studies NEB-302, NEB-305, and NEB-202 had the same Inclusion and Exclusion Criteria. Additionally, the prohibited and restricted medications for these studies were identical.

Inclusion Criteria (Reproduced from Sponsor, Study NEB-302, page 30)

- Written informed consent.
- Age ≥ 18.
- High probability for compliance and study completion.
- Adult ambulatory patients with mild to moderate hypertension:
  - At Visit 1 (day -42 to -28), an average sitting diastolic blood pressure of ≥ 95 mm Hg and ≤ 109 mm Hg if not currently receiving antihypertensive treatment
  - At Visit 2 (day -28 to -14), an average sitting diastolic blood pressure of > 80 mm Hg and ≤ 109 mm Hg if patient currently receiving antihypertensive therapy treatment
- Patients currently receiving antihypertensive treatment with an average sitting diastolic blood pressure ≤ 80 mm Hg were permitted to continue the screening process only if the adverse event profile of their current antihypertensive medication(s) warranted a change in drug treatment.
- At randomization, Visit 3 (day 0), an average sitting diastolic blood pressure of ≥ 95 mm Hg and ≤ 109 mm Hg.

Exclusion Criteria (Reproduced from Sponsor, Study NEB-302, page 30)

- Secondary hypertension
- Malignant hypertension (retinal hemorrhage, exudates, or papillary edema)
- History or presence of asthma, bronchospasm, or chronic obstructive airway disease
- Bradycardia (heart rate < 50 bpm) at rest in the supine position prior to randomization
- Chronic atrial fibrillation or recurrent tachyarrhythmia
- Sick sinus syndrome, including second or third degree AV block
- Diabetics with HbA1c ≥ 10% during the screening period
- History of sensitivity or significant adverse reaction to beta-blockers
- Myocardial infarction or cerebrovascular accident within 6 months of screening Visit 1. If the screening Visit 1 ECG exhibited diagnostic pathological Q waves and the timing of the event associated with these Q waves was unknown, the patient was excluded.
- Heart failure requiring treatment. A left ventricular ejection fraction of ≥ .040, if measured within 12 months of the trial.
- Hemodynamically significant valvular heart disease
- Presence of severe peripheral vascular disease
- Any major contraindication to stopping antihypertensive medications for a period of up to 18 weeks

Exclusion Criteria (Reproduced from Sponsor, Study NEB-302, page 30)(continued)

- Significant thyroid, renal, or hepatic disease (TSH > 1.5 times the upper limit of normal, urine protein > 1+, creatinine > 2.2 mg/dL, AST [SGOT] and/or ALT [SGPT] greater than twice the upper limit of normal)
- A positive pregnancy test (beta-HCG) result, or a nursing female patient, or a female of childbearing potential who was not using appropriate contraception as determined by the principal investigator.
- Presence of any condition that in the judgment of the investigator, may have jeopardized the participant's adherence to the protocol or ability to complete the trial
- Concomitant therapy with at least one of the prohibited or restricted medications that may have affected blood pressure
- BMI > 35 kg/m^2 and obesity as measured by waist circumference > 102 cm (40 inches) in men or > 88 cm in women **(For Study NEB-202 and NEB-306 only, BMI > 40 kg/m^2)**
- Investigational drug use within 30 days of signing the informed consent
- Previous exposure to nebivolol for the treatment of hypertension
- Exaggerated systolic hypertension defined as an average sitting systolic blood pressure > 199 mm Hg

Prohibited Medications (Reproduced from Sponsor, Study NEB-302, page 35)

- Oral and ophthalmic beta-adrenergic blocking agents (e.g., atenolol, metoprolol, propranolol, timolol)
- Angiotensin converting enzyme inhibitors (ACEI, e.g., enalapril, captopril, ramipril)
- Angiotensin II receptor blockers (ARB, e.g., losartan, valsartan)
- Calcium channel blockers (CCB, e.g., amlodipine, diltiazem, nifedipine, verapamil, nicardipine, and felodipine)
- Alpha-1 receptor blockers (e.g., phentolamine, phenoxybenzamine, terazosin).
- Diuretics (e.g., furosemide, hydrochlorothiazide, spironolactone)
- Medications possibly affecting blood pressure (e.g., all anti-depressants with blood pressure altering effects including tricyclic anti-depressants and MAO inhibitors).
- Theophylline or beta-agonists.
- Drugs liable to cause salt retention (e.g., systemic corticosteroids)
- Long-acting oral nitrates (e.g., Isordil®, isosorbide dinitrate)
- Treatment with a protease inhibitor within 180 days of the initiation of screening.
- Centrally acting alpha agonists (e.g., clonidine hydrochloride).

Restricted Medications (Reproduced from Sponsor, Study NEB-302, page 36)

- Non-steroidal anti-inflammatory drugs (NSAIDs): patients could not exceed 5 consecutive days of NSAID use. For 3 days prior to Visits 3 (Randomization) and 7 (Study Day 84), patients could not use NSAIDs.
- Acetylsalicylic acid: patients could not use acetylsalicylic acid in excess of 162 mg daily.
- Short acting nitrates (sublingual nitroglycerin): patients could not use short acting nitrates within 4 hours of clinic visits.

Restricted Medications (Reproduced from Sponsor, Study NEB-302, page 36) (continued)

- Decongestants and antihistamines: once enrolled, patients could not use these agents within 3 days of Visits 3 (Randomization) and 7 (Study Day 84).
- Selective serotonin reuptake inhibitors (SSRIs): patients could use SSRIs only if the patient was on a stable dose for at least 3 months prior to Visit 1, was known to be compliant on the medication, and agreed to maintain this current stable dose for the study duration

6.1.4 Efficacy Findings

For Studies NEB-302, 305, and 202, Table 7 outlines the study drug regimen.

Table 7. Regimens Used in Studies NEB-302, 305, and 202

Study	Doses
NEB-302	Placebo Nebivolol 1.25, 2.5, 5, 10, 20, and 30/40* *Safety only
NEB-305	Placebo Nebivolol 5, 10, and 20 mg
NEB-202	Placebo Nebivolol 2.5, 5, 10, 20, and 40 mg
Adapted from Sponsor.	

Study NEB-302

There were 1,573 patients screened with 1,295 patients entering the single-blind phase and 913 patients randomized. Four of the randomized patients never took study medication, so there were only 909 patients in the ITT population (81 placebo, 83 nebivolol 1.25 mg, 82 nebivolol 2.5 mg, 165 nebivolol 5 mg, 166 nebivolol 10 mg, 166 nebivolol 20 mg, and 166 nebivolol 30/40 mg). Nineteen patients (11.4%) in the nebivolol 30/40 mg group were not titrated to 40 mg because at two weeks, their trough sitting heart rate did not exceed 55 bpm. The number of subjects completing the study through Day 84 was 710/828 (85.7%) randomized to nebivolol and 67/81 (82.7%) randomized to placebo. None of the patients who discontinued study medication prior to Day 84 remained in the study. For Study NEB-302, the results of step-down trend testing and LS mean change in DBP and SBP at trough and peak from baseline to end of study is shown in Table 8 and Table 9.

In step-up trend testing in the ITT LOCF population for sitting diastolic and sitting systolic blood pressure at trough from baseline to end of study, only the placebo to nebivolol 20 mg contrast was statistically significant ($p < 0.001$).

Table 8. Summary of Results of the Step-Down Trend Test and LS Mean Change in DBP and SBP (mm Hg) at Trough from Baseline to End of Study (ITT LOCF) (NEB-302)

	Sitting			Standing			Supine		
	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff
Placebo									
DBP	---	-2.9	---	---	0	---	---	-2.5	---
SBP	---	2.2	---	---	3.8	---	---	0.6	---
Nebivolol 1.25 mg									
DBP	< 0.001	-8.0	-5.1	< 0.001	-4.6	-4.5	0.018	-5.5	-3.0
SBP	0.002	-4.4	-6.6	0.002	-3.0	-6.8	0.011	-4.7	-5.3
Nebivolol 2.5 mg									
DBP	< 0.001	-8.5	-5.6	< 0.001	-6.5	-6.4	< 0.001	-7.6	-5.1
SBP	< 0.001	-6.3	-8.4	< 0.001	-6.3	-10.1	< 0.001	-8.3	-8.9
Nebivolol 5 mg<									
DBP	< 0.001	-8.4	-5.5	< 0.001	-5.2	-5.2	< 0.001	-7.4	-4.9
SBP	< 0.001	-5.9	-8.1	< 0.001	-4.1	-8.0	< 0.001	-7.6	-8.2
Nebivolol 10 mg									
DBP	< 0.001	-9.2	-6.3	< 0.001	-6.6	-6.6	< 0.001	-7.9	-5.4
SBP	< 0.001	-7.0	-9.2	< 0.001	-5.3	-9.1	< 0.001	-7.1	-7.7
Nebivolol 20 mg									
DBP	< 0.001	-9.8	-6.9	< 0.001	-7.4	-7.3	< 0.001	-8.4	-5.9
SBP	< 0.001	-6.5	-8.6	< 0.001	-5.1	-8.9	< 0.001	-7.1	-7.8
Nebivolol 30/40 mg									
DBP	---	-11.2	-8.3	---	-9.1	-9.1	---	-10.1	-7.6
SBP	---	-9.5	-11.7	---	-8.5	-12.4	---	-10.9	-11.5

Data Source: Tables 2.1.1, 2.2.1, 2.5.1, 2.6.1, 2.9.1, and 2.10.1

[a] **p-value from step-down trend test; step-down testing begins with placebo to nebivolol 20 mg and proceeds to step down until the test contains only placebo and nebivolol 1.25 mg**

[b] **From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group**

[c] **LS mean change in DBP or SBP from baseline to end of study**

(Reproduced from Sponsor, Table 11.4-13, page 91)

Table 9. Summary of Results of the Step-Down Trend Test and LS Mean Change in DBP and SBP (mm Hg) at Peak from Baseline to End of Study (ITT LOCF) (NEB-302)

	Sitting			Standing			Supine		
	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff
Placebo									
DBP	---	-5.4	---	---	-3.5	---	---	-4.3	---
SBP	---	-3.1	---	---	-3.4	---	---	-3.8	---
Nebivolol 1.25 mg									
DBP	0.005	-9.1	-3.8	0.014	-6.7	-3.2	0.029	-7.1	-2.8
SBP	0.029	-7.6	-4.5	0.184	-6.2	-2.8	0.120	-7.0	-3.2
Nebivolol 2.5 mg									
DBP	<0.001	-10.1	-4.7	<0.001	-8.1	-4.7	<0.001	-8.7	-4.4
SBP	0.015	-8.1	-5.0	0.028	-8.1	-4.7	0.008	-9.4	-5.6
Nebivolol 5 mg<									
DBP	<0.001	-10.7	-5.4	<0.001	-8.9	-5.4	<0.001	-9.0	-4.7
SBP	<0.001	-9.5	-6.5	<0.001	-10.1	-6.7	<0.001	-9.8	-6.0
Nebivolol 10 mg									
DBP	<0.001	-11.6	-6.2	<0.001	-10.3	-6.9	<0.001	-9.4	-5.1
SBP	<0.001	-11.0	-7.9	<0.001	-10.8	-7.4	<0.001	-11.3	-7.5
Nebivolol 20 mg									
DBP	<0.001	-13.2	-7.8	<0.001	-11.6	-8.1	<0.001	-10.8	-6.5
SBP	<0.001	-13.1	-10.0	<0.001	-11.8	-8.4	<0.001	-11.9	-8.1
Nebivolol 30/40 mg									
DBP	---	-13.9	-8.5	---	-12.8	-9.3	---	-12.0	-7.7
SBP	---	-14.0	-10.9	---	-14.1	-10.7	---	-14.0	-10.2

Data Source: Tables 2.3.1, 2.4.1, 2.7.1, 2.8.1, 2.11.1, and 2.12.1
[a] p-value from step-down trend test; step-down testing begins with placebo to nebivolol 20 mg and proceeds to step down until the test contains only placebo and nebivolol 1.25 mg
[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group
[c] LS mean change in DBP or SBP from baseline to end of study

(Reproduced from Sponsor, Table 11.4-14, page 92)

The overall responder rates for the analysis were nebivolol 55.2% (457/828) and placebo 24.7% (20/81), as seen in Table 10.

Table 10. Responder Rates[a] by Treatment. Evaluation of Possible Predictors of Responders (ITT LOCF) (NEB-302)

Treatment	Total	Responder n (%)[b]	p-value[c]
Placebo	81	20 (24.7)	
Nebivolol 1.25 mg	83	38 (45.8)	0.008
Nebivolol 2.5 mg	82	41 (50.0)	0.001
Nebivolol 5 mg	165	83 (50.3)	< 0.001
Nebivolol 10 mg	166	89 (53.6)	< 0.001
Nebivolol 20 mg	166	99 (59.6)	< 0.001
Nebivolol 30/40 mg	166	107 (64.5)	N/A

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Based on Wald Chi-Square Test for trend from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group; Step-down testing scheme begins with treatments placebo through Nebivolol 20 mg and proceeds to step-down until the trend test contains only placebo and nebivolol 1.25 mg
NS: P-values should not be used in the context of step-down trend testing (see analysis plan for explanation)

(Reproduced from Sponsor, Study NEB-302, Table 2.13.1, page 648)

Table 11 shows the percent of responders, by treatment group, at weeks 2, 4, 8, and 12.

Table 11. Responder[a] Rates by Treatment and Visit (ITT LOCF) (NEB-302)

Visit	Placebo n(%)[b]	Nebivolol 1.25 mg n (%)[b]	Nebivolol 2.5 mg n (%)[b]	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Nebivolol 30/40 mg n (%)[b]	Total n (%)[b]
Day 14	22 (27.2)	39 (47.0)	33 (40.2)	94 (57.0)	89 (53.6)	99 (59.6)	111 (66.9)	487 (53.6)
Day 28	28 (34.6)	52 (62.7)	42 (51.2)	81 (49.1)	93 (56.0)	96 (57.8)	115 (69.3)	507 (55.8)
Day 56	21 (25.9)	44 (53.0)	44 (53.7)	95 (57.6)	100 (60.2)	102 (61.4)	108 (65.1)	514 (56.5)
Day 84	20 (24.7)	38 (45.8)	41 (50.0)	83 (50.3)	89 (53.6)	99 (59.6)	107 (64.5)	477 (52.5)

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm hg at endpoint of interest or has decreased by ≥ 10 mm hg from baseline
[b] Percentage is the percentage of responders within that category
Cross Reference: Data Listings 10.1.1, 10.2.1, and 10.4

(Reproduced from Sponsor, Table 2.13.5, page 652)

The difference in response rate between study groups was evident by the first two weeks of treatment (56% nebivolol (465/828) vs. 27.2% placebo (22/81)). Responder rates generally increased by dose and plateaued by Days 28 to 56.

Correlation of Peak and Trough Plasma Nebivolol Levels with Reductions in Sitting Diastolic Blood Pressure and Heart Rate at Peak and Trough (NEB-302)

Although the sponsor attempted to describe the effect of *d*- and *l*-nebivolol on reduction of diastolic blood pressure and heart rate in hypertensive patients in NEB-302, Dr. Mishina found the Emax model proposed by the sponsor to be unacceptable. The Emax model used an "unreasonably low EC50 value of 0.068 ng/mL" to reflect the effect of nebivolol on diastolic blood pressure. According to Dr. Mishina, this low EC50 value was "220 fold higher than the in *vitro* affinity of nebivolol to β_1-adrenoceptors in human myocardium (Ki 5-15 ng/mL)." In NEB-302, the average *d*-nebivolol plasma concentration associated with diastolic blood pressure reduction was 6 ng/mL, similar in magnitude to the Ki value. For heart rate reduction, the sponsor used an EC50 value of 0.0017 ng/mL. For both diastolic blood pressure and heart rate reduction, the "EC50 values estimated by the sponsor [did] not reflect the physiologic parameters for ß-adrenoceptor activity of nebivolol" (Mishina E, Executive Summary, 2005, Clinical Pharmacology Review, Cardio-Renal Division, NDA 21,742). As such, Dr. Mishina found the PK/PD population models proposed by the sponsor to be unacceptable.

Conclusions (NEB-302)

In the ITT LOCF population, nebivolol 1.25, 2.5, 5, 10, 20 mg, and 30/40 mg had statistically significant effects on the primary endpoint, change in sitting diastolic blood pressure at trough from baseline to end of study. In the step-up trend test for the primary endpoint, only the placebo to nebivolol 20 mg contrast was statistically significant.

For all trough secondary endpoints in the ITT LOCF population, nebivolol 1.25 mg through 30/40 mg was statistically significant. For sitting systolic blood pressure at trough from baseline to Day 84, the step-up trend test in the ITT LOCF population was significant only for the placebo to nebivolol 20 mg contrast.

For all peak secondary endpoints in the ITT LOCF population, all doses of nebivolol significantly lowered blood pressure from baseline to end of study, with the exception of nebivolol 1.25 mg which did not significantly lower standing and supine systolic blood pressure. The PK/PD population model proposed by the sponsor was unacceptable.

Study NEB-305

There were 1,288[14] patients screened with 1,138 patients entering the single-blind phase and 811 patients randomized. There were 807 patients in the ITT population (75 placebo, 244 nebivolol 5 mg, 244 nebivolol 10 mg, and 244 nebivolol 20 mg). Four randomized patients did not take double-blind study medication and were not included in the ITT. The number of subjects completing the study through Day 84 was 641/732 (87.6%) randomized to nebivolol and 61/75 (81.3%) randomized to placebo. None of the patients who discontinued study medication remained in the study. According to the sponsor, fourteen patients received the wrong medication bottles because study sites did not follow TeleTrial® instructions. Of these 14 patients, 1 patient failed screening and never took study drug medication, 8 patients received incorrectly labeled bottles of study medication, and 5 patients received the wrong study medication or dose.

Of the 8 patients who received incorrectly labeled bottles of study medication, 4 patients did not complete the study because the investigational site was closed for GCP violations, 1 patient experienced an adverse event and withdrew from the study, and 3 patients completed the study.

Of the 5 patients who received the wrong study medication or dose, 4 patients received only 1 incorrect bottle of study medication but still completed the study, and 1 patient was withdrawn due to a protocol violation.

There was also one patient who received nebivolol 5 mg during the placebo run-in phase instead of placebo, but then went on to correctly receive nebivolol 5 mg during the double-blind phase and completed the study.

For Study NEB-305, the results of step-down trend testing and LS mean change in DBP and SBP at trough and peak from baseline to end of study are shown in Table 12 and Table 13.

For step-up trend testing in the ITT LOCF population for sitting diastolic blood pressure at trough from baseline to end of study, only the placebo to nebivolol 20 mg contrast was statistically significant ($p < 0.001$).

Step-up trend testing in the ITT LOCF population for sitting systolic blood pressure at trough from baseline to end of study, was statistically significant for nebivolol 5 mg ($p = 0.036$), nebivolol 10 mg ($p = 0.008$), and nebivolol 20 mg ($p < 0.001$) contrasts.

[14]**Two patients were counted twice in the total number of screened patients because they were screened twice. Patient 1642000965 and 1642001741 are the same patient who failed screening once (withdrew consent) and qualified the second time as 1642001741. Patient 2662000585 and 2662001167 are the same patient who failed screening the first time (did not meet inclusion/exclusion criteria) and qualified the second time as 2662001167.**

Table 12. Summary of Results of the Step-Down Trend Test and LS Mean Change in DBP and SBP (mm Hg) from Baseline to End of Study (Day 84) at Trough (ITT LOCF) (NEB-305)

	Sitting			Standing			Supine		
	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff
Placebo									
DBP	---	-4.6	---	---	-3.7	---	---	-3.4	---
SBP	---	-0.4	---	---	-0.9	---	---	1.0	---
Nebivolol 5 mg									
DBP	0.002	-7.8	-3.2	0.002	-6.9	-3.2	<0.001	-7.8	-4.4
SBP	0.035*	-4.2	-3.8	0.016*	-5.3	-4.4	0.012*	-3.6	-4.6
Nebivolol 10 mg									
DBP	<0.001	-8.5	-3.9	<0.001	-7.2	-3.5	<0.001	-7.7	-4.3
SBP	0.086	-3.5	-3.1	0.107	-3.8	-3.0	0.082	-2.2	-3.2
Nebivolol 20 mg<									
DBP	<0.001	-9.1	-4.5	<0.001	-8.1	-4.4	<0.001	-8.4	-5.0
SBP	<0.001	-6.7	-6.3	0.002	-7.2	-6.4	<0.001	-5.9	-7.0

Data Source: Tables 2.1.1, 2.2.1, 2.5.1, 2.6.1, 2.9.1, and 2.10.1

* **p-value associated with lower dose not applicable in the context of step-down trend testing due to the nonsignificant result at the higher dose.**

[a] **p-value from step-down trend test; step-down testing begins with placebo to nebivolol 20 mg and proceeds to step down until the test contains only placebo and nebivolol 5 mg**

[b] **From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group**

[c] **LS mean change in DBP or SBP from baseline to end of study**

(Reproduced from Sponsor, Study NEB-305, Table 11.4-13, page 88)

Table 13. Summary of Results of the Step-Down Trend Test and LS Mean Change in DBP and SBP (mm Hg) from Baseline to End of Study (Day 84) at Peak (ITT LOCF) (NEB-305)

	Sitting			Standing			Supine		
	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff
Placebo									
DBP	---	-7.0	---	---	-6.3	---	---	-6.1	---
SBP	---	-4.7	---	---	-3.1	---	---	-2.1	---
Nebivolol 5 mg									
DBP	<0.001	-10.5	-3.5	<0.001	-10.1	-3.8	<0.001	-10.8	-4.7
SBP	0.069	-7.7	-3.1	0.005	-8.0	-5.0	0.002	-7.5	-5.4
Nebivolol 10 mg									
DBP	<0.001	-11.6	-4.6	<0.001	-11.7	-5.4	<0.001	-11.0	-4.9
SBP	0.004	-9.5	-4.9	<0.001	-9.3	-6.2	<0.001	-7.8	-5.7
Nebivolol 20 mg<									
DBP	<0.001	-12.2	-5.2	<0.001	-11.8	-5.5	<0.001	-11.4	-5.3
SBP	<0.001	-10.7	-6.0	<0.001	-10.7	-7.6	<0.001	-9.3	-7.2

Data Source: Tables 2.3.1, 2.4.1, 2.7.1, 2.8.1, 2.11.1, and 2.12.1

[a] **p-value from step-down trend test; step-down testing begins with placebo to nebivolol 20 mg and proceeds to step down until the test contains only placebo and nebivolol 5 mg**

[b] **From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group**

[c] **LS mean change in DBP or SBP from baseline to end of study**

(Reproduced from Sponsor, Study NEB-305, Table 11.4-14, page 89)

The overall responder rates for the analysis were nebivolol 67.2% (492/732) and placebo 49.3% (37/75), as seen in Table 14.

Table 14. Responder Rates[a] by Treatment. Evaluation of Possible Predictors of Responders (ITT LOCF) (NEB-305)

Treatment	Total N	Responder n (%)[b]	p-value[c]
Placebo	75	37 (49.3)	
Nebivolol 5 mg	244	161 (66.0)	0.009
Nebivolol 10 mg	244	163 (66.8)	0.005
Nebivolol 20 mg	244	168 (68.9)	0.002

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Based on Wald Chi-Square Test for trend from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group; Step-down testing scheme begins with treatments placebo through Nebivolol 20 mg and proceeds to step-down until the trend test contains only placebo and Nebivolol 5 mg
NS: P-values should not be used in the context of step-down trend testing (see analysis for explanation)
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Study NEB-305, Table 2.13.1, page 528)

Table 15 below shows the percent of responders, by treatment group, at weeks 2, 4, 8, and 12. The difference in response rate between study groups was evident by the first two weeks of treatment (67.9% (497/732) nebivolol vs. 45.3% (34/75) placebo). Responder rates generally plateaued by Day 28.

Table 15. Responder[a] Rates by Treatment and Visit (ITT LOCF) (NEB-305)

Visit	Placebo n (%)b	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Total n(%)[b]
Day 14	34 (45.3)	152 (62.3)	165 (67.6)	180 (73.8)	531 (65.8)
Day 28	41 (54.7)	160 (65.6)	172 (70.5)	183 (75.0)	556 (68.9)
Day 56	39 (52.0)	156 (63.9)	165 (67.6)	178 (73.0)	538 (66.7)
Day 84	37 (49.3)	161 (66.0)	163 (66.8)	168 (68.9)	529 (65.6)

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at endpoint of interest or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
Cross Reference: Data Listings 10.1.1, 10.2.1, and 10.4

(Reproduced from Sponsor, Study NEB-305, Table 2.13.5, page 532)

Women (71.7%) and Non-Blacks (68.5%) had significantly higher response rates than men (60.2%) and Blacks (45.7%), respectively ($p < 0.001$).

Conclusions (NEB-305)

In the ITT LOCF Population, for the primary endpoint, change in sitting diastolic blood pressure from baseline until end of study, nebivolol 5, 10, and 20 mg were statistically significant by step-down trend testing. In the step-up trend test for the primary endpoint, only the placebo to nebivolol 20 mg contrast was statistically significant.

For secondary diastolic endpoints at trough and peak, nebivolol 5, 10, and 20 mg were statistically significant by step-down trend testing in the ITT LOCF Population while sitting, standing, or supine.

For secondary systolic endpoints at trough, only nebivolol 20 mg was statistically significant by step-down trend testing in the ITT LOCF Population while sitting, standing, or supine. For sitting systolic blood pressure at trough from baseline to Day 84, the step-up trend test in the ITT LOCF population was significant for nebivolol 5, 10, and 20 mg contrasts.

For secondary systolic endpoints at peak, all nebivolol doses were significant by step-down trend testing with the exception of nebivolol 5 mg for sitting systolic blood pressure.

Study NEB-202

There were 568[15] patients screened with 485 patients entering the single-blind phase and 301 patients randomized. One randomized patient did not take study drug and comprised the Non-ITT Population. The other 300 randomized patients took double-blind study medication and comprised the ITT Population (49 placebo, 49 nebivolol 2.5 mg, 50 nebivolol 5 mg, 51 nebivolol 10 mg, 50 nebivolol 20 mg, and 51 nebivolol 40 mg). The number of patients completing the study through Day 84 was 218/251 (86.9%) randomized to nebivolol and 41/49 (83.7%) randomized to placebo. None of the patients who discontinued study medication prior to Day 84 remained in the study. For Study NEB-202, the results of step-down trend testing and LS mean change in DBP and SBP at trough and peak from baseline to end of study are shown in Table 16 and Table 17. For the primary efficacy endpoint, nebivolol 5 mg through 40 mg was statistically significant.

[15] **One patient went through the screening process twice and had two patient numbers (1053001251 and 1053003967). This patient was double-counted in the patient count of 569 screened patients. The actual number of patients screened, therefore, was only 568.**

Table 16. Summary of Results of the Step-Down Trend Test, LS Mean, and Difference from Placebo in LS Mean Change in Blood Pressure from Baseline to End of Study (Day 84) at Trough (ITT LOCF) (NEB-202)

Blood Pressure Parameter	Placebo	Nebivolol 2.5 mg			Nebivolol 5 mg			Nebivolol 10 mg			Nebivolol 20 mg			Nebivolol 40 mg		
	LS[c] Mean	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]
Sitting																
DBP	-2.8	0.084	-5.7	-2.9	0.004	-7.7	-4.9	<0.001	-8.9	-6.1	<0.001	-8.9	-6.0	<0.001	-8.3	-5.5
SBP	-0.4	0.611*	-1.9	-1.5	0.383	-3.0	-2.6	0.044	-6.4	-6.0	0.005	-7.6	-7.3	0.002	-7.2	-6.8
Standing																
DBP	-5.1	0.651	-5.9	-0.8	0.044	-8.7	-3.6	0.003	-9.7	-4.6	0.002	-9.4	-4.3	<0.001	-10.1	-5.0
SBP	-4.0	>0.999*	-4.0	0.0	0.292*	-7.2	-3.2	0.175*	-7.2	-3.2	0.093	-8.1	-4.1	0.016	-10.2	-6.2
Supine																
DBP	-4.4	0.056	-7.8	-3.3	0.028	-8.2	-3.8	0.001	-10.1	-5.7	0.001	-9.6	-5.2	0.001	-9.5	-5.1
SBP	-5.4	0.943*	-5.1	0.2	0.965*	-5.5	-0.1	0.142*	-9.6	-4.3	0.175*	-7.4	-2.1	0.054	-9.6	-4.3

Data Source: Table 2.1.1, Table 2.2.1, Table 2.5.1, Table 2.6.1, Table 2.9.1, Table 2.10.1

[a] P-value from step-down trend test. Step-down testing began with placebo to nebivolol 40 mg and proceeded to step down until the test contained only placebo and nebivolol 2.5 mg.

[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and metabolism rate

[c] LS mean change in DBP or SBP from baseline to end of study; difference from placebo in LS mean change in DBP or SBP from baseline to end of study

***: P-values associated with lower doses are not applicable in the context of step-down trend testing due to the non-significant result at the higher dose.**

Note: P-value and LS mean difference are not applicable for placebo; therefore, these columns are not displayed.

(Reproduced from Sponsor, Study NEB-202, Table 11.4.1.3-1, page 93)

Table 17. Summary of Results of the Step-Down Trend Test, LS Mean, and Difference from Placebo in LS Mean Change in Blood Pressure from Baseline to End of Study (Day 84) at Peak (ITT LOCF) (NEB-202)

Blood Pressure Parameter	Placebo	Nebivolol 2.5 mg			Nebivolol 5 mg			Nebivolol 10 mg			Nebivolol 20 mg			Nebivolol 40 mg		
	LS[c] Mean	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]
Sitting																
DBP	-3.8	0.008	-8.6	-4.8	<0.001	-10.6	-6.8	<0.001	-12.3	-8.5	<0.001	-10.9	-7.1	<0.001	-11.4	-7.6
SBP	-3.0	0.108	-7.8	-4.8	0.011	-10.6	-7.6	0.003	-11.4	-8.5	0.001	-12.1	-9.2	<0.001	-12.2	-9.2
Standing																
DBP	-4.6	0.122	-7.6	-3.0	0.001	-10.7	-6.1	<0.001	-11.5	-6.9	<0.001	-10.0	-5.4	<0.001	-10.5	-5.9
SBP	-3.9	0.208	-7.9	-4.0	0.007	-12.4	-8.5	0.006	-11.5	-7.5	0.009	-11.4	-7.5	0.010	-11.6	-7.7
Supine																
DBP	-5.5	0.022	-9.8	-4.3	0.005	-10.7	-5.3	<0.001	-11.9	-6.5	<0.001	-11.8	-6.3	<0.001	-11.8	-6.3
SBP	-4.9	0.138	-9.5	-4.6	0.028	-11.7	-6.8	0.004	-13.6	-8.7	0.002	-13.6	-8.7	0.002	-13.4	-8.5

Data Source: Table 2.3.1, Table 2.4.1, Table 2.7.1, Table 2.8.1, Table 2.11.1, Table 2.12.1

[a] P-value from step-down trend test. Step-down testing began with placebo to nebivolol 40 mg and proceeded to step down until the test contained only placebo and nebivolol 2.5 mg.

[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and metabolism rate

[c] LS mean change in DBP or SBP from baseline to end of study; difference from placebo in LS mean change in DBP or SBP from baseline to end of study

***: P-values associated with lower doses are not applicable in the context of step-down trend testing due to the non-significant result at the higher dose.**

Note: P-value and LS mean difference are not applicable for placebo; therefore, these columns are not displayed.

(Reproduced from Sponsor, Study NEB-202, Table 11.4.1.3-2, page 94)

Using step-up trend testing in the ITT LOCF Population for sitting diastolic blood pressure at trough from baseline to end of study including nebivolol 40 mg, the nebivolol contrast ranging from placebo to 40 mg was statistically significant ($p < 0.001$). Using the step-up trend test excluding nebivolol 40 mg, the nebivolol contrasts ranging from placebo to 20 mg ($p < 0.001$) and from 2.5 mg to 20 mg ($p = 0.047$) were significant.

Using step-up trend testing in the ITT LOCF Population for sitting systolic blood pressure at trough from baseline to end of study including nebivolol 40 mg, the nebivolol contrast ranging

from placebo through nebivolol 40 mg was significant (p = 0.002). Using the step-up trend test excluding nebivolol 40 mg, the nebivolol contrasts ranging from placebo to nebivolol 20 mg (p = 0.005) and from nebivolol 2.5 mg to 20 mg (p = 0.032) were significant.

The overall responder rates for the analysis were nebivolol 60.2% (151/251) and placebo 26.5% (13/49), as seen in Table 18. In Table 19, the difference in response rate between study groups by visit was evident by the first two weeks of treatment (50.2% (126/251) nebivolol vs. 22.4% (11/49) placebo.

Table 18. Responder Rates[a] by Treatment. Evaluation of Possible Predictors of Responders (ITT LOCF) (NEB-202)

Treatment	Total N	Responder n (%)[b]	p-value[c]
Placebo	49	13 (26.5)	
Nebivolol 2.5 mg	49	18 (36.7)	0.287
Nebivolol 5 mg	50	29 (58.0)	0.002
Nebivolol 10 mg	51	30 (58.8)	<0.001
Nebivolol 20 mg	50	32 (64.0)	<0.001
Nebivolol 40 mg	51	29 (56.9)	<0.001

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Based on Wald Chi-Square Test for trend from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, and age group; Step-down testing scheme begins with treatments placebo through Nebivolol 40 mg and proceeds to step-down until the trend test contains only placebo and Nebivolol 2.5 mg
NS: P-values should not be used in the context of step-down trend testing (see analysis plan for explanation)
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Study NEB-202, Table 2.13.1, page 480)

Table 19. Responder[a] Rates by Treatment and Visit (ITT LOCF) (NEB-202)

Visit	Placebo n (%)[b]	Nebivolol 2.5 mg n (%)[b]	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Nebivolol 40 mg n (%)[b]	Total n (%)[b]
Day 14	11 (22.4)	21 (42.9)	24 (48.0)	25 (49.0)	26 (52.0)	30 (58.8)	137 (45.7)
Day 28	11 (22.4)	23 (46.9)	25 (50.0)	23 (45.1)	29 (58.0)	31 (60.8)	142 (47.3)
Day 56	16 (32.7)	23 (46.9)	24 (48.0)	24 (47.1)	32 (64.0)	30 (58.8)	149 (49.7)
Day 84	13 (26.5)	18 (36.7)	29 (58.0)	30 (58.8)	32 (64.0)	29 (56.9)	151 (50.3)

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at endpoint of interest or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
Cross Reference: Data Listings 10.1.1, 10.2.1, and 10.4

(Reproduced from Sponsor, Study NEB-202, Table 2.13.5, page 484)

Conclusions (NEB-202)

For the primary endpoint in the ITT LOCF Population, nebivolol 5 mg through 40 mg was statistically significant by step-down trend testing.

For trough sitting diastolic and systolic pressure from baseline to end of study, the nebivolol contrast from placebo to 40 mg was statistically significant by step-up trend testing including nebivolol 40 mg. Excluding nebivolol 40 mg, the step-up trend test was significant for the nebivolol contrast from placebo to 20 mg as well as from 2.5 to 20 mg for both sitting diastolic and systolic pressure from baseline to end of study.

For the other trough diastolic secondary endpoints, nebivolol 5 mg through 40 mg was statistically significant by step-down trend testing.

For trough sitting systolic blood pressure, nebivolol 10 mg through 40 mg was significant by step-down trend testing. For trough standing systolic blood pressure, only nebivolol 40 mg was statistically significant. For trough supine systolic blood pressure, no nebivolol doses were significant.

For peak sitting diastolic blood pressure, nebivolol 2.5 mg through 40 mg was statistically significant by step-down trend testing. For standing and supine peak diastolic blood pressure, nebivolol 5 mg through 40 mg was significant.

For peak systolic blood pressure while sitting, standing, and supine, nebivolol 5 mg through 40 mg was statistically significant.

Studies NEB-302, NEB-305, and NEB-202

In the Integrated Summary of Efficacy, the sponsor analyzed the primary endpoint for the "total placebo-controlled population" comprised of 2,016 ITT patients from Studies NEB-302, NEB-305, and NEB-202. A total of 1,811 patients received nebivolol in the three monotherapy trials. The sponsor also analyzed the primary and key secondary endpoints for the "general hypertensive population" comprised of 1,716 ITT patients from Studies NEB-302 and NEB-305. Lastly, the sponsor combined 300 Black patients from Study NEB-202 with 132 Black patients from Study NEB-302 and 105 Black patients from Study NEB-305 for a total pool of 537 Black patients. In the Agency statistical analysis, performed by Jasmine Choi of the Cardio-Renal Division, only Study NEB-202 was used to determine the efficacy of nebivolol in the Black Population to avoid inflating type 1 error by pooling all Black patients.

Of the 2,016 ITT patients, 845 entered a double-blind extension phase and received up to an additional 9 months of treatment with nebivolol 5, 10 or 20 mg and possible concomitant diuretic or calcium channel blockade therapy.

In studies NEB-302 and NEB-305, there were 125/1716 (7.3%) diabetics. The diabetics were not evenly distributed among the treatment groups, ranging from 4.9% to 12.2% in the nebivolol dosing groups. This difference was statistically significant by the sponsor's Chi-Square test ($p = 0.028$). Additionally, compared to the total placebo-controlled population, the general hypertensive population had a higher proportion of patients $\geq$ 65 years of age who did not meet inclusion criteria but were still enrolled in the studies. In studies NEB-302 and NEB-305, there

were 22/340 (6.5%) and 18/1376 (1.3%) of patients, respectively, ≥ 65 years of age, who had enrollment trough sitting DBPs less than the protocol-specified 95 mm Hg.

The summary of the ITT Population in Studies NEB-302, NEB-305, and NEB-202 is described in Table 20.

Table 20. Summary of Intent-to-Treat Populations for NEB-302, NEB-305, and NEB-202

Study Number	Placebo N	Nebivolol 1.25 mg N	Nebivolol 2.5 mg N	Nebivolol 5 mg N	Nebivolol 10 mg N	Nebivolol 20 mg N	Nebivolol 30/40 mg N	Total N
302	81	83	82	165	166	166	166	909
305	75	N/A	N/A	244	244	244	N/A	807
202	49	N/A	49	50	51	50	51	300
TOTAL								2,016

(Adapted from Sponsor, Integrated Summary of Efficacy, Table 7.1-01, page 56)

The demographic and baseline characteristics of the ITT Population in Studies NEB-302, NEB-305, and NEB-202 are shown in Table 21 below. Baseline sitting diastolic and systolic blood pressures were similar between treatment groups, as seen in Table 22.

Table 21. Demographic and Baseline Characteristics of Subjects (NEB-302, NEB-305, and NEB-202)

Parameter	Placebo n (%)	Nebivolol 1.25 mg n (%)	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 30/40 mg n (%)	Total N (%)
NEB-302								
Age (years)								
N	81	83	82	165	166	166	166	909
Mean (SD)	56.0 (11.6)	55.5 (11.5)	53.4 (12.3)	54.9 (11.8)	55.2 (12.5)	54.1 (11.6)	54.3 (11.6)	54.7 (11.8)
Median	57.0	56.0	54.0	54.0	54.5	54.0	54.0	54.0
Range	24.0 to 80.0	28.0 to 84.0	24.0 to 81.0	25.0 to 82.0	23.0 to 83.0	22.0 to 82.0	26.0 to 78.0	22.0 to 84.0
Age Group								
< 65	64 (79.0)	65 (78.3)	68 (82.9)	132 (80.0)	125 (75.3)	134 (80.7)	128 (77.1)	716 (78.8)
≥65	17 (21.0)	18 (21.7)	14 (17.1)	33 (20.0)	41 (24.7)	32 (19.3)	38 (22.9)	193 (21.2)
Gender								
Male	46 (56.8)	46 (55.4)	53 (64.6)	96 (58.2)	93 (56.0)	92 (55.4)	92 (55.4)	518 (57.0)
Female	35 (43.2)	37 (44.6)	29 (35.4)	69 (41.8)	73 (44.0)	74 (44.6)	74 (44.6)	391 (43.0)
Race[a]								
Black	11 (13.6)	12 (14.5)	13 (15.9)	23 (13.9)	23 (13.9)	25 (15.1)	25 (15.1)	132 (14.5)
Non-Black	70 (86.4)	71 (85.5)	69 (84.1)	142 (86.1)	143 (86.1)	141 (84.9)	141 (84.9)	777 (85.5)
Caucasian	61 (75.3)	60 (72.3)	60 (73.2)	120 (72.7)	114 (68.7)	112 (67.5)	113 (68.1)	640 (70.4)
Asian	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	2 (1.2)	1 (0.6)	6 (0.7)
Hispanic	9 (11.1)	10 (12.0)	9 (11.0)	21 (12.7)	24 (14.5)	25 (15.1)	25 (15.1)	123

Parameter	Placebo n (%)	Nebivolol 1.25 mg n (%)	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 30/40 mg n (%)	Total N (%)
								(13.5)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	2 (1.2)	2 (1.2)	8 (0.9)
NEB-302								
Diabetes Status								
Yes	7 (8.6)	9 (10.8)	10 (12.2)	11 (6.7)	17 (10.2)	14 (8.4)	20 (12.0)	88 (9.7)
No	74 (91.4)	74 (89.2)	72 (87.8)	154 (93.3)	149 (89.8)	152 (91.6)	146 (88.0)	821 (90.3)
Metabolism								
Poor	4 (4.9)	5 (6.0)	6 (7.3)	10 (6.1)	11 (6.6)	12 (7.2)	11 (6.6)	59 (6.5)
Extensive	77 (95.1)	78 (94.0)	76 (92.7)	155 (93.9)	155 (93.4)	154 (92.8)	155 (93.4)	850 (93.5)
BMI (kg/m^2)[bc]								
< 30	44 (54.3)	43 (51.8)	45 (54.9)	91 (55.2)	102 (61.4)	101 (60.8)	84 (50.6)	510 (56.1)
≥ 30	37 (45.7)	40 (48.2)	37 (45.1)	74 (44.8)	64 (38.6)	65 (39.2)	82 (49.4)	399 (43.9)
NEB-305								
	Placebo	**N/A**	**N/A**	**5 mg**	**10 mg**	**20 mg**	**N/A**	**Total**
Age (years)								
N	75	-	-	244	244	244	-	807
Mean (SD)	51.2 (10.0)	-	-	53.9 (11.1)	53.8 (11.2)	53.4 (11.1)	-	53.4 (11.0)
Median	50.0	-	-	54.0	53.0	53.0	-	53.0
Range	27.0 to 73.0	-	-	23.0 to 79.0	22.0 to 82.0	28.0 to 80.0	-	22.0 to 82.0
Age Group								
< 65	67 (89.3)	-	-	199 (81.6)	197 (80.7)	197 (80.7)	-	660 (81.8)
≥65	8 (10.7)	-	-	45 (18.4)	47 (19.3)	47 (19.3)	-	147 (18.2)
Gender								
Male	39 (52.0)	-	-	131 (53.7)	131 (53.7)	131 (53.7)	-	432 (53.5)
Female	36 (48.0)	-	-	113 (46.3)	113 (46.3)	113 (46.3)	-	375 (46.5)
Race[a]								
Black	11 (14.7)	-	-	31 (12.7)	33 (13.5)	30 (12.3)	-	105 (13.0)
Non-Black	64 (85.3)	-	-	213 (87.3)	211 (86.5)	214 (87.7)	-	702 (87.0)
Caucasian	60 (80.0)	-	-	190 (77.9)	191 (78.3)	192 (78.7)	-	633 (78.4)
Asian	0 (0.0)	-	-	4 (1.6)	2 (0.8)	3 (1.2)	-	9 (1.1)
Hispanic	4 (5.3)	-	-	19 (7.8)	17 (7.0)	19 (7.8)	-	59 (7.3)
Other	0 (0.0)	-	-	0 (0.0)	1 (0.4)	0 (0.0)	-	1 (0.1)
Diabetes Status								
Yes	4 (5.3)	-	-	9 (3.7)	12 (4.9)	12 (4.9)	-	37 (4.6)
No	71 (94.7)	-	-	235 (96.3)	232 (95.1)	232 (95.1)	-	770 (95.4)

Parameter	Placebo n (%)	Nebivolol 1.25 mg n (%)	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 30/40 mg n (%)	Total N (%)
NEB-305								
Metabolism								
Poor	4 (5.3)	-	-	15 (6.1)	15 (6.1)	16 (6.6)	-	50 (6.2)
Extensive	71 (94.7)	-	-	229 (93.9)	229 (93.9)	228 (93.4)	-	757 (93.8)
BMI (kg/m^2)[b]								
< 30	48 (64.0)	-	-	152 (62.6)	145 (59.4)	137 (56.4)	-	482 (59.9)
≥ 30	27 (36.0)	-	-	91 (37.4)	99 (40.6)	106 (43.6)	-	323 (40.1)
Missing[c]	0			1	0	1	-	2
NEB-202								
	Placebo	**N/A**	**2.5 mg**	**5 mg**	**10 mg**	**20 mg**	**40 mg**	**Total**
Age (years)								
N	49		49	50	51	50	51	300
Mean (SD)	49.7 (9.1)		49.9 (9.6)	51.6 (10.5)	50.5 (10.5)	51.3 (10.8)	52.3 (12.0)	50.9 (10.4)
Median	49.0		49.0	51.0	49.0	51.5	51.0	50.0
Range	34.0 to 70.0		33.0 to 75.0	26.0 to 77.0	29.0 to 79.0	28.0 to 74.0	28.0 to 79.0	26.0 to 79.0
Age Group								
< 65	44 (89.8)		45 (91.8)	44 (88.0)	45 (88.2)	45 (90.0)	42 (82.4)	265 (88.3)
≥65	5 (10.2)		4 (8.2)	6 (12.0)	6 (11.8)	5 (10.0)	9 (17.6)	35 (11.7)
Gender								
Male	23 (46.9)		26 (53.1)	22 (44.0)	22 (43.1)	21 (42.0)	22 (43.1)	136 (45.3)
Female	26 (53.1)		23 (46.9)	28 (56.0)	29 (56.9)	29 (58.0)	29 (56.9)	164 (54.7)
Diabetes Status								
Yes	6 (12.2)		7 (14.3)	8 (16.0)	6 (11.8)	7 (14.0)	9 (17.6)	43 (14.3)
No	43 (87.8)		42 (85.7)	42 (84.0)	45 (88.2)	43 (86.0)	42 (82.4)	257 (85.7)
Metabolism								
Poor	0 (0.0)		1 (2.0)	1 (2.0)	2 (3.9)	1 (2.0)	2 (3.9)	7 (2.3)
Extensive	49 (100.0)		48 (98.0)	49 (98.0)	49 (96.1)	49 (98.0)	49 (96.1)	293 (97.7)
BMI (kg/m^2)[b]								
< 30	21 (42.9)		26 (53.1)	26 (52.0)	26 (51.0)	25 (50.0)	20 (39.2)	144 (48.0)
≥30	28 (57.1)		23 (46.9)	24 (48.0)	25 (49.0)	25 (50.0)	31 (60.8)	156 (52.0)

(a) Test of race is black vs. non-black
(b) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
(c) Missing not used in percentage calculation or testing

(Reproduced from Sponsor, NEB-302 (Table 1.1.1, pages 131 and 132), NEB-305 (Table 1.1.1, pages 119 and 120), and NEB-202 (Table 1.1.1, page 132 and 133)

Table 22. Baseline Sitting Diastolic and Systolic Blood Pressure (NEB-302, NEB-305, NEB-202)

NEB-302								
	Placebo	**Nebivolol 1.25 mg**	**Nebivolol 2.5 mg**	**Nebivolol 5 mg**	**Nebivolol 10 mg**	**Nebivolol 20 mg**	**Nebivolol 30/40 mg**	**Total**
Sitting Diastolic Blood Pressure (mm Hg)								
N	81	83	82	165	166	166	166	909
Mean (SD)	100.3 (4.3)	98.9 (4.5)	99.8 (3.5)	99.6 (3.9)	99.5 (4.1)	99.4 (3.5)	99.3 (3.6)	99.5 (3.9)
Median	99.0	98.0	99.0	99.0	99.0	99.0	99.0	99.0
Range	95.0 to 113.0	77.0 to 110.0	95.0 to 109.0	83.0 to 108.0	84.0 to 109.0	90.0 to 109.0	90.0 to 109.0	77.0 to 113.0
Sitting Systolic Blood Pressure (mm Hg)								
N	81	83	82	165	166	166	166	909
Mean (SD)	154.9 (15.8)	152.2 (14.4)	150.1 (13.4)	152.6 (13.3)	155.8 (14.7)	151.9 (15.4)	153.1 (14.5)	153.1 (14.6)
Median	153.0	149.0	151.0	151.0	155.0	150.0	151.0	152.0
Range	126.0 to 197.0	129.0 to 195.0	123.0 to 185.0	127.0 to 189.0	127.0 to 195.0	116.0 to 195.0	123.0 to 196.0	116.0 to 197.0
NEB-305								
Sitting Diastolic Blood Pressure (mm Hg)								
N	75	N/A	N/A	244	244	244		807
Mean (SD)	98.7 (3.3)			99.1 (3.8)	98.9 (4.4)	99.2 (3.7)		99.0 (3.9)
Median	98.0			98.0	98.0	99.0		98.0
Range	89.0 to 108.0			89.0 to 111.0	80.0 to 119.0	90.0 to 112.0		80.0 to 119.0
Sitting Systolic Blood Pressure (mm Hg)								
N	75	N/A	N/A	244	244	244		807
Mean (SD)	149.9 (12.5)			151.8 (13.2)	150.5 (13.1)	151.9 (14.8)		151.3 (13.6)
Median	149.0			151.0	151.0	150.0		150.0
Range	126.0 to 192.0			119.0 to 195.0	121.0 to 187.0	117.0 to 191.0		117.0 to 195.0
NEB-202								
Sitting Diastolic Blood Pressure (mm Hg)								
N	49	N/A	49	50	51	50	51	300
Mean (SD)	100.8 (4.0)		99.5 (4.3)	100.5 (4.4)	100.3 (4.6)	101.5 (4.7)	98.7 (3.9)	100.2 (4.4)
Median	100.0		99.0	100.0	100.0	101.0	99.0	100.0
Range	95.0 to 111.0		83.0 to 107.0	91.0 to 109.0	86.0 to 111.0	90.0 to 115.0	89.0 to 107.0	83.0 to 115.0
Sitting Systolic Blood Pressure (mm Hg)								
N	49	N/A	49	50	51	50	51	300
Mean (SD)	151.4 (13.9)		148.6 (13.6)	151.7 (13.6)	154.2 (13.6)	156.4 (12.7)	150.9 (15.3)	152.2 (13.9)
Median	150.0		147.0	150.0	150.0	155.0	148.0	150.0
Range	121.0 to 180.0		113.0 to 179.0	121.0 to 181.0	128.0 to 187.0	131.0 to 186.0	126.0 to 188.0	113.0 to 188.0
Cross References: Data Listings 10.1.1, 10.1.2, and 10.1.3								

(Reproduced from Sponsor, NEB-302 (Table 1.2.1, pages 138 and 139), NEB-305 (Table 1.2.1, pages 128 and 129), and NEB-202 (Table 1.2.1, pages 139 and 140)

Primary and Secondary Efficacy Results for the General Hypertensive Population (NEB-302 and NEB-305)

Table 23 summarizes the step down trend test results in NEB-302 and NEB-305 for the primary efficacy endpoint, change in mean trough diastolic blood pressure at end of study compared with baseline. By the sponsor's and Agency's statistical analysis, all nebivolol doses were statistically significant ($p < 0.0001$ for all doses in NEB-302 and $p \leq 0.0015$ for all doses in NEB-305). Additionally, the sponsor's analysis for step-up trend testing in the general hypertensive population found incremental increases in efficacy between nebivolol 1.25 mg, 2.5 mg, and 5 mg, with no further increases in efficacy at higher doses.

Table 23. Primary Analysis Results of Pivotal Studies (NEB-302 and NEB-305) (Sponsor's Analysis, confirmed by Jasmine Choi, Cardio-Renal Division)

Treatment	N	Baseline Mean	Mean at the End of Study	LS Mean Change from Baseline (SE)	Step-Down trend Test p-value
NEB-302					
Placebo	81	100.3	97.1	-2.9 (1.1)	-
1.25 mg	83	98.9	90.8	-8.0 (1.1)	<0.0001
2.5 mg	82	99.8	91.1	-8.5 (1.1)	<0.0001
5 mg	165	99.6	91.0	-8.4 (1.0)	<0.0001
10 mg	166	99.5	90.2	-9.2 (0.9)	<0.0001
20 mg	166	99.4	89.5	-9.8 (0.9)	<0.0001
30/40 mg	166	99.3	88.0	-11.2 (0.9)	<0.0001
NEB-305					
Placebo	75	98.7	91.4	-4.6 (1.3)	-
5 mg	244	99.1	88.5	-7.8 (1.0)	0.0015
10 mg	244	98.9	87.7	-8.5 (1.0)	0.0009
20 mg	244	99.2	87.2	-9.1 (1.0)	0.0002

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 11 and from Sponsor, Integrated Summary of Efficacy, Table 7.3-02, page 60)

For the secondary analysis, change of sitting systolic blood pressure at trough at end of study, compared with baseline, step down trend testing was statistically significant for all doses in NEB-302 ($p \leq 0.002$) and for nebivolol 20 mg only in NEB-305 ($p < 0.001$).

Table 24. Analysis Results of the Trough Sitting SBP in NEB-302 and NEB-305

	NEB-302			NEB-305		
Treatment	**N**	**LS Mean Change**	**p-value***	**N**	**LS Mean Change**	**p-value***
Trough Sitting SBP						
Placebo	81	2.2	-	75	-0.4	-
Nebivolol						
1.25 mg	83	-4.4	0.002	N/A	N/A	N/A
2.5 mg	82	-6.3	<0.001	N/A	N/A	N/A
5 mg	165	-5.9	<0.001	244	-4.2	0.035
10 mg	166	-7.0	<0.001	244	-3.5	0.086
20 mg	166	-6.5	<0.001	244	-6.7	<0.001
30/40 mg	166	-9.5	N/A	N/A	N/A	N/A
* step-down trend test p-value from an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group.						

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 12 and from Sponsor, Integrated Summary of Efficacy, Table 7.3-04, page 65)

Sponsor's Analysis (General Hypertensive Population; NEB-302 and NEB-305)
The sponsor summarizes the primary efficacy endpoint results in Table 25 below. All nebivolol doses significantly lowered sitting diastolic blood pressure at trough.

Table 25. Analysis of Sitting Diastolic Blood Pressure at Trough on Day 84 (General Hypertensive Population [302/305]: ITT, LOCF)

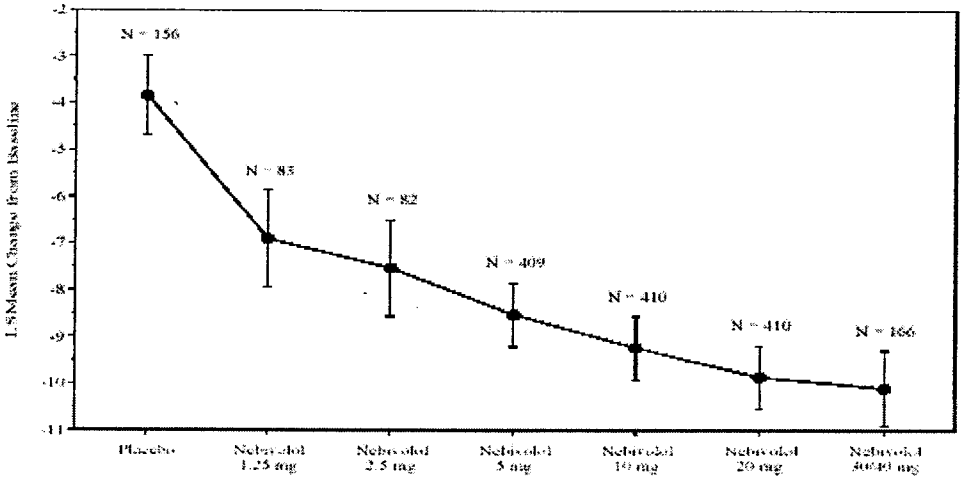
Treatment	N	Baseline Mean	Treatment Mean	Change from Baseline			
				Mean (SD)	LS Mean (SE)[a]	LS Mean Difference[a,c]	Step-Down p-Value[a,b]
Placebo	156	99.5	94.4	-5.1 (8.1)	-3.8 (0.9)		
Nebivolol							
1.25 mg	83	98.9	90.8	-8.0 (7.7)	-6.9 (1.0)	-3.1	0.005
2.5 mg	82	99.8	91.1	-8.7 (7.7)	-7.5 (1.0)	-3.7	<0.001
5 mg	409	99.3	89.5	-9.8 (7.9)	-8.5 (0.7)	-4.7	<0.001
10 mg	410	99.2	88.7	-10.5 (8.2)	-9.2 (0.7)	-5.4	<0.001
20 mg	410	99.2	88.1	-11.1 (8.6)	-9.9 (0.7)	-6.0	<0.001
30/40 mg	166	99.3	88.0	-11.3 (8.3)	-10.1 (0.8)	-6.3	<0.001

Data Source: ISE Table 2.1.1
[a] **From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group.**
[b] **Step-down testing scheme began with treatments placebo through nebivolol 30/40 mg and proceeded to step-down until the trend test contained only placebo and nebivolol 1.25 mg.**
[c] **Based on pairwise comparison of treatment vs. placebo**

(Reproduced from Sponsor, Table 7.3-03, Integrated Summary of Efficacy, page 61)

For the general hypertensive population, the sponsor's representation of the LS mean change from baseline to end of treatment for sitting diastolic blood pressure is shown in Table 26 below.

Table 26. LS Mean Change from Baseline to End of Treatment (Day 84) in Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment +/- S.E. (General Hypertensive Population [302/305]: ITT, LOCF)

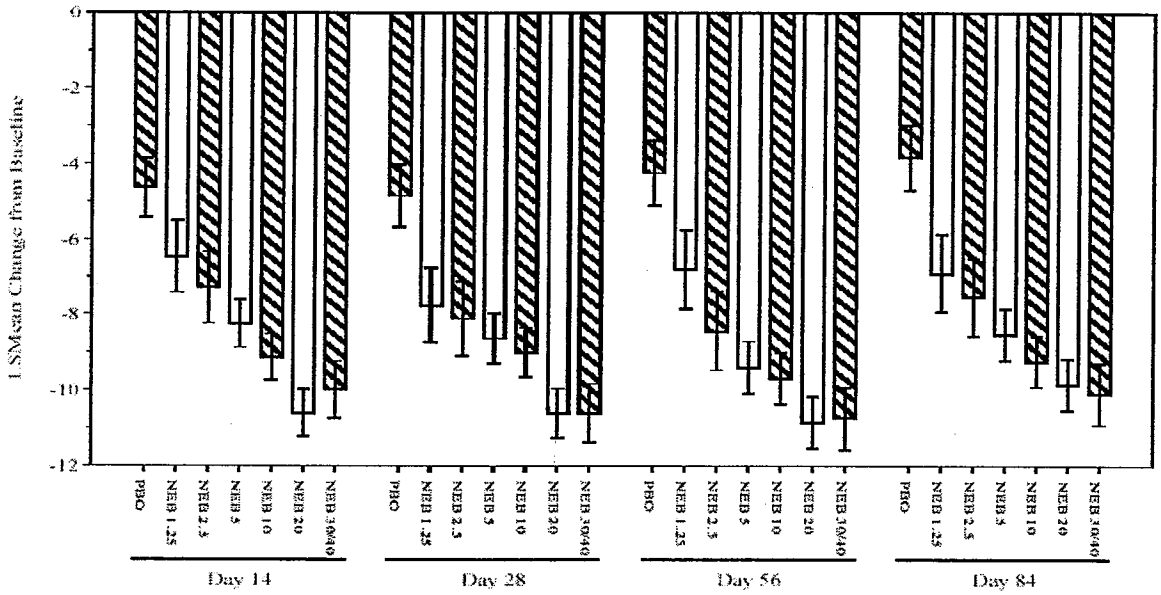


Data Source: ISE Figure 1.15.1

(Reproduced from Sponsor, Figure 7.3-01, Integrated Summary of Efficacy, page 62)

From the sponsor's analysis, the antihypertensive effect of nebivolol was evident by Day 14, as seen in Figure 4.

Figure 4. Bar Graph of LS Mean Change from Baseline to Each Visit in Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment +/- S.E.. General Hypertensive Population (NEB-302, NEB-305), (ITT LOCF)



(Reproduced from Sponsor, Figure 1.15, Integrated Summary of Efficacy, page 447)

For sitting systolic blood pressure at trough, the sponsor summarizes the results for the general hypertensive population in Table 27.

Table 27. Analysis of Sitting Systolic Blood Pressure at Trough on Day 84 (General Hypertensive Population [302/305]: ITT, LOCF)

Treatment	N	Baseline Mean	Treatment Mean	Change from Baseline			
				Mean (SD)	LS Mean (SE)[a]	LS Mean Difference[a,c]	Step-Down p-Value[a,b]
Placebo	156	152.5	148.0	-4.5 (13.4)	0.7 (1.4)		
Nebivolol							
1.25 mg	83	152.2	145.1	-7.1 (12.3)	-2.4 (1.7)	-3.1	0.094
2.5 mg	82	150.1	141.5	-8.6 (13.6)	-4.5 (1.7)	-5.2	0.005
5 mg	409	152.1	141.3	-10.8 (13.5)	-5.7 (1.2)	-6.4	<0.001
10 mg	410	152.7	141.9	-10.7 (14.7)	-5.7 (1.1)	-6.4	<0.001
20 mg	410	151.9	139.5	-12.4 (15.5)	-7.5 (1.1)	-8.2	<0.001
30/40 mg	166	153.1	140.7	-12.4 (15.7)	-7.6 (1.4)	-8.2	<0.001

Data Source: ISE Table 2.2.1

[a] **From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group.**

[b] **Step-down testing scheme began with treatments placebo through nebivolol 30/40 mg and proceeded to step-down until the trend test contained only placebo and nebivolol 1.25 mg.**

[c] **Based on pairwise comparison of treatment vs. placebo**

(Reproduced from Sponsor, Table 7.3-05, Integrated Summary of Efficacy, page 66)

For the general hypertensive population, Table 28 and Table 29 show the trough to peak ratio for sitting diastolic and systolic blood pressure at trough, respectively.

Table 28. Trough to Peak Ratio for Sitting Diastolic Blood Pressure, by Treatment and Overall. General Hypertensive Population (NEB-302/NEB-305) (ITT LOCF)

Treatment	Non-Placebo Subtracted	Placebo Subtracted	
	Ratio[a] (Raw Mean)	Ratio[b] (Raw Mean)	Ratio[b,c] (LS Mean)
Placebo	0.625		
Nebivolol 1.25 mg	0.808	1.652	1.616
Nebivolol 2.5 mg	0.791	1.281	1.238
Nebivolol 5 mg	0.761	0.999	1.009
Nebivolol 10 mg	0.754	0.938	0.945
Nebivolol 20 mg	0.751	0.906	0.909
Nebivolol 30/40 mg	0.765	0.939	0.938
Total Nebivolol	0.760	0.963	1.021

[a] Ratio of trough sitting diastolic blood pressure to peak sitting diastolic blood pressure
[b] Ratio of placebo subtracted trough sitting diastolic blood pressure to placebo subtracted peak sitting diastolic blood pressure
[c] From an ANCOVA with factor treatment and covariates baseline value, EM or PM classification, diabetes status, gender, race, and age group
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.3.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.11.1, Integrated Summary of Efficacy, page 263)

Table 29. Trough to Peak Ratio for Sitting Systolic Blood Pressure, by Treatment and Overall. General Hypertensive Population (NEB-302/NEB-305) (ITT LOCF)

Treatment	Non-Placebo Subtracted	Placebo Subtracted	
	Ratio[a] (Raw Mean)	Ratio[b] (Raw Mean)	Ratio[b,c] (LS Mean)
Placebo	0.475		
Nebivolol 1.25 mg	0.671	2.538	1.971
Nebivolol 2.5 mg	0.828	4.783	2.383
Nebivolol 5 mg	0.741	1.247	1.244
Nebivolol 10 mg	0.664	0.938	0.947
Nebivolol 20 mg	0.705	0.977	0.978
Nebivolol 30/40 mg	0.720	1.025	1.028
Total Nebivolol	0.707	1.072	1.170

[a] Ratio of trough sitting systolic blood pressure to peak sitting systolic blood pressure
[b] Ratio of placebo subtracted trough sitting systolic blood pressure to placebo subtracted peak sitting systolic blood pressure
[c] From an ANCOVA with factor treatment and covariates baseline value, EM or PM classification, diabetes status, gender, race, and age group
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.3.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.11.1, Integrated Summary of Efficacy, page 265)

In the general hypertensive population, nebivolol had a statistically significant effect on heart rate at all doses, as shown in Table 30 and Figure 5.

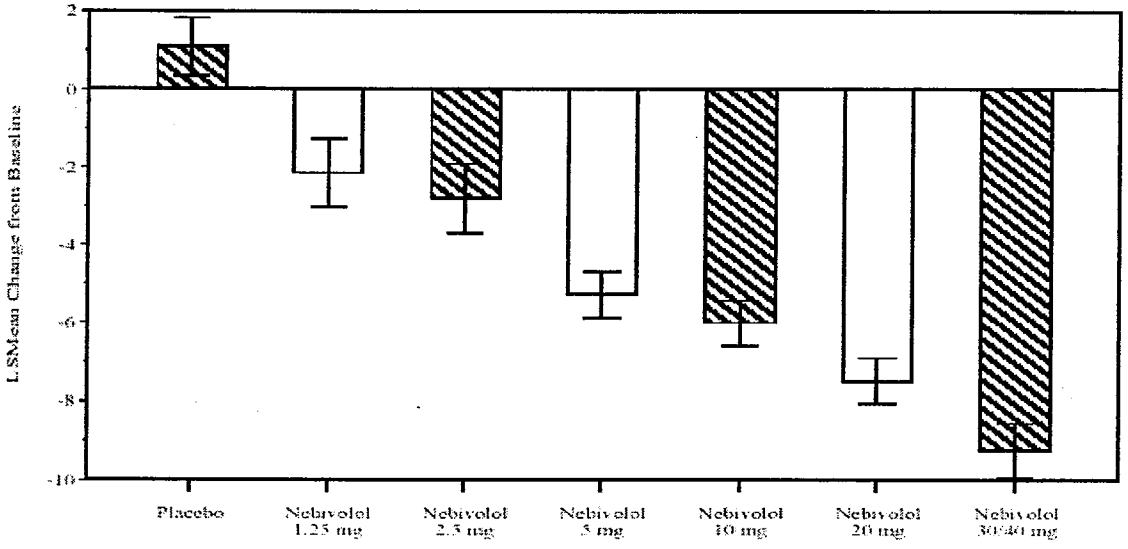
Table 30. Mean Change from Baseline to End of treatment (Day 84) in Trough Sitting Heart Rate (bpm) by Treatment. General Hypertensive Population (NEB-302/NEB-305) (ITT LOCF)

Treatment	N	Baseline Mean	Treatment Mean	Change From Baseline					
				Mean (SD)	LS Mean (SE)[a]	Step-Down p-value[a,b]	LS Mean Difference[a,c]	95% C.I.[a,c]	p-value[a,c]
Placebo	156	73.0	73.3	0.2 (7.8)	1.1 (0.7)				
Nebivolol 1.25 mg	83	72.6	69.9	-2.7 (8.9)	-2.1 (0.9)	<0.001	-3.2	(-5.1, -1.4)	<0.001
Nebivolol 2.5 mg	82	73.6	69.8	-3.8 (7.6)	-2.8 (0.9)	<0.001	-3.9	(-5.7, -2.0)	<0.001
Nebivolol 5 mg	409	72.9	66.8	-6.1 (8.4)	-5.3 (0.6)	<0.001	-6.4	(-7.6, -5.1)	<0.001
Nebivolol 10 mg	410	71.8	65.6	-6.3 (8.5)	-6.0 (0.6)	<0.001	-7.1	(-8.4, -5.8)	<0.001
Nebivolol 20 mg	410	72.8	64.6	-8.3 (8.3)	-7.5 (0.6)	<0.001	-8.6	(-9.8, -7.3)	<0.001
Nebivolol 30/40 mg	166	71.7	62.3	-9.4 (7.8)	-9.3 (0.7)	<0.001	-10.3	(-11.9, -8.8)	<0.001

[a] From an ANCOVA with factor treatment and covariates baseline heart rate, EM or PM classification, diabetes status, gender, race, and age group
[b] Step-down testing scheme begins with treatments placebo through Nebivolol 30/40 mg and proceeds to step-down until the trend test contains only placebo and Nebivolol 1.25 mg
[c] Based on pairwise comparison of Treatment vs. Placebo
NS: P-values associated with lower doses should not be used in the context of step-down trend testing
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.9.1, Integrated Summary of Efficacy, page 259)

Figure 5. Bar Graph of LS Mean Change from Baseline to End of Treatment (Day 84) in Trough Sitting Heart Rate (bpm) by Treatment +/- S.E. (General Hypertensive Population [302/305]: ITT, LOCF)



Data Source: ISE Figure 1.25.2

(Reproduced from Sponsor, Figure 7.3-03, Integrated Summary of Efficacy, page 72)

The sponsor provides a summary of significant dose ranges for all study points for the general hypertensive population in Table 31.

Table 31. Summary of Significant Dose Ranges for All Study Endpoints (General Hypertensive Population [302/305]: ITT, LOCF)

	1.25mg	2.5mg	5mg	10mg	20mg	30/40mg
Sitting DBP (trough)[a]	•	•	•	•	•	•
Standing DBP (trough)[a]		•	•	•	•	•
Sitting DBP (peak)[a]		•	•	•	•	•
Standing DBP (peak)[a]		•	•	•	•	•
Responder rate[b]		•	•	•	•	•
Sitting SBP (trough)[a]		•	•	•	•	•
Standing SBP (trough)[a]		•	•	•	•	•
Sitting SBP (peak)[a]			•	•	•	•
Standing SBP (peak)[a]			•	•	•	•
Sitting heart rate (trough)[a]	•	•	•	•	•	•

Data Source: ISE Table 2.1.1, ISE Table 2.2.1, ISE Table 2.3.1, ISE Table 2.4.1, ISE Table 2.5.1, ISE Table 2.6.1, ISE Table 2.7.1, ISE Table 2.8.1, ISE Table 2.9.1, ISE Table 2.10.1

[a] Based on p-value of step-down trend test

[b] Based on p-value of Wald Chi-Square Test

(Reproduced from Sponsor, Table 12.1-01, Integrated Summary of Efficacy, page 142)

The sponsor defined a responder as "a patient whose average sitting diastolic blood pressure at trough at end of study was either < 90 mm Hg or had decreased by ≥ 10 mm Hg from baseline."[16] In studies NEB-302 and NEB-305, the percent responders increased dose-dependently in the nebivolol treatment groups. All nebivolol doses were statistically significant in both studies, using a Wald Chi-Square Test with treatment as factor and baseline blood pressure, metabolism of nebivolol, diabetes status, ethnicity, age, and gender as covariates. Table 32 below summarizes the response rates for NEB-302 and NEB-305.

Table 32. Responder Rates in NEB-302 and NEB-305

	NEB-302			NEB-305		
Treatment	**Total N**	**Responder N (%)**	**p-value**	**Total N**	**Responder N (%)**	**p-value**
Placebo	81	20 (24.7)		75	37 (49.3)	
Nebivolol						
1.25 mg	83	38 (45.8)	0.008	-	-	-
2.5 mg	82	41 (50.0)	0.001	-	-	-
5 mg	165	83 (50.3)	<0.001	244	161 (66.0)	0.009
10 mg	166	89 (53.6)	<0.001	244	163 (66.8)	0.005
20 mg	166	99 (59.6)	<0.001	244	168 (68.9)	0.002
30/40 mg	166	107 (64.5)	N/A	-		-

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 12 and from Sponsor, NEB-302, Table 2.13.1, page 648 and NEB-305, Table 2.13.1, page 528)

The sponsor's pooled analysis for NEB-302 and NEB-305 showed patients taking nebivolol 1.25 mg did not significantly respond to treatment.

[16] **Sponsor, Study NEB-302, page 100.**

Table 33. Responder Rates by Treatment. General Hypertensive Population (NEB-302/NEB-305) (ITT LOCF)

Treatment	Total n	Responder n (%)[b]	p-value[c]
Placebo	156	57 (36.5)	
Nebivolol 1.25 mg	83	38 (45.8)	0.180
Nebivolol 2.5 mg	82	41 (50.0)	0.026
Nebivolol 5 mg	409	244 (59.7)	<0.001
Nebivolol 10 mg	410	252 (61.5)	<0.001
Nebivolol 20 mg	410	267 (65.1)	<0.001
Nebivolol 30/40 mg	166	107 (64.5)	<0.001

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Based on Wald Chi-Square Test for trend from logistic regression with factor treatment and covariates baseline sitting diastolic blood pressure, EM or PM classification, diabetes status, gender, race, and age group
NS: P-values should not be sued in the context of step-down trend testing
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.10.1, Integrated Summary of Efficacy, page 261)

Black Population (NEB-202)

Ms. Choi of the Cardio-Renal Division obtained different p-values than the sponsor for the primary efficacy endpoint, but the overall interpretation was unchanged. Nebivolol 5 mg, 10 mg, 20 mg, and 40 mg significantly reduced trough diastolic blood pressure at end of study, compared with baseline ($p = 0.0187$, $p = 0.0032$, $p = 0.0019$, and $p = 0.0014$, respectively). Nebivolol 2.5 mg, however, was not statistically significant in reducing trough diastolic blood pressure. To avoid inflating the type 1 error, Ms. Choi did not combine the results of NEB-202 with the Black populations in studies NEB-302 and NEB-305. The primary analysis for NEB-202 is listed in Table 34.

Table 34. Primary Analysis Results for Sitting Diastolic Blood Pressure at Trough (ITT LOCF) (NEB-202)

Treatment	N	Baseline Mean	Mean at the End of Study	LS mean Change from Baseline	Step-Down Trend Test p-value
Placebo	49	100.8	96.4	-2.8 (2.1)	-
Nebivolol					
2.5 mg	49	99.5	92.8	-5.7 (2.1)	0.14
5 mg	50	100.5	91.4	-7.7 (2.1)	0.0187
10 mg	51	100.3	90.0	-8.9 (2.0)	0.0032
20 mg	50	101.5	90.9	-8.9 (2.1)	0.0019
40 mg	51	98.7	89.6	-8.3 (2.0)	0.0014

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 13)

For the secondary efficacy analysis, sitting systolic blood pressure at trough, nebivolol 10 mg, 20 mg, and 40 mg was statistically significant, as seen in Table 35 below. Although Ms. Choi's p-values were slightly different than those obtained from the sponsor, the overall interpretation was the same.

Table 35. Mean Change from Baseline to End of Study in Sitting Systolic Blood Pressure at Trough (ITT LOCF) (NEB-202)

Treatment	N	Baseline Mean	Mean at the End of Study	LS mean Change From Baseline	Step-Down Trend Test p-value
Placebo	49	151.4	147.8	-0.4 (3.8)	-
Nebivolol					
2.5 mg	49	148.6	144.0	-1.9 (3.7)	0.611
5 mg	50	151.7	145.8	-3.0 (3.7)	0.383
10 mg	51	154.2	144.0	-6.4 (3.6)	0.044
20 mg	50	156.4	144.4	-7.6 (3.7)	0.005
40 mg	51	150.9	141.4	-7.2 (3.5)	0.002

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 14)

In NEB-202, change from baseline in trough sitting heart rate was statistically significant ($p \leq 0.008$) for nebivolol 10 mg, 20 mg, and 40 mg, as shown in Table 36. Because change in heart rate was assessed as a safety parameter, the sponsor analyzed heart rate using an OC method.

Table 36. Mean Change from Baseline at Day 84 (End of Study) in Heart Rate by Treatment (ITT OC) (NEB-202)

Treatment	N	Baseline Mean	Treatment Mean	Change From Baseline					
				Mean (SD)	LS Mean (SE)[a]	Step-Down p-value[a,b]	LS Mean Difference[a,c]	95% C.I.[a,c]	p-value[a,c]
Placebo	40	71.9	69.5	-2.4 (8.0)	-2.4 (2.7)				
Nebivolol 2.5 mg	43	73.5	68.3	-5.2 (9.7)	-4.4 (2.6)	0.240[NS]	-2.0	(-5.3, 1.3)	0.240[NS]
Nebivolol 5 mg	41	73.3	68.6	-4.7 (8.1)	-3.9 (2.6)	0.369	-1.5	(-4.9, 1.8)	0.369[NS]
Nebivolol 10 mg	47	71,1	64.3	-6.8 (9.0)	-7.2 (2.5)	0.008	-4.8	(-8.1, -1.6)	0.004
Nebivolol 20 mg	45	75.9	68.0	-7.9 (8.8)	-5.9 (2.6)	0.009	-3.5	(-6.8, -0.2)	0.039
Nebivolol 40 mg	44	74.7	65.1	-9.6 (9.6)	-7.8 (2.6)	<0.001	-5.4	(-8.8, -2.1)	0.002

[a] From an ANCOVA with factor treatment and covariates baseline value, EM or PM classification, diabetes status, gender, and age group
[b] Step-down testing scheme begins with treatments placebo through Nebivolol 40 mg and proceeds to step-down until the trend test contains only placebo and Nebivolol 2.5 mg
[c] Based on pairwise comparison of Treatment vs. Placebo
NS: P-values associated with lower doses should not be used in the context of step-down trend testing (see analysis plan for explanation)
Cross Reference: Data Listings 1, 10.1.1-10.3.3, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.9.1, Integrated Summary of Efficacy, page 259)

At the end of study, responder rates were statistically significant for nebivolol 5 mg and above ($p < 0.002$ for nebivolol 5 mg and $p < 0.001$ for nebivolol 10 mg, 20 mg, and 40 mg), as shown in Table 37.

Table 37. Responder Rates[a] by Treatment (ITT LOCF) (NEB-202)

Treatment	Total N	Responder n (%)[b]	p-value[c]
Placebo	49	13 (26.5)	-
Nebivolol			
2.5 mg	49	18 (36.7)	0.287
5 mg	50	29 (58.0)	0.002
10 mg	51	30 (58.8)	<0.001
20 mg	50	32 (64.0)	<0.001
40 mg	51	29 (56.9)	<0.001

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Based on Wald Chi-Square Test for trend from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, and age group; Step-down testing scheme begins with treatments placebo through Nebivolol 40 mg and proceeds to step-down until the trend test contains only placebo and Nebivolol 2.5 mg
NS: P-values should not be used in the context of step-down trend testing (see analysis plan for explanation)
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3)

(Reproduced from Sponsor, NEB-202, Table 2.13.1, page 480)

I summarize the efficacy results for NEB-302, NEB-305, and NEB-202, according to diastolic and systolic parameters at peak and trough in Table 38 and Table 39. For actual p-values, please also see the individual tables for these parameters in the specific studies discussed earlier in this Integrated Review.

Table 38. Statistically Significant Nebivolol Doses According to Diastolic Blood Pressure Parameters at Trough and Peak in Studies NEB-302, 305, and 202

Nebivolol Dose	Study	Trough DBP			Peak DBP		
		Sitting	Standing	Supine	Sitting	Standing	Supine
1.25 mg	302	X	X	X	X	X	X
	305	---	---	---	---	---	---
	202	---	---	---	---	---	---
2.5 mg	302	X	X	X	X	X	X
	305	---	---	---	---	---	---
	202	NS	NS	NS	X	NS	X
5 mg	302	X	X	X	X	X	X
	305	X	X	X	X	X	X
	202	X	X	X	X	X	X
10 mg	302	X	X	X	X	X	X
	305	X	X	X	X	X	X
	202	X	X	X	X	X	X
20 mg	302	X	X	X	X	X	X
	305	X	X	X	X	X	X
	202	X	X	X	X	X	X
30/40 mg	302	Safety (X)	Safety (X)	Safety (X)	Safety (X)	Safety (X)	Safety (X)
	305	N/A	N/A	N/A	N/A	N/A	N/A
	202						
40 mg	302	Safety (X)	Safety (X)	Safety (X)	Safety (X)	Safety (X)	Safety (X)
	305	---	---	---	---	---	---
	202	X	X	X	X	X	X

NEB-202: Black Population only
X: Statistically significant
---: Not applicable (dose not studied)
NS: Not significant

(Adapted from Sponsor by Hicks K, Studies NEB-302, 305, and 202)

Table 39. Statistically Significant Nebivolol Doses According to Systolic Blood Pressure Parameters at Trough and Peak in Studies NEB-302, 305, and 202

Nebivolol Dose	Study	Trough SBP			Peak SBP		
		Sitting	Standing	Supine	Sitting	Standing	Supine
1.25 mg	302	X	X	X	X	NS	NS
	305	—	—	—	—	—	—
	202	—	—	—	—	—	—
2.5 mg	302	X	X	X	X	X	X
	305	—	—	—	—	—	—
	202	NS	NS	NS	NS	NS	NS
5 mg	302	X	X	X	X	X	X
	305	NS	NS	NS	NS	X	X
	202	NS	NS	NS	X	X	X
10 mg	302	X	X	X	X	X	X
	305	NS	NS	NS	X	X	X
	202	X	NS	NS	X	X	X
20 mg	302	X	X	X	X	X	X
	305	X	X	X	X	X	X
	202	X	NS	NS	X	X	X
30/40 mg	302	Safety (X)	Safety (X)	Safety (X)	Safety (X)	Safety (X)	Safety (X)
	305						
	202						
40 mg	302	Safety (X)	Safety (X)	Safety (X)	Safety (X)	Safety (X)	Safety (X)
	305	—	—	—	—	—	—
	202	X	X	NS	X	X	X

NEB-202: Black Population only
X: Statistically significant
—: Not applicable (dose not studied)
NS: Not significant

(Adapted from Sponsor by Hicks K, Studies NEB-302, 305, and 202)

For diastolic blood pressure parameters at trough, Blacks required higher doses of nebivolol for statistical efficacy, compared with the general hypertensive population. In NEB-302, comprised predominantly of Non-Blacks, nebivolol 1.25 mg through 40 mg significantly reduced sitting, standing, and supine diastolic blood pressure at trough from baseline to end of study. In NEB-202, comprised of Blacks only, nebivolol 5 mg and above was statistically significant in reducing sitting, standing, and supine diastolic blood pressure at trough.

For diastolic blood pressure parameters at peak, Blacks required higher doses of nebivolol for statistical efficacy, compared with the general hypertensive population. In NEB-302, nebivolol 1.25 mg through 40 mg significantly reduced sitting, standing, and supine diastolic blood pressure at peak. In NEB-202, nebivolol 2.5 mg and above significantly reduced diastolic blood pressure while sitting and supine, but nebivolol 5 mg was required to significantly reduce standing diastolic blood pressure at peak.

For systolic blood pressure parameters at trough, the general hypertensive population had inconsistent results in NEB-302 and NEB-305. In NEB-302, nebivolol 1.25 mg through 40 mg significantly reduced systolic blood pressure parameters at trough while in NEB-305, only nebivolol 20 mg was statistically significant. In NEB-202, nebivolol at doses of at least 10 mg were required to achieve efficacy for sitting systolic blood pressure at trough, but nebivolol 40 mg was required for significant efficacy in treating standing systolic blood pressure. No dose of nebivolol in NEB-202 was statistically significant in reducing supine systolic blood pressure at trough, suggesting that particular individuals in the Black population may be more resistant to nebivolol therapy and require higher or twice daily dosing.

For systolic blood pressure parameters at peak, nebivolol also appeared to be less effective in the Black population. In NEB-302, nebivolol 1.25 mg through 40 mg significantly reduced sitting systolic blood pressure at peak. In NEB-202, nebivolol 5 mg and above significantly reduced sitting systolic blood pressure at peak.

In summary, it appears Blacks require higher doses of nebivolol for efficacy in treating some systolic and diastolic parameters at peak and trough.

Sponsor's Analysis (Total Placebo-Controlled Population) (NEB-302, NEB-305, and NEB-202)

Although the Agency did not pool the three nebivolol monotherapy trials, the sponsor performed this pooled analysis and found all nebivolol doses to be significant for the primary efficacy endpoint, as shown in Table 40.

Table 40. Mean Change from Baseline to End of Teatment (Day 84) in Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment. Total Placebo-Controlled Population (NEB-302/NEB-305/NEB-202)

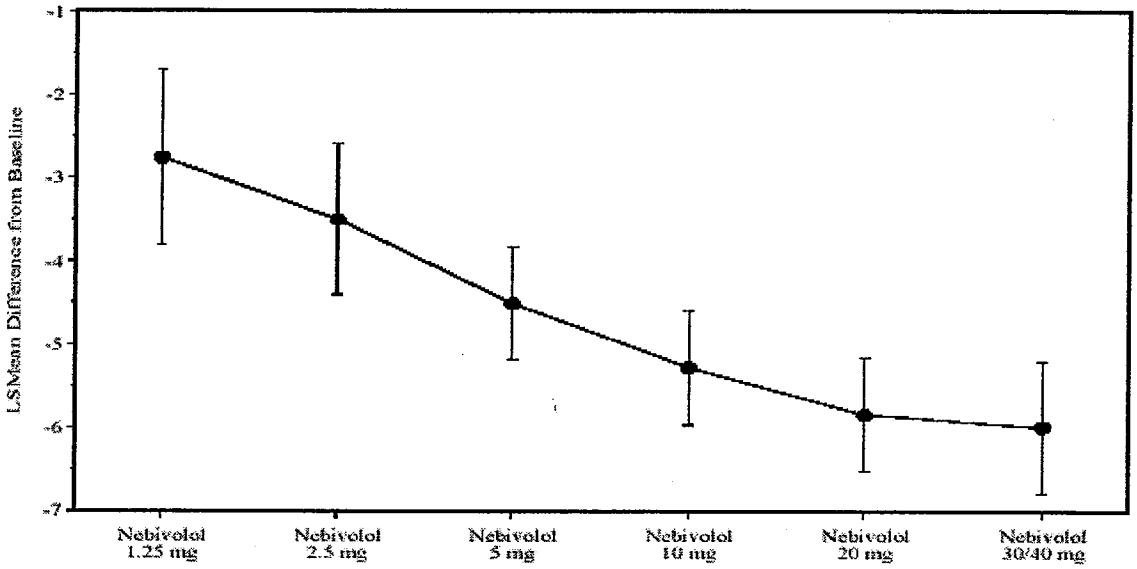
Treatment	N	Baseline Mean	Treatment Mean	Change From Baseline						
				Mean (SD)	LS Mean (SE)[a]	Step-Down p-value[a,b]	LS mean Diff[a,c]	95% C.I.[a,c]	p-value[a,c]	Step-Up p-value[a,b]
Placebo	205	99.8	94.9	-5.0 (8.3)	-4.4 (0.7)					<0.001
Nebivolol 1.25 mg	83	98.9	90.8	-8.0 (7.7)	-7.1 (1.0)	0.009	-2.8	(-4.8, -0.7)	0.009	<0.001
Nebivolol 2.5 mg	131	99.7	91.7	-8.0 (7.8)	-7.9 (0.8)	<0.001	-3.5	(-5.3, -1.7)	<0.001	<0.001
Nebivolol 5 mg	459	99.4	89.7	-9.7 (8.0)	-8.9 (0.6)	<0.001	-4.5	(-5.8, -3.2)	<0.001	0.016
Nebivolol 10 mg	461	99.3	88.9	-10.4 (8.2)	-9.7 (0.6)	<0.001	-5.3	(-6.6, -3.9)	<0.001	0.287
Nebivolol 20 mg	460	99.5	88.4	-11.1 (8.6)	-10.2 (0.6)	<0.001	-5.8	(-7.2, -4.5)	<0.001	0.822[NS]
Nebivolol 30/40 mg	217	99.1	88.4	-10.8 (8.1)	-10.4 (0.7)	<0.001	-6.0	(-7.5, -4.4)	<0.001	

[a] From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group
[b] Step-down testing scheme begins with treatments placebo through Nebivolol 30/40 mg and proceeds to step-up until the trend test contains only the 20 and 30/40 mg Nebivolol doses
[c] Based on pairwise comparison of Treatment vs. Placebo
NS: P-values associated with lower doses should not be used in the context of step-down trend testing; P-values associated with higher doses should not be used in the context of step-up trend testing
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.1.3, Integrated Summary of Efficacy, page 244)

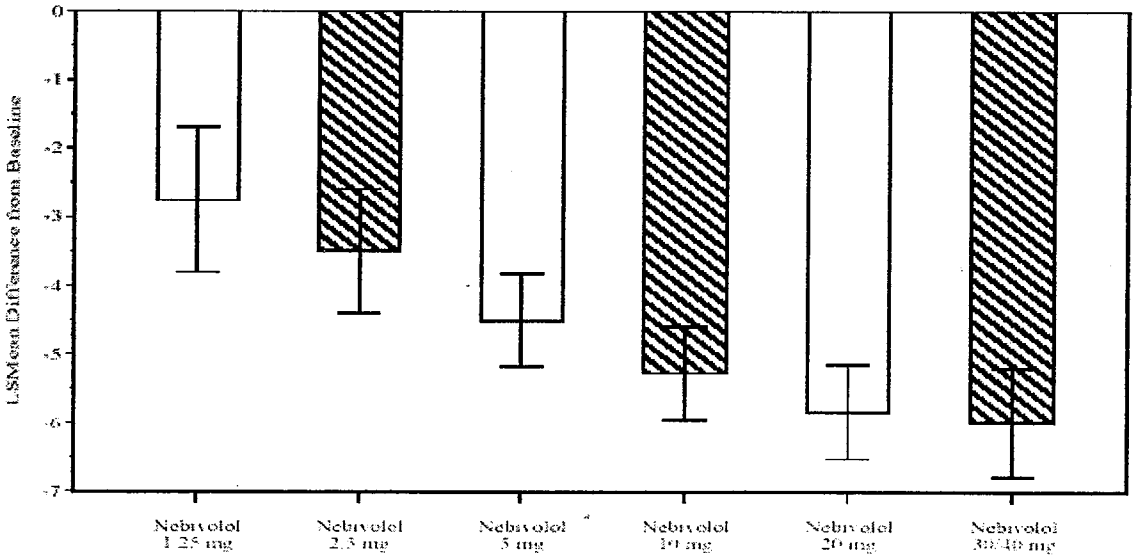
Graphically, the sponsor represents the changes in LS mean difference in trough sitting diastolic blood pressure in Figure 6 and Figure 7.

Figure 6. LS Mean Difference from Baseline to End of treatment (Day 84) in Trough Sitting Diastolic Blood pressure (mm Hg) by Treatment +/- S.E. (Total Placebo-Controlled Population) (NEB-302/NEB-305/NEB-202)



(Reproduced from Sponsor, Figure 1.29.1, Integrated Summary of Efficacy, page 469)

Figure 7. Bar Graph of LS Mean Difference from Baseline to End of Treatment (Day 84) in Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment +/- S.E. (Total Placebo-Controlled Population) (NEB-302/NEB-305/NEB-202)



(Reproduced from Sponsor, Figure 1.29.2, Integrated Summary of Efficacy, page 470)

Subgroup Analysis (NEB-302, NEB-305, and NEB-202)

Gender, Race, and Age

In these three pivotal studies, all subgroups experienced a decrease in sitting diastolic blood pressure at trough, as seen in Tables 42 through 44.

Table 41. Subgroup Analysis on Age, Gender, and Race (NEB-302)

	Placebo	Nebivolol 1.25 mg	Nebivolol 2.5 mg	Nebivolol 5 mg	Nebivolol 10 mg	Nebivolol 20 mg	Nebivolol 30/40 mg
AGE							
< 65							
N	64	65	68	132	125	134	128
LS mean[a]	-2.3	-8.1	-8.3	-8.3	-9.2	-9.6	-11.5
≥ 65							
N	17	18	14	33	41	32	38
LS mean[a]	-6.0	-7.9	-9.5	-9.4	-9.6	-10.8	-10.6
GENDER							
Male							
N	46	46	53	96	93	92	92
LS Mean[a]	-2.2	-7.1	-7.9	-8.1	-8.4	-9.3	-11.9
Female							
N	35	37	29	69	73	74	74
LS Mean[a]	-4.2	-9.2	-9.2	-8.9	-10.5	-10.6	-6.5
RACE							
Black							
N	11	12	13	23	23	25	25
LS mean[a]	-0.5	-10.5	-6.2	-6.7	-8.9	-4.3	-10.6
Non-Black							
N	70	71	69	142	143	141	141
LS mean[a]	-5.1	-9.3	-10.5	-10.4	-11.0	-12.5	-13.1

Data source: Table 2.16
[a] LS mean change in DBP from baseline to end of study

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 19 and Sponsor, NEB-302, Table 11.4-17, page 98)

Table 42. Subgroup Analysis on Age, Gender, and Race (NEB-305)

	Placebo	Nebivolol 5 mg	Nebivolol 10 mg	Nebivolol 20 mg
AGE				
< 65				
N	67	198	197	196
LS mean[a]	-3.9	-7.6	-8.1	-8.8
≥ 65				
N	8	45	47	47
LS mean[a]	-9.6	-9.9	-11.1	-11.8
GENDER				
Male				
N	39	130	131	131
LS Mean[a]	-5.7	-8.5	-9.5	-9.4
Female				
N	36	113	113	112
LS Mean[a]	-3.9	-7.5	-7.6	-9.3
RACE				
Black				
N	11	31	33	30
LS mean[a]	-5.3	-10.7	-8.2	-8.7
Non-Black				
N	64	212	211	213
LS mean[a]	-5.9	-8.9	-10.0	-10.8

[a] **LS mean change in DBP from baseline to end of study**

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 20 and Sponsor, NEB-305, Table 2.15, pages 538-543)

Table 43. Subgroup Analysis on Age and Gender (NEB-202)

	Placebo	Nebivolol 2.5 mg	Nebivolol 5	Nebivolol 10 mg	Nebivolol 20 mg	Nebivolol 40 mg
AGE						
< 65						
N	44	45	44	45	45	42
LS mean[a]	-4.0	-6.7	-7.8	-8.8	-9.3	-9.0
≥ 65						
N	5	4	6	6	5	9
LS mean[a]	1.9	3.5	-9.8	-13.0	-8.1	-8.9
GENDER						
Male						
N	23	26	22	22	21	22
LS Mean[a]	-1.7	-7.8	-10.9	-9.1	-9.7	-9.0
Female						
N	26	23	28	29	29	29
LS Mean[a]	-1.1	-1.1	-2.4	-6.2	-5.6	-5.4

[a] **LS mean change in DBP from baseline to end of study**

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 20 and Sponsor, NEB-202, Table 11.4.2.8.1-1, page 98)

BMI, Diabetes Status, and EM/PM Classification

For all subgroups in NEB-302, NEB-305, and NEB-202, there was a decrease in sitting diastolic blood pressure at end of study, compared with baseline, as seen in Tables 34 through 36. In NEB-305, diabetics in the placebo group had a greater reduction in sitting diastolic blood pressure, compared with all nebivolol treatment groups.

Table 44. Subgroup Analysis on BMI, Diabetes Status, and EM or PM Classification (NEB-302)

	Placebo	Nebivolol 1.25 mg	Nebivolol 2.5 mg	Nebivolol 5 mg	Nebivolol 10 mg	Nebivolol 20 mg	Nebivolol 30/40 mg
BMI							
< 30							
N	44	43	45	91	102	101	84
LS mean[a]	-5.0	-9.8	-9.6	-10.7	-11.0	-11.4	-13.8
≥ 30							
N	37	40	-37	74	64	65	82
LS mean[a]	-0.4	-5.8	-7.0	-5.6	-6.7	-7.7	-8.1
Diabetes							
Yes							
N	7	9	10	11	17	14	20
LS mean[a]	-4.9	-9.3	-14.7	-6.9	-10.7	-13.2	-10.9
No							
N	74	74	72	154	149	152	146
LS mean[a]	-2.1	-7.1	-7.0	-7.8	-8.4	-8.8	-10.7
EM/PM							
PM							
N	4	5	6	10	11	12	11
LS mean[a]	-2.7	-8.9	-12.8	-10.8	-13.6	-10.0	-11.0
EM							
N	77	78	76	155	155	154	155
LS mean[a]	-2.1	-7.1	-7.2	-7.4	-7.9	-8.8	-10.3

[a] **LS mean change in DBP from baseline to end of study**

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 21 and Sponsor, NEB-302, Table 11.4-18, page 99)

Table 45. Subgroup Analysis on BMI, Diabetes Status, and EM or PM Classification (NEB-305)

	Placebo	Nebivolol 5 mg	Nebivolol 10 mg	Nebivolol 20 mg
BMI				
< 30				
N	48	152	145	137
LS mean[a]	-4.4	-7.6	-8.3	-9.5
≥ 30				
N	27	91	99	106
LS mean[a]	-5.1	-9.0	-9.4	-9.4
Diabetes				
Yes				
N	4	9	12	12
LS Mean[a]	-11.8	-9.9	-7.7	-8.4
No				
N	71	234	232	231
LS Mean[a]	-4.9	-8.5	-9.3	-9.9
EM/PM				
PM				
N	4	15	15	16
LS mean[a]	-5.7	-9.8	-9.3	-10.8
EM				
N	71	228	229	227
LS mean[a]	-5.2	-8.4	-9.2	-9.7

[a] LS mean change in DBP from baseline to end of study

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 22 and Sponsor, NEB-305, Table 2.15, pages 544-549)

Table 46. Subgroup Analysis on BMI and Diabetes Status (NEB-202)

	Placebo	Nebivolol 2.5 mg	Nebivolol 5	Nebivolol 10 mg	Nebivolol 20 mg	Nebivolol 40 mg
BMI						
< 30						
N	21	26	26	26	25	20
LS mean[a]	-2.1	-8.3	-8.5	-8.0	-12.5	-9.0
≥ 30						
N	28	23	24	25	25	31
LS mean[a]	-4.4	-4.4	-8.2	-10.9	-6.2	-8.7
DIABETES						
Yes						
N	6	7	8	6	7	9
LS Mean[a]	-2.2	-7.1	-3.3	-6.6	-11.4	-9.9
No						
N	43	42	42	45	43	42
LS Mean[a]	-4.3	-6.7	-9.8	-10.5	-9.5	-9.4

[a] LS mean change in DBP from baseline to end of study

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 22 and Sponsor, NEB-202, Table 11.4.2.8.1-2, page 99)

Study NEB-203

NEB-203 was a Pilot, Phase II, double blind, randomized, multicenter, active-comparator, five treatment parallel group dose finding and mechanistic study in patients with mild to moderate hypertension. The primary focus of this study was to record preliminary data on exercise tolerance and to evaluate data collection methodology and dosing options for subsequent Phase III studies. The sponsor did not power NEB-203 to determine superiority of one treatment group over another, even between nebivolol groups. Study NEB-203 had two phases. Phase I consisted of screening, followed by washout/single-blind placebo run in (up to 42 days). Phase II consisted of randomization and double-blind treatment for 28 days. Patients were randomized to atenolol 50 mg, atenolol 100 mg, nebivolol 5 mg, nebivolol 10 mg, or nebivolol 20 mg.

Inclusion Criteria for Study NEB-203 (Reproduced from Sponsor, page 33)

- Signed informed consent
- Males or Females[17] age ≥ 18 years
- High probability for compliance and study completion
- Ability to perform sustained dynamic exercise on a cycle ergometer
- Ambulatory blood pressures as follows
  - At screening Visit 1, an average sitting DBP of ≥ 95 mm Hg and ≤ 109 mm Hg if not currently receiving antihypertensive treatment
  - At screening Visit 1, an average sitting DBP of ≥ 80 mm Hg and ≤ 109 mm Hg if currently receiving antihypertensive treatment
  - At screening Visit 1, patients currently receiving antihypertensive treatment with an average sitting DBP < 80 mm Hg were permitted to continue the screening process only if the adverse event (AE) profile of their current antihypertensive medication(s) warranted a change indrug treatment
  - At randomization, Visit 3, an average sitting DBP ≥ 95 mm Hg and ≤ 109 mm Hg.

Exclusion criteria, prohibited medication, and restricted medications were identical to those in NEB-302. For NSAIDs in NEB-203, however, use could not exceed 2 consecutive days, compared with 5 days for NEB-302. Additionally, SSRIs in NEB-203 were prohibited unless the patient was on a stable dose for at least 2 months prior to Visit 1, compared with 3 months for NEB-302.

The primary endpoint was the percent change in sub-maximal exercise duration by cycle ergometer at peak at end of treatment compared with baseline. The primary analysis was ITT OC, because peak submaximal exercise duration had only one scheduled post-baseline measurement.

In NEB-203, there were 254 patients screened with 227 patients entering the single-blind phase and 115 patients randomized (24 atenolol 50 mg, 21 atenolol 100 mg, 23 nebivolol 5 mg, 23 nebivolol 10 mg, and 24 nebivolol 20 mg). A total of 7 patients withdrew from the study, including 6 patients (28.6%) in the atenolol 100 mg group and 1 patient (4.3%) in the nebivolol

[17]**Women could not be pregnant or nursing. Women of childbearing potential were required to use appropriate contraception to participate in this study.**

10 mg group. Of the 6 patients in the atenolol 100 mg group who withdrew, 3 withdrew consent, 2 were lost to follow-up, and 1 was withdrawn due to "other." The withdrawal in the nebivolol 10 mg group was due to the adverse event of a myocardial infarction.

The numbers of subjects completing the study through Day 28 was 69/70 (98.6%) for nebivolol and 39/45 (86.7%) for atenolol. The sponsor stated the number of patients completing the study was not the same as the number of patients completing the end-of-study submaximal ETTs. Of the patients randomized to nebivolol, 4% (1/23) and 9% (2/23) in the nebivolol 5 mg and 10 mg treatment groups, respectively, did not perform the final submaximal ETT. All patients in the nebivolol 20 mg treatment group completed the final submaximal ETT. Of the patients randomized to atenolol, 4% (1/23) and 38% (8/21) in the atenolol 50 mg and 100 mg treatment groups, respectively, did not perform the final submaximal ETT. The results of the final submaximal ETT are shown in Table 47. By the end of the study, patients randomized to atenolol 50 mg and 100 mg treatment groups increased their exercise duration by 3.7% and 9.2%, respectively. Patients taking nebivolol 5 mg increased their exercise duration by 7.1%, while patients taking nebivolol 10 mg and 20 mg decreased their exercise duration by 10.4% and 8.9%, respectively.

Table 47. Mean Percent Change From Baseline to End of Study (Day 28) in Peak Sub-Maximal Exercise Duration (min) by Treatment: Primary Analysis (ITT OC Population) (NEB-203)

Treatments	N[a]	Baseline Mean	Treatment Mean	Percent Change From Baseline		Comparisons
				Mean (SD)	LS Mean (SE)[b]	
Atenolol						Atenolol vs. Nebivolol
50mg	23	10.8	10.5	4.3 (36.6)	3.7 (6.2)	(-23.0, 2.0)[c]
100mg	13	12.0	12.6	8.2 (33.4)	9.2 (8.2)	0.098[b]
Nebivolol						Nebivolol Comparison[d]
5mg	22	11.0	12.3	7.4 (30.5)	7.1 (6.3)	5mg vs. 20mg: 0.072
10mg	21	10.5	9.4	-9.3 (15.8)	-10.4 (6.5)	5mg vs. 10mg: 0.056[e]
20mg	24	12.2	10.8	-10.1 (29.7)	-8.9 (6.1)	10mg vs. 20mg: 0.866[e]

Data Source: Table 2.2.1
[a]Missing data were not imputed; therefore, the numbers reported are not expected to match the number of patients who completed the trial
[b]From an ANCOVA with factors treatment and covariate baseline value
[c]95% C.I. and p-value from the contrast of nebivolol vs. atenolol
[d] P-value is not applicable due to previous non-significant result in hierarchical testing scheme

(Reproduced from Sponsor, Table 11.4.1.1.1-1, page 74)

A total of 43/115 (37.4%) of patients had major protocol violations in NEB-203.

Responder rates for nebivolol 5 mg, 10 mg, and 20 mg ranged from 52.2% to 79.2%. Responder rates for atenolol 50 mg and 100 mg were 70.8% and 52.6%, respectively. There was no statistically significant difference in response rates between pooled nebivolol and pooled atenolol groups, according to the sponsor's analysis presented in Table 48.

Table 48. Responder Rates by Treatment (ITT LOCF Population) (NEB-203)

Treatments	Total n	Responder[a] N (%)[b]	Atenolol vs. Nebivolol[c,d]	Nebivolol Comparisons[c]
Atenolol				
50mg	24	17 (70.8)	0.161	5mg vs. 20mg: 0.058
100mg	19	10 (52.6)		5 mg vs. 10mg: 0.015[e]
Nebivolol				10mg vs. 20mg: 0.468[e]
5mg	23	12 (52.2)		
10mg	23	20 (87.0)		
20mg	24	19 (79.2)		

Data Source: Table 2.12.1
[a]A subject is a responder if their average trough sitting DBP <90 mmHg at end of study or has decreased by ≥10 mmHg from baseline
[b]Percentage is the percentage of responders within that category
[c]Based on the Wald Chi-Square Test for trend form logistic regression with factor treatment and covariate baseline sitting DBP
[d]P-value from the contrast of nebivolol vs. atenolol
[e] P-value is not applicable due to previous non-significant result in hierarchical testing scheme

(Reproduced from Sponsor, Table 11.4.1.2.3.5-1, page 94)

Conclusions (NEB-203)

Although there were a significant number of protocol violations in Study NEB-203 and 38% of patients in the atenolol 100 mg group did not complete the final sub-maximal ETT, patients in the atenolol 50 mg, atenolol 100 mg, and nebivolol 5 mg treatment groups increased exercise duration by 3.7%, 9.2%, and 7.1%, respectively. Patients in the nebivolol 10 mg and nebivolol 20 mg treatment groups, however, decreased exercise duration by 10.4% and 8.9%. I recommend additional studies in hypertensive patients to more thoroughly evaluate nebivolol's effect on exercise tolerance.

Study NEB-321

This was a Phase III, double-blind, 12-week multi-center, randomized, placebo-controlled, parallel group study. The study had two phases. Phase I consisted of screening, followed by a 14 ± 3 day washout period of prior beta blockade, if required. Phase II consisted of baseline measurements, randomization, and double-blind treatment. Prior to randomization, patients underwent a medical history, physical examination, measurement of vital signs while supine, sitting, and standing, 12 lead ECGs, laboratory assessments, and genomics testing. Randomized to receive placebo or nebivolol 5, 10, or 20 mg once daily for 84 days, patients were stratified in all treatment arms by race, age, gender, diabetes status, metabolism of nebivolol, and use/non-use of an angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and diuretic. Following randomization on Day 1, there were three follow-up visits during Week 2 (14 ± 3 days), Week 6 (42 ± 5 days), and Week 12 (84 ± 7 days).

The inclusion criteria were slightly different from those used for NEB-302, NEB-305, and NEB-202.

Inclusion Criteria for Study NEB-321 (Reproduced from Sponsor, page 28)[18]

- signed informed consent
- age ≥ 18 years
- postmenopausal, surgically sterile, or agreed to use effective method of birth control
- **ambulatory and taking at least one antihypertensive medication (excluding prohibited medications) and no more than two antihypertensive medications including either ACE inhibitor, ARB, or diuretic**
- **mild to moderate hypertension, at screening and baseline defined as sitting DBP ≥ 90 mm Hg and ≤ 109 mm Hg; measured in the office using a sphygmomanometer**
- if taking beta-blocker at screening, a washout period of 14 ± 3 days before randomization was required
- high probability for compliance and completion of the study

Exclusion criteria were similar to those for NEB-302, except secondary hypertension was not an exclusion criterion for NEB-321. Additionally, patients enrolled in NEB-321 could not perform alternating shift or night work.

The primary efficacy endpoint was the change from baseline (Day 1) to Week 12 (Day 84) Visit in sitting diastolic blood pressure taken at trough (24 ± 3 hours post-previous morning's dose). The primary analysis was ITT with LOCF.

There were 1,171 patients screened with 669 patients randomized at 80 sites. A total of 669 patients comprised the ITT population (167 placebo, 168 nebivolol 5 mg, 168 nebivolol 10 mg, and 166 nebivolol 20 mg). The numbers of subjects completing the study through Day 84 was 452/502 (90.0 %) randomized to nebivolol and 146/167 (87.4 %) randomized to placebo. Seven patients (1.0%) who did not meet inclusion criteria were randomized, because there was a misclassification of their medications at screening. The medical monitor allowed these patients to remain in the study, although these patients were excluded from the PP population.

All nebivolol doses significantly reduced sitting trough diastolic blood pressure in a dose-dependent fashion from baseline to end of study, as shown in Table 49.

[18]**Bolded inclusion criteria represent the changes from NEB-302, NEB-305, and NEB-202.**

Table 49. Change from Baseline to Week 12 in Sitting DBP at Trough (ITT LOCF) (Study NEB-321)

Treatment	N	Baseline Mean (SD) (mm Hg)	Week 12 Treatment Mean (SD) (mm Hg)	Mean Change from Baseline (SD)	LS Mean Change from Baseline (SE)[a]	Hochberg's Adjusted p-value[a,b]	LS mean Difference (95% CI)[a,c]
Placebo	167	96.4 (4.57)	92.5 (9.04)	-3.9 (8.86)	-3.3 (1.04)		
Nebivolol							
5 mg	168	96.4 (4.55)	89.3 (9.66)	-7.1 (8.95)	-6.6 (1.04)	< 0.001	-3.3 (-5.2, -1.5)
10 mg	168	95.8 (5.07)	88.6 (9.39)	-7.2 (9.08)	-6.8 (1.05)	< 0.001	-3.5 (-5.4, -1.7)
20 mg	166	96.5 (5.22)	87.8 (9.24)	-8.6 (8.30)	-7.9 (1.06)	< 0.001	-4.6 (-6.5, -2.8)

Source: Table 7.1.
Baseline=Last value prior to dosing on Day 1. SD=Standard Deviation. SE=Standard Error.
[a] **From an ANCOVA model with treatment, race, age, gender, diabetes status, predicted nebivolol metabolism, use of ACE inhibitors, use of ARBs, use of diuretics as factors, and baseline measurement as a covariate.**
[b] **Level of significance: $p \leq 0.05$; p-values obtained from the pairwise comparisons between each of the 3 nebivolol dose groups and placebo were adjusted as described in Section 9.7.1.3.1.**
[c] **LS mean difference from pairwise comparison of nebivolol treatment vs. placebo.**
(Reproduced from Sponsor, Table 11-1, page 58)

I summarized the results for the secondary endpoints in Table 50 and Table 51.

Table 50. Summary of Results of LS Mean Change in DBP, SBP, and HR from Baseline to End of Study (Day 84) at Trough (ITT LOCF) (Study NEB-321)

	Sitting			Standing			Supine		
Treatment	p-value[a,b]	LS Mean Change from Baseline[a]	LS Mean Difference[a,c]	p-value[a,b]	LS Mean Change from Baseline[a]	LS Mean Difference[a,c]	p-value[a,b]	LS Mean Change from Baseline[a]	LS Mean Difference[a,c]
Placebo									
DBP	-	-3.3	-	-	-3.0	-	-	-2.3	-
SBP	-	-0.1	-	-	-2.1	-	-	0.7	-
HR	-	-3.0	-	-	-3.5	-	-	-2.9	-
Nebivolol 5 mg									
DBP	< 0.001	-6.6	-3.3	< 0.001	-6.6	-3.6	< 0.001	-5.8	-3.5
SBP	< 0.001	-5.7	-5.7	0.045	-5.8	-3.7	0.003	-4.2	-4.9
HR	< 0.001	-7.3	-4.3	<0.001	-8.6	-5.2	< 0.001	-6.8	-3.9
Nebivolol 10 mg									
DBP	< 0.001	-6.8	-3.5	< 0.001	-6.5	-3.5	< 0.001	-5.8	-3.5
SBP	0.015	-3.7	-3.7	0.176	-4.3	-2.2	0.055	-2.1	-2.9
HR	< 0.001	-7.6	-4.6	< 0.001	-8.5	-5.0	< 0.001	-7.1	-4.2
Nebivolol 20 mg									
DBP	< 0.001	-7.9	-4.6	< 0.001	-7.5	-4.6	< 0.001	-6.4	-4.2
SBP	< 0.001	-6.3	-6.2	0.005	-7.2	-5.1	0.005	-3.8	-4.5
HR	< 0.001	-10.6	-7.6	<0.001	-11.5	-8.0	< 0.001	-9.6	-6.7

Source: Table 7.1, 10.1, 11.1, 12.1, 14.1, 16.1, 18.1, 20.1, 22.1, 24.1
Baseline=Last value prior to dosing on Day 1. SD-Standard Deviation. SE=Standard Error.
[a] From an ANCOVA model with treatment, race, age, gender, diabetes status, nebivolol metabolism, use of ACE inhibitors, use of ARBs, use of diuretics as factors, and baseline measurement as a covariate.
[b] Level of significance: $p \leq 0.05$; p-values obtained from the pairwise comparisons between each of the 3 nebivolol dose groups and placebo were placed in ascending order and adjusted as described in Section 9.7.1.3.1.
[c] LS mean difference from pairwise comparison of nebivolol treatment vs. placebo (95% Confidence Interval)

p-value is Hochberg's adjusted p-value
(Compiled by Hicks K)

Table 51. Summary of Results of LS Mean Change in DBP, SBP, and HR from Baseline to End of Study (Day 84) at Peak (ITT LOCF) (Study NEB-321)

	Sitting			Standing			Supine		
Treatment	p-value[a,b]	LS Mean Change from Baseline[a]	LS Mean Difference[a,c]	p-value[a,b]	LS Mean Change from Baseline[a]	LS Mean Difference[a,c]	p-value[a,b]	LS Mean Change from Baseline[a]	LS Mean Difference[a,c]
Placebo									
DBP	-	-9.3	-	-	-8.6	-	-	-9.1	-
SBP	-	-7.4	-	-	-7.2	-	-	-6.5	-
HR	-	-0.4	-		-0.3		-	-0.7	-
Nebivolol 5 mg									
DBP	< 0.001	-12.5	-3.2	< 0.001	-12.1	-3.5	< 0.001	-12.5	-3.4
SBP	< 0.001	-13.1	-5.7	0.003	-12.3	-5.1	< 0.001	-11.7	-5.2
HR	< 0.001	-6.8	-6.4	< 0.001	-7.6	-7.3	< 0.001	-6.7	-6.0
Nebivolol 10 mg									
DBP	< 0.001	-13.3	-4.0	< 0.001	-12.5	-3.9	< 0.001	-12.6	-3.6
SBP	< 0.001	-13.0	-5.6	0.006	-11.6	-4.4	< 0.001	-11.4	-4.9
HR	< 0.001	-8.0	-7.6	< 0.001	-8.4	-8.1	< 0.001	-7.1	-6.4
Nebivolol 20 mg									
DBP	< 0.001	-13.6	-4.3	0.001	-11.7	-3.1	< 0.001	-12.2	-3.2
SBP	< 0.001	-13.3	-5.9	0.002	-12.7	-5.5	< 0.001	-12.4	-5.9
HR	< 0.001	-10.3	-9.9	< 0.001	-10.8	-10.5	< 0.001	-9.2	-8.5

Source: Table 9.1, 11.1, 13.1, 21.1, 23.1, 15.1, 17.1, 25.1
Baseline=Last value prior to dosing on Day 1. SD-Standard Deviation. SE=Standard Error.
[a] From an ANCOVA model with treatment, race, age, gender, diabetes status, nebivolol metabolism, use of ACE inhibitors, use of ARBs, use of diuretics as factors, and baseline measurement as a covariate.
[b] Level of significance: $p \leq 0.05$; p-values obtained from the pairwise comparisons between each of the 3 nebivolol dose groups and placebo were placed in ascending order and adjusted as described in Section 9.7.1.3.1.
[c] LS mean difference from pairwise comparison of nebivolol treatment vs. placebo (95% Confidence Interval)

p-value is Hochberg's adjusted p-value
(Compiled by Hicks K)

The response rate was dose-dependent and ranged from 53.0% to 65.1% in the nebivolol treatment groups, as shown in Table 52.

Table 52. Percent of Patients with a Reduction in Sitting Diastolic Blood Pressure to < 90 mm Hg at Day 84 or a Reduction of at least 10 mm Hg from Baseline to Day 84 (ITT LOCF) (Study NEB-321)

Responder	Placebo (N=167)	Nebivolol 5 mg (N=168)	Nebivolol 10 mg (N=168)	Nebivolol 20 mg (N=166)	Total (N=669)
Yes	69 (41.3%)	89 (53.0%)	101 (60.1%)	108 (65.1%)	367 (54.9%)
No	98 (58.7%)	79 (47.0%)	67 (39.9%)	58 (34.9%)	302 (45.1%)
Total Observed	167 (100%)	168 (100%)	168 (100%)	166 (100%)	669 (100%)
p-value (a) (Hochberg adjusted)		0.028	0.001	< 0.001	
p-value (a) (Unadjusted)		0.028	< 0.001	< 0.001	

(a) From logistic regression analysis for multiple pairwise comparisons of Nebivolol vs. Placebo with treatment, race, age, gender, history of diabetes, nebivolol metabolism, use of ACE inhibitors, use of angiotensin receptor blockers, use of diuretics, and baseline measurement as independent variables in the model and reduction or no reduction in Sitting Diastolic Blood Pressure taken at trough.

(Reproduced from Sponsor, Table 28.1, page 267)

Conclusions (NEB-321)

Compared to placebo, nebivolol 5, 10, and 20 mg doses significantly reduced trough sitting DBP and SBP in patients on background antihypertensive therapy. Nebivolol 10 mg did not significantly reduce supine and standing SBP at trough.

Study NEB-306

This was a Phase III double-blind, multicenter, parallel group, 9-month extension study with an optional 4 week randomized withdrawal phase. In response to discussions with the FDA on October 9, 2002,[19] Mylan added the 4 week follow-up phase to assess rebound effects from the abrupt withdrawal of nebivolol. The 9-month extension study did not include a control group. Only the 4 week follow-up phase was double-blind and placebo-controlled, and patients were randomized in a 2:1 fashion to placebo or nebivolol 5, 10, or 20 mg.

In the 9-month extension phase, patients received one of four possible treatments based on the average sitting heart rate and diastolic blood pressure measured at the study visit and the therapy they were already receiving. After the investigator recorded this data in the TeleTrial® system, Teletrial® instructed the investigator to assign adjunct therapy, if necessary, according to a detailed algorithm.

The four possible treatments were

- nebivolol once daily monotherapy (5 mg, 10 mg, or 20 mg)
- nebivolol once daily (5 mg, 10 mg, or 20 mg) plus Level 1 adjunct therapy
- nebivolol once daily (5 mg, 10 mg, or 20 mg) plus Level 2 adjunct therapy
- nebivolol once daily (5 mg, 10 mg, or 20 mg) plus another antihypertensive medication ("other")[20]

[19] **Information provided by the sponsor on page 29 of the protocol.**

[20] **The "other" category consisted of patients receiving nebivolol in conjunction with an antihypertensive in a different class other than a diuretic or calcium channel blocker. Similarly, patients in the "other" category**

There were 5 visits during the extension phase, including Visit E1 (Day 0), Visit E2 (Day 28), Visit E3 (Day 91), Visit E4 (Day 182), and Visit E5 (Day 273, end of Extension Phase). The study permitted titration of nebivolol during Visit E2 through E4. At study Visit E2 and study Visits E3 and E4, Level 1 and Level 2 adjunct therapy was allowed, respectively. As shown in Table 161, adjunctive therapy consisted of the open-label use of the following medications:

Table 53. Adjunctive Therapy (NEB-306)

Open-Label Application	Therapeutic Classification
According to the Original Protocol	
Level 1 = thiazide/thiazide-like diuretic without triamterene	Diuretic
Level 2 = thiazide/thiazide-like diuretic combination product with triamterene	Potassium-sparing diuretic
According to Amendment 1	
Level 1 = amlodipine 5 mg	Calcium channel blocker
Level 2 = amlodipine 10 mg	Calcium channel blocker

(Reproduced from Sponsor, Table 9.4.2-2, page 39)

Patients who received adjunctive antihypertensive therapy in the 9-month extension phase could not participate in the randomized withdrawal phase.

In the randomized withdrawal phase (4-week follow-up period), there were 4 study visits on Days 0, 7, 14, and 28.

Inclusion criteria were similar to those already described for NEB-302. Additionally, patients could enter NEB-306 only if they had successfully completed NEB-202, NEB-302, and NEB-305. For the 4-week randomized withdrawal study, there was a separate consent form, and patients could enter this study only if they received nebivolol monotherapy (5 mg, 10 mg, or 20 mg) in the 9-month extension phase.

Exclusion criteria were identical to those for NEB-302 with the following exceptions:

- NEB-306 excluded patients with a BMI > 40 kg/m^2, compared to a BMI > 35 kg/m^2 in NEB-302.
- NEB-306 did not exclude patients with diabetes and a HbA1c $\geq$ 10%, compared with NEB-302, NEB-305, and NEB-202.
- NEB-306 did not exclude patients with prior exposure to nebivolol for the treatment of hypertension in NEB-202, NEB-302, or NEB-305
- The NEB-306 randomized withdrawal phase excluded patients from the 9-month extension study who received adjunctive therapy.

Out of 2,016 ITT patients from the feeder studies, 845 patients entered the 9-month extension phase. NEB-302, NEB-305, and NEB-202 enrolled 129, 366, and 350 patients, respectively. By the end of the extension phase or at early termination, there were 607, 206, 21, and 11 patients receiving nebivolol, nebivolol + diuretic, nebivolol + calcium channel blocker (CCB), and

could also be on nebivolol plus adjunct therapy in addition to an additional antihypertensive medication which could be a diuretic, calcium channel blocker or other type of antihypertensive.

nebivolol + "other" regimen, respectively. The number of subjects completing the study through Day 273 was 393/845 (46.5%), including 268/607 (44.2%) nebivolol, 110/206 (53.4%) nebivolol + diuretic, 7/21 (33.3%) nebivolol + CCB, and 8/11 (72.7%) nebivolol + other patients.

Although 268 patients on nebivolol monotherapy were eligible for the 4-week randomized withdrawal study, fewer patients enrolled. Reasons for reduced enrollment in Study NEB-306 included many of the investigative sites choosing not to participate, patients already completing the extension phase prior to the approval of Amendment 1 which added the follow-up phase, or the sponsor terminating the study early so the results could be included in the NDA dossier. After exclusion of patients for the above reasons, 56 patients were eligible for the 4-week randomized withdrawal trial, and 28 patients enrolled and completed the follow-up phase. In a 2:1 randomization, 18 patients received placebo and 10 patients received nebivolol. Of the 10 patients receiving nebivolol, 5, 4, and 1 patient(s) received nebivolol 5 mg, 10 mg, and 20 mg, respectively.

9-Month Extension Phase (NEB-306)

The primary efficacy results for the ITT OC Population in the 9-month extension phase are shown in Table 54.

Table 54. Mean Change From Baseline in Sitting Diastolic Blood Pressure (mm Hg) at Trough by Treatment (ITT OC) (9-Month Extension Phase) (Study NEB-306)

Treatment by Visit[a]	N	Baseline Mean[b]	Treatment Mean	Change From Baseline		
				Mean	SE	95% CI
Day 273 (Visit E5)						
Nebivolol	266	97.8	82.8	-15.0	0.4	(-15.9, -14.1)
Nebivolol + Diuretic	125	100.2	88.3	-12.0	0.6	(-13.2, -10.8)
Nebivolol + CCB[c]	7	102.0	95.3	-6.7	4.3	(-17.1, 3.7)
Nebivolol + Other	9	99.0	84.3	-14.7	3.1	(-21.8, -7.6)

Data source: Table 2.1.1
[a]See Table 9.7.1.5-1 for the relative day ranges for each visit.
[b]Baseline represents the baseline in the feeder study (NEB-202, NEB-302, or NEB-305)
[c]CCB = Calcium channel blocker

(Reproduced from Sponsor, Table 11.4.1.1.1-1, page 68)

There were numerous secondary endpoints for the 9-month extension phase, and I describe these results in the Appendix.

The responder rates by treatment for the 9-month extension study are described in Table 55. Nebivolol + calcium channel blocker had the lowest responder rate (40.0%), according to the sponsor's analysis.

Table 55. Responder[a] Rates by Treatment--Primary Method (ITT OC) (9-Month Extension Phase) (Study NEB-306)

Treatment[b]	Total	Responders[a]	
		N	(%)
Nebivolol	583	456	(78.2)
Nebivolol + Diuretic	206	135	(65.5)
Nebivolol + CCB[c]	20	8	(40.0)
Nebivolol + Other	11	8	(72.7)
Total	820	607	(74.0)

Data Source: Table 2.13.1.1
[a] A responder was defined as a patient whose average trough sitting diastolic blood pressure was < 90 mm Hg at the end of the study or had decreased ≥ 10 mm Hg from baseline of the feeder study.
[b] Treatment classification was based on the treatment being received at the end of the study
[c] CCB=Calcium Channel Blocker

(Reproduced from Sponsor, Table 11.4.1.1.2.4-1, page 78)

4-Week Follow-Up Phase (Randomized Withdrawal Study) (NEB-306)

A total of 28 patients participated in the 4-week follow-up phase, including (18) placebo, (5) nebivolol 5 mg, (4) nebivolol 10 mg, and (1) nebivolol 20 mg patients. In the patients assigned to placebo, the change in mean sitting diastolic blood pressure at trough from the last visit of the extension phase through the 4-week follow-up phase was 3.1, 3.8, and 4.4 mm Hg on Days 7, 14, and 28, respectively. According to the sponsor, at Day 28, the sitting diastolic blood pressure at trough was -11.4 mm Hg (95% Confidence Interval: -14.5, -8.3), which was markedly below the value at baseline of the feeder studies. For sitting diastolic blood pressure at trough, Table 56 shows the change from baseline for the placebo and combined nebivolol treatment groups in the 4-week follow-up phase.

Table 56. Sitting Diastolic Blood Pressure at Trough (Raw Mean Change-from-Baseline During Follow-Up) (4-Week Follow-Up Phase) (NEB-306)

Follow-up Day	Name	Placebo	(All) Nebivolol Groups Combined
	N	18	10
	Mean (SE)	-16 (1.27)	-15 (1.87)
Day 7	N	18	10
	Mean (SE)	-13 (1.37)	-17 (1.92)
Day 14	N	18	10
	Mean (SE)	-12 (1.22)	-16 (2.43)
Day 28	N	18	10
	Mean (SE)	-11 (1.47)	-14 (2.54)

(Reproduced from Sponsor, Table 7.1, page 464)

Similarly, from the end of the extension phase to Days 7, 14, and 28 of the follow-up study, the mean sitting systolic blood pressure at trough in the placebo patients increased by 5.2, 4.3, and 7.4 mm, respectively. At Day 28, the sitting systolic blood pressure at trough for the placebo patients was -15.8 (95% Confidence Interval: -21.3, -10.2), which was below the baseline value of the feeder studies, according to the sponsor's analysis. Table 57 shows the change in sitting

systolic blood pressure at trough for the placebo and combined nebivolol treatment in the 4-week follow-up phase.

Table 57. Sitting SBP at Trough (Raw Mean Change-from-Baseline During Follow-Up) (NEB-306)

Follow-up Day	Name	Placebo	(All) Nebivolol Groups Combined
	N	18	10
	Mean (SE)	-21 (3.64)	-18 (4.68)
Day 7	N	18	10
	Mean (SE)	-17 (2.90)	-19 (4.14)
Day 14	N	18	10
	Mean (SE)	-17 (3.51)	-21 (4.81)
Day 28	N	18	10
	Mean (SE)	-16 (2.63)	-21 (5.75)

(Reproduced from Sponsor, Table 7.2, page 465)

Table 58 shows responder rates by treatment for the ITT Follow-up Population using the primary method and the baseline from the feeder study.

Table 58. Responder[a] Rates by Treatment–Primary Method (Population: Intent-to-Treat Follow-Up) (NEB-306)

Parameter Treatment	Total[b] n	Responder[a] n (%)
Placebo	18	13 (72.2%)
Nebivolol 5 mg	5	4 (80.0%)
Nebivolol 10 mg	4	2 (50.0%)
Nebivolol 20 mg	1	1 (100.0%)
Total	28	20 (71.4%)

(a) A responder is defined as a patient whose average trough sitting diastolic blood pressure < 90 mm Hg at end of study (last non-missing post-baseline visit) or has decreased by ≥ 10 mm Hg from baseline of feeder study
(b) Includes only patients with non-missing results
Cross Reference: NEB-306 Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, and Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, 10.3.1-10.3.3 in NEB-302, NEB-305, or NEB-202

(Reproduced from Sponsor, Table 2.13.1.2, page 434)

Although only a small number of patients participated in the randomized withdrawal study, the placebo response rate of 72.2% suggests nebivolol did not cause rebound hypertension. Nebivolol 10 mg had the lowest response rate at 50.0%, while Nebivolol 20 mg had the highest response rate at 100.0%.

Conclusions (NEB-306)

Nebivolol monotherapy significantly decreased sitting diastolic (-15.0 mm Hg) and systolic blood pressure (-14.8 mm Hg) at trough from baseline to end to treatment in the 9-month extension phase. For sitting diastolic and systolic blood pressure at trough, the nebivolol + calcium channel blocker treatment group appeared to be least effective. In the 4-week follow-up phase, abrupt withdrawal of nebivolol did not cause rebound hypertension.

Good Clinical Practice Issues (GCP) for Pivotal Trials

There were GCP issues associated with various sites, but for the pivotal studies, the sponsor examined results for the primary endpoint before and after excluding potential GCP violators. By the sponsor's analyses, the results did not change. In the Appendix under each pivotal study, I discuss the details of potential GCP violators.

The preliminary results of the Agency's inspections include the following findings:

- Dr. Graff (NEB-321, Site 635) did not always follow protocol, as visits, vital signs, and dosing were outside the study window for some patients. One patient with asthma was enrolled despite meeting exclusion criteria.
- Dr. Lasseter (NEB-305, Site 118) did not always sign physical examinations, and it was unclear to the Food and Drug Administration who was conducting the physical examinations.
- Dr. Herron (NEB-202, Site 323) did not follow protocol in that the screening blood pressure for two subjects was outside entry criteria.

According to the Agency, the above findings did not seem to affect data integrity.

The Agency inspection for Dr. — (NEB-302 and NEB-306, Site 223) was delayed because he claimed his office was closed. Prior to the NDA, the Agency received a complaint from the sponsor about Dr. —. The sponsor terminated Dr. — for inadequate record-keeping during IND 33,060. The Agency intiated the inspection in August 2004 and found inadequate records, with two versions of progress notes available for each subject. One set of records reported adverse events, and the other set of records stated the subject did not have any adverse events. Approximately 8-10 patients were enrolled despite meeting exclusion criteria for chronic obstructive pulmonary disease (COPD). For these patients, many of these records were rewritten to remove the diagnosis of COPD. Effective July 5, 2004, Dr. — had his New York State medical license suspended for 12 months, with the last 10 months stayed. Dr. — was to be under probation for the subsequent 3 years. Because of all of these issues, the Agency considers data from Dr. — site unreliable.

Bertek Pharmaceuticals, Inc. also reported sites 145 (Dr. Robertson) and 233 (Drs. Winter and Bailey) to the Agency for studies 302 and 306. The Agency inspected both sites. The FDA also inspected Site 263 (Dr. Kaladas NEB-305 and NEB-306). In Dr. Kaladas' case, the Agency did not take any action, because the enrollment of patients failing to meet inclusion criteria did not occur while he was the principal investigator. The sponsor excluded Dr. Kaladas' data because the FDA found foreign tablets in study drug bottles returned by 3 subjects. These tablets were probably related to a research study conducted at the site one year prior.

6.1.5 Clinical Microbiology

Not applicable. Nebivolol is not an antimicrobial.

6.1.6 Efficacy Conclusions

Nebivolol reduced sitting diastolic blood pressure at trough in both Blacks and Non-Blacks. For some primary and secondary endpoints at peak and trough, Blacks required higher doses of

nebivolol for significant efficacy. In NEB-305, diabetics receiving placebo experienced a greater reduction in sitting diastolic blood pressure than all nebivolol treatment groups.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Below, I summarize the safety findings for NEB-122. Please see Dr. Salma Lemtouni's review for a summary of the safety findings from the pivotal studies.

NEB-122 was a randomized, open, placebo- and active-controlled, parallel-group safety evaluation of electrocardiographic intervals and blood pressure in normal healthy volunteers. The study planned for 260 subjects, randomized 285 subjects, and administered at least one dose of study drug to 281 subjects. Of these 281 subjects, 72 subjects received nebivolol 20/40 mg, 69 subjects received atenolol 100/200 mg, 69 subjects received moxifloxacin 400 mg, and 71 subjects received placebo daily for seven days. A total of 269 subjects received all 7 days of scheduled treatment, including 71 subjects in the nebivolol group, 61 subjects in the atenolol group, 68 subjects in the moxifloxacin group, and 69 subjects in the placebo group. There were three poor metabolizers in both the nebivolol and atenolol groups. For subjects in the nebivolol 20/40 mg and atenolol 100/200 mg groups, subjects received the lower dose for three days and were only escalated to the higher dose if the heart rate (HR) was greater than 51 and the PR interval was < 220 msec on Day 4. In the nebivolol group, 65/72 subjects (90.3%) increased their dose from 20 mg to 40 mg. In the atenolol group, 60/69 (87.0%) subjects increased their dose from 100 mg to 200 mg.

The primary endpoint was the change in the average QTc interval from Day 0 to 2 hours after dosing on Day 7. The sponsor calculated QTc using three methods, including the population correction factor (0.329), Bazett's Formula, and Fridericia's Formula. The secondary endpoint was the change in average QTc intervals from Day 0 to all other evaluation times and change in other ECG intervals (PR, RR, QRS, QT) and HR from Day 0 to all other evaluation times.

In NEB-122, continuous 24-hour 12-lead ECG records were obtained on Days 0, 1, 4, and 7 of dose administration. The central laboratory measured at least three consecutive ECG intervals from single 12-lead tracings. These 12-lead tracings, as well as blood samples for PK, were obtained prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 10, 12, 14, 16, 18, and 24 hours post dosing. Additionally, standard 12-lead ECGs were performed on Day 0 and every 12 hours on Days 1 through 7. On Day 4, the atenolol and nebivolol subjects were on telemetry for two hours prior to dosing to determine if they met dose escalation criteria (heart rate > 51 bpm and PR interval < 220 msec). There were a total of 4231 time points evaluated in the nebivolol group and 4,071 time points evaluated in the placebo group.

Subjects underwent laboratory testing, consisting of a SMA 18 chemistry panel, complete blood count with differential white blood cell count and platelet count, and urinalysis during screening (days -14 to -2) and at study exit.