CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-742

MEDICAL REVIEW

10/11/07

Request for Consultation dated July 31, 2007

Responses to Questions from Cardio-Renal

In regard to: Nebivolol Tablets
NDA 21-742

From: Harry Handelsman, DO, Medical Officer, DRUP
Suresh Kaul, M.D., M.P.H, Acting Medical Team Leader, DRUP
Mark S. Hirsch, MD, Acting Deputy Director, DRUP

Date: October 11, 2007

1. Specific Instructions to the Consultant

"We received the results of NEB-PK-03, entitled 'Effects of Nebivolol on Adrenal Function, Luteinizing Hormone, and Testosterone Levels in Healthy Male Volunteers'. (We) have had the opportunity to review the study and have written a draft review, but (we) would also appreciate your consultative input...The questions to you include:

1) Do you find the methods of hormone sampling in this study to be acceptable and the results to be reliable?

2) Does the significant number of drop-outs in this study make the results uninterpretable?

3) For mean total testosterone levels, there was a large standard deviation in all treatment groups and wide confidence intervals for least square mean differences in both drug treatments groups. Do these large and wide intervals suggest that these T levels (and assay) are inaccurate and unreliable?

4) In the nebivolol treatment group, there was an increase in mean total and free T levels at Day 56. Could these increases become clinically significant over a longer period of time, and could there be clinically meaningful effects on the breast or testicles?

5) Do you agree with the sponsor's conclusions that nebivolol and atenolol did not demonstrate any significant changes in gonadal function? Do you think that nebivolol at the 10 mg dose is unlikely to cause effects on gonadal function with long-term use?

6) Based on the results of NEB-PK-03, do you think the findings in the preclinical toxicokinetic study in male mice are species specific and not relevant to humans?"

2. Regulatory History

The Division of Cardio-Renal Drug Products requests another consultation for nebivolol, a beta-blocker. The regulatory history for this product includes the following:

On May 31, 2005, NDA 21-742 for Nevibolol Tablets received an "Approvable" action. The "Approvable" deficiency was:

> *"A highly statistically significant and dose-related increase in benign and malignant Leydig cell tumors was observed in male mice. The findings appear with exposure only several times the clinically attained blood levels. This effect may be endocrinologically mediated. Other possibly endocrinologically mediated effects were also seen in long-term toxicology studies of rats – reductions in adrenal and ovary weights, dystocia, and interference with cyclicity. If an endocrine mechanism can be established and if this mechanism is not relevant; e.g., because it is not active at clinical doses, the mouse findings may not be of concern. It will therefore be necessary for you to establish the mechanism by which nebivolol is responsible for these findings and demonstrate that these findings are not relevant in humans."*

Reference is made to the original DRUP consult from Drs. Handelsman, Hirsch and Shames dated February 4, 2005 and an Endocrine consult from Drs. Stadel and Orloff dated January 31, 2005. Further reference is made to the Sponsor's End-of-Review Meeting Brochure dated February 10, 2006 and official minutes of that April 21, 2006, meeting.

As stated in our original consult, and in agreement with Drs. Stadel and Orloff, there appear to be 7 mechanisms described in the literature for the development of LCTs in rodents. Two of these are considered to be not relevant to humans (GnRH and dopamine agonism). Five are potentially clinically relevant. These are:

1. Estrogen receptor agonism.
2. Androgen receptor antagonism.
3. Inhibition of testosterone biosynthesis.
4. Inhibition of 5-alpha-reductase activity.
5. Inhibition of aromatase activity.

In their meeting package of February 10, 2006, the Sponsor stated that preclinical studies had already established the mechanism of LCTs in mice for nebivolol to be increases in serum LH (GnRH agonism), a mechanism not relevant to humans. During the April 21, 2006, End-of-Review meeting, the Agency voiced concerns that the data was not yet adequate to draw this conclusion. To fully address the concern about LCTs, the Agency recommended an additional preclinical study and an additional clinical study. The preclinical study would be designed to demonstrate the functional role of LH, by showing reduction in serum LH and decrease in LCTs with "add-back" of dihydrotestosterone (DHT). The human study would be designed to demonstrate the lack of clinically

relevant mechanism; of most importance: that nebivolol does not reduce serum total testosterone in healthy adult males.

The protocol for a "DHT add-back" mouse study was submitted on May 8, 2006. DRUP participated in an internal meeting with the Cardio-Renal Division on May 17, 2006 to discuss and provide comments on that mouse protocol. Comments for the mouse protocol were then conveyed to the Sponsor by Cardio-Renal on May 25, 2006.

On May 26, 2006, the Sponsor submitted a new clinical protocol (NEB-PK-03) designed to assess the direct effects of nebivolol on adrenal function, luteinizing hormone, and total testosterone in healthy men. Cardio-Renal Division requested specific consultation from DRUP on this protocol on June 7, 2006 and we provide responses to 7 specific questions on June 9, 2006. Study NEB-PK-03 was conducted from September 6, 2006 to February 28, 2007.

On May 31, 2007, the Sponsor submitted a Complete Response to Approvable, including the results of the requested preclinical and clinical studies. On July 31, 2007, Cardio-Renal requested consultative input from DRUP on the results of NEB-PK-03 and our responses to the 6 specific questions above.

3. Brief Overview of NEB-PK-03

Study NEB-PK-03 was a randomized, double-blind, placebo- and active-controlled parallel-group study in approximately 120 healthy male subjects ages 18 to 50 years comparing nebivolol to placebo for the primary endpoint of area under the curve (AUC) from time zero to 120 minutes of ACTH-stimulated serum cortisol levels on Day 56. The study consisted of one week of single-blind, matching-placebo run-in, then one week of double-blind, "low-dose" treatment (nebivolol 5 mg/day or atenolol 50 mg/day or placebo), followed by six weeks of double-blind, "high-dose" treatment (nebivolol 10 mg/day or atenolol 100 mg/day or placebo).

One of the secondary pharmacodynamic endpoints was the mean serum level of total testosterone (ng/dL) on Day 56. Samples for total testosterone were collected on Days 1 and 7 of single-blind placebo treatment, and during double-blind treatment on Day 56. The comparison of nebivolol to placebo for serum total testosterone was analyzed using an Analysis of Covariance (ANCOVA) model. This analysis was the based on the ITT population, defined as all subjects who had data for Days 1, 7, and 56.

Additional endpoints included free testosterone levels (calculated from total testosterone and SHBG levels. If the primary and secondary endpoints required additional explanation, sufficient plasma/serum samples were taken on Days 7 and 56 and frozen for possible measurements of estradiol, dihydrotestosterone, prolactin, and follicle-stimulating hormone.

A total of 596 subjects were screened and 157 subjects were randomized to double-blind treatment, including 55 subjects to nebivolol, 50 subjects to atenolol, and 52 subjects to placebo. Table 1 shows the subject disposition.

Table 1. Sponsor's Analysis: Number (%) of Subjects Discontinued from the Study--Randomized Population (NEB-PK-03)

	Placebo (N=52) n (%)	*Atenolol (N=50) n (%)*	*Nebivolol (N=55) n (%)*	*Total (N=157) n (%)*
Completed study	48 (92.3)	29 (58.0)	42 (76.4)	119 (75.8)
Withdrawn from study	4 (7.7)	21 (42.0)	13 (23.6)	38 (24.2)
Reason for withdrawal				
Other	3[a] (5.8)	15[b] (30.0)	8[c] (14.5)	26 (16.6)
Protocol violation	1 (1.9)	4 (8.0)	2 (3.6)	7 (4.5)
Adverse event	0	2 (4.0)	2 (3.6)	4 (2.5)
Consent withdrawn	0	0	1 (1.8)	1 (0.6)
Lost to follow-up	0	0	0	0

a Three subjects were withdrawn because of protocol-specified safety criteria: 2 subjects because of low blood pressure (1 systolic and 1 diastolic) outside protocol parameters, and 1 subject because of low pulse rate outside protocol parameters.

b One subject was withdrawn because of Investigator's discretion. The remaining 14 subjects in this group were withdrawn because of protocol-specified safety criteria: 8 subjects because of low blood pressure outside protocol parameters (5 diastolic, 1 systolic and diastolic, and 2 unspecified) and 6 subjects because of low pulse rate outside protocol parameters.

c Eight subjects were withdrawn because of protocol-specified safety criteria: 4 subjects were withdrawn because of low blood pressure outside protocol parameters (1 diastolic, 2 systolic, and 1 systolic and diastolic) and 4 subjects were withdrawn because of low pulse rate outside protocol parameters.

Cross-reference: Tables 14.1.3 and 14.1.4.

The effects of nebivolol, atenolol, and placebo on mean luteinizing hormone and mean total testosterone at Day 56 are shown in Tables 2 and 3, respectively. At Day 56, nevibolol and atenolol did not significantly affect serum LH (Table 2), while nebivolol increased and atenolol decreased mean total testosterone in a nonsignificant fashion (Table 3).

Table 2. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Luteinizing Hormone Levels at Day 56--Intent-to-Treat Population (NEB-PK-03)

Luteinizing hormone levels, IU/L	Placebo (N=48)	Atenolol (N=29)	Nebivolol (N=42)
Mean (SD)			
Day 7 (baseline)	4.40 (1.386)	4.29 (1.513)	4.72 (1.828)
Day 56	4.52 (1.428)	4.31 (1.352)	4.76 (1.965)
LSM[a] (SE)	4.24 (0.31)	4.09 (0.34)	4.32 (0.29)
LSMD[a,b] (90% CI)	—	-0.15 (-0.63, 0.34)	0.08 (-0.36, 0.52)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.

b Active minus placebo (expressed as IU/L).

N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 56; LSM = least squares mean; LSMD = least squares mean differences.

Cross-reference: Table 14.4.2.1.

(Reproduced from Sponsor, Clinical Study Report, Table 11.1.1.2.1-1, page 76 of 5947)

Table 3. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Total Testosterone Levels at Day 56--ITT Population (NEB-PK-03)

Total testosterone levels, ng/dL	Placebo (N=48)	Atenolol (N=29)	Nebivolol (N=42)
Mean (SD)			
Day 7 (baseline)	551.9 (138.59)	542.6 (125.50)	561.7 (156.21)
Day 56	549.0 (130.51)	516.1 (173.88)	588.4 (167.08)
LSM[a] (SE)	578.92 (25.71)	553.06 (28.13)	606.00 (23.78)
LSMD[a,b] (90% CI)	—	-25.85 (-66.31, 14.61)	27.08 (-9.41, 63.58)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.

b Active minus placebo (expressed as ng/dL).

N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 56; LSM = least squares mean; LSMD = least squares mean differences.

Cross-reference: Table 14.4.2.2.

(Reproduced from Sponsor, Clinical Study Report, Table 11.1.1.2.2-1, page 77 of 5947)

Table 4, as derived from Dr. Sonia Castillo's statistical review, presents the unadjusted change from baseline in total testosterone level (ng/dL) for each treatment group. The placebo group had a 2.9 ng/dL mean decrease from baseline (-0.53% change) compared to a 26.6 ng/dL mean increase from baseline (4.52% change) for the nebivolol group. Neither treatment group had a significantly different change from baseline (p-value>0.10).

Table 4
Study NEB-PK-03: Change from Baseline in Total Testosterone Level (ng/dL) for the ITT Population* by Treatment Group

	Day 56 (s.e.)	Baseline (s.e.)	Change from Baseline (s.e.)	Percent Change from Baseline	p-value
Placebo (n=48)	549.0 (18.8)	551.9 (20.0)	-2.9 (14.3)	-0.53%	0.841
Nebivolol (n=42)	588.4 (25.8)	561.7 (24.1)	26.6 (16.5)	4.52%	0.114

Source: Statistical Reviewer's calculations based on dataset D_PD.xpt, which is located in the EDR at \\Cdsesub1\N21742\N_000\2007-04-27\N21742\crt\datasets\neb-pk-03.
* ITT Population includes all subjects who had data for Days 1, 7 and 56.

Dr. Castillo also conducted an analysis of the adjusted change from baseline in total serum testosterone for nebivolol versus placebo. In that adjusted analysis, the placebo group has a 37ng/dL increase from baseline while the nevibolol group had a 63ng/dL increase from baseline. The adjusted mean difference between groups was 26ng/dL and was not significant.

According to Dr. Castillo, no patient in any treatment group showed a serum testosterone value in the hypogonadal range; that is $\leq$ 350ng/dL.

Finally, Dr. Castillo was asked to perform analyses of the dataset in order to determine if the study was adequate to detect a clinically meaningful difference between nebivolol and placebo in the change from baseline for serum total testosterone. Dr. Castillo used two methods for this analysis: first, she assessed the power needed to detect varying changes from baseline for nebivolol compared to placebo while holding the change-from-baseline in serum total T for placebo as constant (Table 5, as derived from Dr. Castillo's review). Second, she assessed the sample size needed to detect a significant difference between groups for varying changes-from-baseline while holding the change-from-baseline in serum total T for placebo as constant (Table 6, as derived from Dr. Castillo's review).

These analysis demonstrate that the study had 99% power to detect a reduction in total testosterone of 20% or greater in serum total T in the nebivolol group compared to the placebo group. Further, only 16 subjects per group were required to detect a 20% or greater reduction in serum total T in the nebivolol group compared to the placebo group. From a clinical perspective, therefore, the study was adequately powered to detect a clinically meaningful difference between groups, and such was not detected.

Table 5
Study NEB-PK-03: Power for Varying Changes from Baseline in Total Testosterone Level (ng/dL) for Nebivolol Compared to Placebo While Holding the Change from Baseline in Total Testosterone Level (ng/dL) for Placebo Constant*

Percent Change from baseline for Nebivolol group	-90%	-80%	-70%	-60%	-50%	-40%	-30%	-20%	-10%	-4.52%
Change from baseline for Nebivolol group	-505.53	-449.36	-393.19	-337.02	-280.85	-224.68	-168.51	-112.34	-56.17	-26.64
Power (%)	***99***	***99***	***99***	***99***	***99***	***99***	***99***	***99***	***78***	***28***
Percent Change from baseline for Nebivolol group	4.52%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Change from baseline for Nebivolol group	26.64	56.17	112.34	168.51	224.68	280.85	337.02	393.19	449.36	505.53
Power (%)	***38***	***84***	***99***	***99***	***99***	***99***	***99***	***99***	***99***	***99***

Source: Statistical Reviewer's calculations.
* Assumptions used are as follow: Nebivolol baseline total testosterone level = 561.7, standard deviation for Nebivolol change from baseline = 106.873, Nebivolol n = 42, Change from baseline for Placebo = -2.895, standard deviation for Placebo change from baseline = 99.323, Placebo n = 48, unequal variances, 1-sided t-test, α-level 0.05

Table 6
Study NEB-PK-03: Sample Size Needed to Detect a Significant Difference for Varying Changes from Baseline in Total Testosterone Level (ng/dL) for Nebivolol Compared to Placebo While Holding the Change from Baseline in Total Testosterone Level (ng/dL) for Placebo Constant*

Percent Change from baseline for Nebivolol group	-90%	-80%	-70%	-60%	-50%	-40%	-30%	-20%	-10%	-4.52%
Change from baseline for Nebivolol group	-505.53	-449.36	-393.19	-337.02	-280.85	-224.68	-168.51	-112.34	-56.17	-26.64
N per group	***3***	***3***	***3***	***3***	***4***	***5***	***8***	***16***	***65***	***325***
Percent Change from baseline for Nebivolol group	4.52%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Change from baseline for Nebivolol group	26.64	56.17	112.34	168.51	224.68	280.85	337.02	393.19	449.36	505.53
N per group	***210***	***53***	***15***	***8***	***5***	***4***	***3***	***3***	***3***	***3***

Source: Statistical Reviewer's calculations.
* Assumptions used are as follow: Nebivolol baseline total testosterone level = 561.7, standard deviation for Nebivolol change from baseline = 106.873, Change from baseline for Placebo = -2.895, standard deviation for Placebo change from baseline = 99.323, unequal variances, 1-sided t-test, α-level 0.05, power=90%

Finally, the Office of Clinical Pharmacology (Dr. Yanning Wang) was asked to conduct pharmacokinetic/pharamacodynamic analyses of the data for all 9 endpoints. The objective of this analysis was to determine if any factor that would increase serum nebivolol concentrations would have an impact on the endocrine results, including serum LH and serum total T. Dr. Wang's analysis, which included results from poor metabolizers of cytochrome P450 26, showed that the results of NEB-PK-03 "does not support the observation from animal data suggesting suppression of male hormone by nebivolol".

4. Responses to the Questions from Cardio-Renal

1) Do you find the methods of hormone sampling in this study to be acceptable and the results to be reliable?

Response: The flow chart of procedures and determinations appears to be acceptable. Assuming that the hormone assays were validated and reliable, then the results are likely to be reliable.

2) Does the significant number of drop-outs in this study make the results uninterpretable?

Response: The number of drop-outs in the nebivolol group was 26 %, versus 40 % for atenolol and 8 % for placebo. The reasons for the drop-outs are well documented. While disposition of the study population obviously needs to be considered, our colleagues in clinical pharmacology and statistics have provided support for the interpretability of the results despite drop-outs.

3) For mean total testosterone levels, there was a large standard deviation in all treatment groups and wide confidence intervals for least square mean differences in both drug treatments groups. Do these large and wide intervals suggest that these T levels (and assay) are inaccurate and unreliable?

Response: Wide confidence intervals in serum T levels are common and can be regarded as being expected.

4) In the nebivolol treatment group, there was an increase in mean total and free T levels at Day 56. Could these increases become clinically significant over a longer period of time, and could there be clinically meaningful effects on the breast or testicles?

Response: The approximately 8 % increase in T levels at end of study does not approach a level of concern. Other agents have been approved with greater increases (dutasteride; up to 18 %) and known clinical problems have not materialized. The only expected AE related to breast or testicles would be breast tenderness and/or gynecomastia, and according to Dr. Hicks, such events were not reported in the nebivolol clinical studies.

5) Do you agree with the sponsor's conclusions that nebivolol and atenolol did not demonstrate any significant changes in gonadal function? Do you think that nebivolol at the 10 mg dose is unlikely to cause effects on gonadal function with long-term use?

Response: We agree that nevibolol did not demonstrate significant changes in serum LH or serum T. Without data from long-term studies, significant effects or lack of effects on gonadal function remain conjectural.

6) Based on the results of NEB-PK-03, do you think the findings in the preclinical toxicokinetic study in male mice are species specific and not relevant to humans?

Response: In our opinion, the results from the human study show no effect on serum LH or serum T in normal healthy men. This finding, coupled with the results from the additional mechanistic study in rodents showing an LH-mediated mechanism, lend support to the assertion that the preclinical results of Leydig cell tumors are not relevant to humans.

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/s/

Harry Handelsman
10/11/2007 01:52:03 PM
MEDICAL OFFICER

Mark S. Hirsch
10/11/2007 02:00:30 PM
MEDICAL OFFICER
I concur.

Suresh Kaul
10/11/2007 02:34:25 PM
MEDICAL OFFICER

10/10/07

CLINICAL CONSULTATION

FROM: Valerie S. W. Pratt, MD, Medical Officer
Division of Metabolism and Endocrinology Products (DMEP), HFD-510

THROUGH: Mary H. Parks, MD, Acting Director, DMEP

TO: Karen A. Hicks, MD, Medical Officer, Cardio-Renal, HFD-110
Melissa Robb, Project Manager, Cardio-Renal, HFD-110

SUBJECT: Endocrine Assessment of the Effects of Nebivolol on Adrenal Function, Luteinizing Hormone, and Testosterone Levels in Healthy Male Volunteers (NEB-PK-03)

DATE CONSULT RECEIVED: July 31, 2007

DATE CONSULT COMPLETED: October 1, 2007

MATERIAL RECEIVED FOR REVIEW: Cardio-renal clinical consult (July 31, 2007); NEB-PK-03 (May 18, 2007) and associated Mylan Bertek Pharmaceuticals Inc. cover letter (May 30, 2007); Form FDA 1571 for IND 33,060 (May 26, 2006); Cardio-Renal Draft Review of NDA 21,742 (July 31, 2007); Previous DMEP Clinical Consults of Nebivolol (February 23, 2006 and May 31, 2006)

ADMINISTRATIVE BACKGROUND

The Cardio-Renal Division previously consulted DMEP on February 23, 2006 to seek advice regarding potential endocrinologic effects (Leydig cell tumors in mice and adrenal suppression in humans) of nebivolol, a new ß1 receptor antagonist that has been developed for the management of hypertension. This consult was completed on March 6, 2006 and our recommendations were discussed with the sponsor at the April 21, 2006 end of review meeting. A second DMEP consult was placed May 31, 2006 to regarding Protocol NEB-PK-03 "Effect of Nebivolol on Adrenal Function, Luteinizing Hormone, and Testoserone Levels in Healthy Male Volunteers." This consult was completed June 7, 2006.

REQUESTED ACTION OF DMEP

Cardio-Renal has asked the following questions:

1. Do you find the methods of hormone sampling in this study to be acceptable and the results to be reliable?
2. Do the significant number of drop-outs in this study make the results uninterpretable?
3. What do you make of the peak ACTH stimulated aldosterone level < 5 ng/dl above basal level on Day 57 in 4 placebo, 2 atenolol, and 3 nebivolol subjects? On Day 8 (baseline), there were 2 placebo, 1 atenolol, and 3 nebivolol subjects who had an

abnormal ACTH stimulated aldosterone level. Post-study, only 1 subject in the placebo group and 1 subject in the nebivolol group still had a peak ACTH-stimulated aldosterone level < 5 ng/dl above unstimulated basal aldosterone level.
4. Do you agree with the sponsor's conclusions that nebivolol and atenolol did not demonstrate any significant changes in adrenal function? Do you think nebivolol is unlikely to cause adrenal insufficiency with long-term use at the 10 mg dose?
5. Do you feel that the population size was sufficient to capture the effects of nebivolol on the adrenal?

BACKGROUND

Beta-adrenergic receptors exist in the adrenal, ovary, testes, pituitary, hypothalamus, and uterus, among other organs. Therefore, beta-blockers could potentially alter levels of hormones produced by these glands.

Nebivolol, a racemic mixture of d- and l-isomers, is a selective ß1-receptor antagonist that has been developed for the treatment of ——— hypertension (proposed dosing range 2.5 – 10 mg; although some patients could potentially receive up to 20 mg twice daily off-label). Nebivolol is currently marketed in other countries for the management of hypertension and for the treatment of ischemic heart disease and heart failure. The sponsor, Mylan Bertek Pharmaceuticals, submitted a new drug application (NDA) for nebivolol to the Cardio-Renal Division on April 30, 2004 to gain approval for marketing nebivolol in the United States. On May 31, 2005, the Agency granted an "approvable" action letter, raising concerns about potential adverse endocrinologic and reproductive effects of nebivolol that were identified in the non-clinical studies. The Agency recommended that the Sponsor conduct a further study.

Mylan Bertek Pharmaceuticals Inc. designed NEB-PK-03 to address these possible endocrine safety issues. DMEP reviewed the protocol and offered comments regarding the study design in the consult dated July 31, 2007.

Protocol NEB-PK-03: Effect of Nebivolol on Adrenal Function, Luteinizing Hormone, and Testosterone Levels in Healthy Male Volunteers

Objectives: To evaluate the effects of nebivolol 10 mg on adrenal function, luteinizing hormone (LH) levels, and total testosterone levels in healthy males.

Study Design: This was a randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers aged 18 to 50 years. This study consisted of one week of single-blind matching-placebo run-in, followed by one week of double-blind low-dose treatment (nebivolol 5 mg/d, atenolol 50 mg/d, or placebo), followed by six weeks of double-blind high-dose treatment (nebivolol 10 mg/d, atenolol 100 mg/d, or placebo).

Population: Randomized population 157. Safety population 157. Intent-to-treat population 119.

Main Inclusion Criteria:

- Signed an informed consent.
- Been a healthy man, 18 to 50 years of age.
- Had normal vital sign values, physical examination findings, serum chemistry results, hematology findings, and urinalysis results; and had negative test results for anti-human inmmunodeficiency virus types 1 and 2, hepatitis B surface antigen, anti-hepatitis C virus antibody, and rapid plasma reagin.
- Been a nonsmoker (having never smoked or not smoked within the prior year).
- Had a body mass index in the range 18.0 to 29.9 kg/m^2.
- Had a sitting pulse rate of not greater than 100 bpm or not less than 60 bpm by vital sign assessment (average of triplicate readings).
- Demonstrated normal results on an adrenocorticotropic hormone (ACTH)-stimulation test, defined as a stimulated cortisol level 19 µg/dL or greater on Day 1.
- Demonstrated normal gonadal function, defined as a total testosterone level of 350 ng/mL or greater on Day 1.

Exclusion Criteria:

- Known hypersensitivity to nebivolol, other β-blocking agents, ACTH-stimulation test, or any excipient in the investigational formulations
- Significant history of cardiovascular, hepatic, endocrine, renal, pulmonary, hematologic, gastrointestinal, urologic (including infertility), immunologic, dermatologic, or neurologic disease
- Known hereditary endocrine dysfunction in family
- History of asthma, hyperglycemia, hypoglycemia, or abnormal glucose tolerance testing
- History of cancer (other than nonmelanoma skin cancer) or testicular mass
- Clinically significant disease state in any body system, in the opinion of the examining physician
- After a 5-minute resting period, an average sitting systolic blood pressure (SBP) greater than 140 mm Hg or less than 105 mm Hg or a sitting diastolic blood pressure (DBP) greater than 90 mm Hg or less than 65 mm Hg at Screening or on Day -1. Triplicate readings were taken to calculate the average. Note: Subjects with blood pressure equal to 140/90 mm Hg were also excluded.
- Clinically significant ECG abnormalities, including a PR interval greater than or equal to 200 ms or less than equal to 100 ms, QT prolongation (QT or QTc $\geq$ 430 ms), sick sinus syndrome, a second- or third-degree atrioventricular block, any type of tachycardia, greater than one PVC on a 12-lead ECG, incomplete left-bundle branch block or complete left- or right-bundle branch block, nonsinus rhythm, or evidence of myocardial ischemia/infarction (acute or during past six months)
- History of alcohol or substance abuse within the prior five years
- Positive test results for drugs of abuse (including alcohol) or cotinine

- Recent (within one month) significant changes in diet or exercise habits
- Consumption of caffeine- or xanthine-containing foods or beverages or of any grapefruit-containing products within 48 hours or alcohol within 72 hours before the start of the study (Day 1)
- Unwillingness to adhere to a standard diet with no added sodium (limited to 4 g/d) throughout the duration of the study or unwillingness to abstain from alcohol, caffeine- and xanthine-containing foods and beverages, and grapefruit-containing juices or foods throughout the duration of the study
- Unwillingness to forgo strenuous or rigorous exercise activities for the duration of the study
- Sexually active and unwilling to use an approved form of birth control while in the study
- Any clinical condition that might affect the absorption, distribution, biotransformation, or exertion of nebivolol or atenolol
- Taken within 14 days before Day 1, any medications, including prescription medications, prescription eye drops, over-the-counter medications, vitamins, nutritional supplements, or herbal remedies. Subjects may have agreed to abstain from taking medications including, nonsteroidal anti-inflammatory drugs, vitamins, nutritional supplements, and herbal remedies throughout the duration of the study, except as medically necessary
- Taken within 60 days before Day 1 any hormone treatment or steroid therapy, including topical steroids, and ophthalmic steroid drops.
- Previously taken nebivolol or prior participation in a study of nebivolol
- Participation in any other clinical investigation using an experimental drug requiring repeated blood draws within 30 days of the start of the study or participation in a blood donation program within the prior 60 days
- Employment by, or family members, employed by, the clinical research organization at which the study was conducted
- Employment as a shift worker or lifestyle that may have affected diurnal hormonal pattern
- Demonstration of adrenal insufficiency, defined as subjects who failed to have at least one post-ACTH-stimulation cortisol level of 19 µg/dL or greater on Day 1
- Hypogonadal, defined as subjects who had a total testosterone level of less than 350 ng/dL on Day 1.

COMMENT: The inclusion and exclusion criteria appear appropriate.

Study Medication: Subjects received a nebivolol-matching placebo tablet plus an atenolol-matching placebo capsule daily during the one-week, single-blind placebo run-in (Days 1 through 7).

At the end of the lead-in period, all subjects who continued to meet the entrance criteria were randomized in a 1:1:1 manner to one of three double-blind treatment sequences (Table 1) within each CYP2D6 phenotype stratum. Extensive metabolizers (EMs) and poor metabolizers (PMs) were randomized to each of the treatment groups through stratification. All study drugs were administered orally as a single daily dose.

Table 1. Dosage Treatment Sequences (Reproduced from the Sponsor, Study NEG-PK-03, Table 9.4.1-1., page 32 of 5947)

Treatment Sequence	*Description*	
	Days 8 Through 14	*Days 15 Through 56*
A	Nebivolol 5-mg tablet + atenolol-matching placebo capsule	Nebivolol 10-mg tablet + atenolol-matching placebo capsule
B	Nebivolol-matching placebo tablet + atenolol 50-mg capsule	Nebivolol-matching placebo tablet + encapsulated atenolol (two 50-mg) capsule
C	Nebivolol-matching placebo tablet + atenolol-matching placebo capsule	Nebivolol-matching placebo tablet + atenolol-matching placebo capsule

Daily dosing in the clinic occurred on Days 1 – 9. On Days 9, 16, 25, and 43, double-blind study medication was dispensed for at-home dosing on Days 10 – 14, 17 – 24, 26 – 42, and 44 – 50. Assuming all doses were well tolerated, the maximum duration of the subjects' participation in the study was 58 days.

COMMENT: The selected nebivolol dose, duration, and placebo- and positive-control are in agreement with the Division's recommendations.

Efficacy Measures

Primary Efficacy: The primary pharmacodynamic end point was the area under the curve ($AUC_{0\text{-}120\ min}$) of ACTH-stimulated (IV dose of 250 µg) serum cortisol levels at the End of Study (EOS) (i.e. Day 57). The $AUC_{0\text{-}120\ min}$ was calculated using the trapezoidal rule based on the pre- and post-ACTH stimulation cortisol levels at 0 hour (pre-ACTH injection), 0.5, 1.0, 1.5, and 2 hours post-ACTH injection.

Secondary Efficacy Endpoints: Secondary pharmacodynamic end points were the mean levels of three basal LH measurements on Day 56 (20 minutes apart as scheduled) and mean serum testosterone on Day 56.

Additional pharmacodynamic end points included free testosterone levels (calculated from total testosterone and sex hormone-binding globulin [SHBG] levels); basal ACTH, basal cortisol, and basal aldosterone levels; and $AUC_{0\text{-}120\ min}$ of serum aldosterone levels after the IV administration of ACTH (250 µg) at EOS.

COMMENT: The methods of hormone sampling and processing, as described in NEB-PK-03, are appropriate and should yield reliable results.

Safety Measures: Safety measurements included adverse events (AEs), clinical laboratory evaluations, vital signs, ECG changes, and physical examination findings including male breast and testicular examinations.

Study Methods:

Withdrawal criteria: A discontinuation occurred if an enrolled subject ceased participation in the study, regardless of circumstances, before completion of the protocol. All subjects who were discontinued were seen for a final safety evaluation. Subjects refusing to come in for a final visit were requested in writing to return for a visit and to return all study medication, if applicable.

Statistical Analyses: The primary, secondary, and additional pharmacodynamic end point analyses were performed on the ITT population. The ITT population was defined as all subjects who had a post-baseline series of cortisol levels after ACTH administration and who took the double blind study medication as assigned.

COMMENT: Based on the Sponsor's definition, the ITT population includes only those subjects who completed the trial and had a full series of cortisol levels after ACTH administration.

Primary Pharmacodynamic End Point Analysis: The primary pharmacodynamic end point was the $AUC_{0\text{-}120\ min}$ of serum cortisol levels after the IV administration of 250 µg ACTH at the End of Study (EOS) (i.e. day 57). By protocol, only subjects who completed the study had a postbaseline series of cortisol levels after ACTH administration. The $AUC_{0\text{-}120\ min}$ was calculated using the trapezoidal rule based on the pre- and post-ACTH stimulation cortisol levels at 0 hour (pre-ACTH injection), 0.5, 1.0, 1.5, and 2 hours post-ACTH injection.

This end point was analyzed using analysis-of-covariance (ANCOVA) model with treatment group, metabolic status (CYP2D6 extensive metabolizers [EM] versus poor metabolizers [PM]) and study center as factors and the corresponding baseline (Day 8) $AUC_{0\text{-}120\ min}$ value as covariate.

Least squares mean differences (LSMD) in the primary pharmacodynamic end point between active treatments and placebo expressed as a percentage of the placebo least square mean (LSM) were presented along with the 90% CI. The primary analysis was the comparison between nebivolol and placebo.

Additional Pharmacodynamic End Point Analyses: The additional pharmacodynamic end points included the free testosterone level (calculated) on Day 56, the basal ACTH level on Day 57, the basal cortisol level on Day 57, the basal aldosterone level on Day 57, and the $AUC_{0\text{-}120\ min}$ of serum aldosterone levels after the IV administration of 250 µg ACTH on Day 57.

The free testosterone level was calculated from the total testosterone level and the SHBG level using the following equation[1]:

$$FT = \frac{T - (N \times FT)}{K_t \times [SHBG - T + (N \times FT)]}$$

in which *FT* is the free testosterone level, *T* is the total testosterone level, K_t is the association constant of SHBG for T, *N* is calculated by $K_a \times C_a + 1$, K_a is the association

constant of albumin for T, and C_a is the albumin concentration. Because the subjects in the study were healthy male volunteers, the following values were used: 1×10^9 *L/mol* for K_t, 3.6×10^4 *L/mol* for K_a, and 6.2×10^{-4} *mol/L* for C_a.

The above additional end points were analyzed using a similar ANCOVA model as for the primary pharmacodynamic end point. LSMD in the additional pharmacodynamic end points between active treatments and placebo were presented along with the 90% CI.

In addition, the proportions of subjects with the following were analyzed using a logistic regression model with treatment group as a factor and the corresponding baseline value as a covariate:

- Unstimulated (basal, time zero) cortisol levels less than 3 µg/dL on Day 57
- Peak ACTH-stimulated cortisol levels (the maximum of cortisol levels at 0.5, 1.0, 1.5, and 2.0 hours post-ACTH injection) that are less than 19 µg/dL on Day 57
- Peak ACTH-stimulated cortisol levels (the maximum of cortisol levels at 0.5, 1.0, 1.5, and 2.0 hours post-ACTH injection) that are less than or equal to 7 µg/dL above time zero (basal) cortisol level on Day 57
- Peak ACTH-stimulated aldosterone levels (the maximum of aldosterone levels at 0.5, 1.0, 1.5, and 2.0 hours post-ACTH injection) that are less than 5 µg/dL above time zero (basal) aldosterone level on Day 57

The odds ratio between active treatments and placebo, along with the 90% CI, were obtained from the logistic regression model.

Subjects with post-ACTH serum cortisol levels less than 19 µg/dL or aldosterone levels less than 5 ng/dL above basal aldosterone levels on Day 57 were summarized along with their test results obtained four weeks following the last dose of the double-blind study medication. An abnormal post-ACTH cortisol level was defined as less than 19 µg/dL peak ACTH-stimulated cortisol level (the maximum of cortisol levels at 0.5, 1.0, 1.5, and 2.0 hours post-ACTH injection). Peak post-ACTH aldosterone levels (the maximum of aldosterone levels at 0.5, 1.0, 1.5, and 2.0 hours post-ACTH injection) less than 5 ng/dL above the time zero (basal) aldosterone level were summarized.

Protocol Amendments:

Amendment 1, dated August 16, 2006, ,incorporated changes reflecting the Agency's recommendations on the study design and to add revisions for better adherence to safety and for compliance purposes.

Amendment 2, dated September 14, 2006, updated the inclusion/exclusion criteria and added administrative changes.

Amendment 3, dated September 25, 2006, included a site requirement for an additional ECG when pulse rate $\geq$ 100 bpm and the investigator determined it medically indicated and made administrative revisions.

Amendment 4, dated November 1, added two clinical sites.

Amendment 5, dated November 21, 2006, initiated the following changes: (1) addition of activities for subjects required to have a repeat ACTH-stimulation test, (2) revision of the volume of blood to be collected during the study, (3) correction of the unit of measure for aldosterone levels per comments from the Agency, and (4) administrative changes.

Results

Patient Disposition: Of the 157 subjects who received double-blind treatment, 119 (76%) completed the study. More subjects in the placebo group (48/52, 92%) than in the nebivolol (42/55, 76%) or atenolol (29/50, 58%) groups completed the study. The most frequent reason for discontinuation was "other," (30% for the atenolol subjects, 14% for the nebivolol subjects, and 5.8% for the placebo subjects. With the exception of one subject in the atenolol group who withdrew because of the investigator's discretion, all the subjects who were discontinued from the study because of the category "other" were withdrawn for vital sign values outside (below) the protocol-specified safety criteria.

Table 2. Number (%) of Subjects Discontinued From the Study – Randomized Population (Reproduced from sponsor, NEB-PK-03, Table 10.2-1., page 67 of 5947)

	Placebo (N=52) n (%)	*Atenolol (N=50) n (%)*	*Nebivolol (N=55) n (%)*	*Total (N=157) n (%)*
Completed study	48 (92.3)	29 (58.0)	42 (76.4)	119 (75.8)
Withdrawn from study	4 (7.7)	21 (42.0)	13 (23.6)	38 (24.2)
Reason for withdrawal				
Other	3[a] (5.8)	15[b] (30.0)	8[c] (14.5)	26 (16.6)
Protocol violation	1 (1.9)	4 (8.0)	2 (3.6)	7 (4.5)
Adverse event	0	2 (4.0)	2 (3.6)	4 (2.5)
Consent withdrawn	0	0	1 (1.8)	1 (0.6)
Lost to follow-up	0	0	0	0

a Three subjects were withdrawn because of protocol-specified safety criteria: 2 subjects because of low blood pressure (1 systolic and 1 diastolic) outside protocol parameters, and 1 subject because of low pulse rate outside protocol parameters.

b One subject was withdrawn because of Investigator's discretion. The remaining 14 subjects in this group were withdrawn because of protocol-specified safety criteria: 8 subjects because of low blood pressure outside protocol parameters (5 diastolic, 1 systolic and diastolic, and 2 unspecified) and 6 subjects because of low pulse rate outside protocol parameters.

c Eight subjects were withdrawn because of protocol-specified safety criteria: 4 subjects were withdrawn because of low blood pressure outside protocol parameters (1 diastolic, 2 systolic, and 1 systolic and diastolic) and 4 subjects were withdrawn because of low pulse rate outside protocol parameters.

Protocol Violations: There were five subjects at site 002 that received incorrect randomization kits for Days 43 through 56 of the study. Three of the subjects terminated early on Days 52 through 53, while the remaining two completed the study. Upon unblinding of the double-blind treatment code following database lock, it was found that these two subjects had received the correct treatment despite receiving the incorrect randomization kits.

Demographics: There was an imbalance between the nebivolol and placebo treatment groups in the proportion of nonwhite versus white subjects: 14% nonwhite in the nebivolol group and 40% nonwhite in the placebo group. A similar imbalance existed between the atenolol group and the placebo group: 24% nonwhite with atenolol and 40% nonwhite with placebo.

Overall, 95% of subjects were extensive metabolizers. Although the numbers were small, there were more poor metabolizers in the nebivolol group (5/55, 9.1%) than in the atenolol group or placebo groups (2/50 [4.0%] and 1/52 [1.9%], respectively).

Demographics of the ITT population were similar to those of the safety population; there were fewer nonwhite subjects in the nebivolol group compared with the placebo group (Table 4).

Table 3. Demographic Characteristics – Safety Population (Reproduced from the Sponsor, Study NEB-PK-03, Table 10.3-1., page 69 of 5947)

Characteristic	*Placebo (N=52)*	*Atenolol (N=50)*	*Nebivolol (N=55)*	*Total (N=157)*
Mean age, y (SD)	30.3 (8.74)	29.3 (9.31)	28.3 (9.00)	29.3 (9.00)
Race, n (%)				
White	31 (59.6)	38 (76.0)	47 (85.5)	116 (73.9)
Nonwhite	21 (40.4)	12 (24.0)	8 (14.5)	41 (26.1)
Black	15 (28.8)	8 (16.0)	4 (7.3)	27 (17.2)
Asian	3 (5.8)	1 (2.0)	2 (3.6)	6 (3.8)
Other	3 (5.8)	3 (6.0)	2 (3.6)	8 (5.1)
Ethnicity, n (%)				
Hispanic	13 (25.0)	15 (30.0)	15 (27.3)	43 (27.4)
Non-Hispanic	39 (75.0)	35 (70.0)	40 (72.7)	114 (72.6)
Mean height, cm (SD)	176.58 (7.24)	175.73 (8.03)	176.88 (8.19)	176.42 (7.80)
Mean weight, kg (SD)	80.98 (10.36)	79.42 (8.65)	78.66 (11.11)	79.67 (10.11)
CYP 2D6 status, n (%)				
Extensive metabolizers	51 (98.1)	48 (96.0)	50 (90.9)	149 (94.9)
Poor metabolizers	1 (1.9)	2 (4.0)	5 (9.1)	8 (5.1)

CYP 2D6 = 2D6 isozyme of cytochrome P-450.

Table 4. Demographic Characteristics – Intent-to-treat Population (Reproduced from the Sponsor, Study NEB-PK-03, Table 10.3-1., page 69 of 5947)

Characteristic	*Placebo (N=48)*	*Atenolol (N=29)*	*Nebivolol (N=42)*	*Total (N=119)*
Mean age, y (SD)	30.4 (8.49)	27.8 (8.83)	28.4 (8.65)	29.1 (8.63)
Race, n (%)				
White	28 (58.3)	21 (72.4)	34 (81.0)	83 (69.7)
Nonwhite	20 (41.7)	8 (27.6)	8 (19.0)	36 (30.3)
Black	15 (31.3)	6 (20.7)	4 (9.5)	25 (21.0)
Asian	3 (6.3)	1 (3.4)	2 (4.8)	6 (5.0)
Other	2 (4.2)	1 (3.4)	2 (4.8)	5 (4.2)
Ethnicity, n (%)				
Hispanic	12 (25.0)	8 (27.6)	12 (28.6)	32 (26.9)
Non-Hispanic	36 (75.0)	21 (72.4)	30 (71.4)	87 (73.1)
Mean height, cm (SD)	176.10 (7.08)	177.05 (8.10)	176.54 (7.99)	176.49 (7.61)
Mean weight, kg (SD)	80.82 (10.20)	80.18 (8.21)	77.31 (10.97)	79.42 (10.09)
CYP 2D6 status, n (%)				
Extensive metabolizers	47 (97.9)	28 (96.6)	38 (90.5)	113 (95.0)
Poor metabolizers	1 (2.1)	1 (3.4)	4 (9.5)	6 (5.0)

CYP 2D6 = 2D6 isozyme of cytochrome P-450.

Concomitant Medications: Concomitant medications were taken by 26% (41/157) of subjects in the safety population: 24% of subjects in the nebivolol treatment group, 26% of subjects in the atenolol group, and 29% of subjects in the placebo group. The saline (sodium chloride) flush administered after the cosyntropin injection was considered by one investigator to be a concomitant medication for all subjects at that site. With the exception of the sodium chloride, there were few concomitant medications and, as might be expected in a population of healthy subjects, the medications taken consisted of over-the-counter medications and antibiotics.

Adrenal Function:

ACTH-stimulated serum cortisol $AUC_{0\text{-}120\ min}$: ACTH-stimulated serum cortisol $AUC_{0\text{-}120\ min}$ was the primary outcome in this trial. On day 57, after 49 days of treatment, nebivolol had no significant effect compared with placebo on the ACTH-stimulated $AUC_{0\text{-}120\ min}$ for serum cortisol levels. As outlined in Table 5 below, the LS mean difference expressed as a percentage of the placebo group (90% CI) was -0.01% (-2.59%, 2.56%).

Table 5. Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Adrenocorticotropic Hormone-Stimulated $AUC_{0\text{-}120\ min}$ of Serum Cortisol Levels at End of Study – Intent-to-Treat Population (Reproduced from sponsor, NEB-PK-03, Table 11.1.1.1-1., page 74 of 5947)

Serum cortisol levels, µg/dL x h	*Placebo (N=48)*	*Atenolol (N=29)*	*Nebivolol (N=42)*
Mean $AUC_{0\text{-}120\ min}$ (SD)			
Day 8 (baseline)	55.04 (6.337)	56.71 (5.629)	55.70 (5.802)
Day 57	55.80 (7.096)	57.98 (6.374)	56.13 (5.645)
LSM[a] (SE)	55.895 (1.01)	57.188 (1.11)	55.887 (0.94)
LSMD[a,b] (90% CI)	—	1.29 (–0.31, 2.90)	–0.01 (–1.45, 1.43)
LSMD[a,c] (90% CI)	—	2.31 (–0.55, 5.18)	–0.01 (–2.59, 2.56)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.
b Active minus placebo (expressed as µg/dL x hour).
c Active minus placebo (expressed as a percentage of placebo least squares mean).
AUC = area under the plasma concentration versus time curve; N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 57; LSM = least squares mean; LSMD = least squares mean differences.

Additional adrenal pharmacodynamic endpoints included the basal ACTH level (ng/dL), basal cortisol level (µg/dL), basal aldosterone level (ng/dL), and $AUC_{0\text{-}120\ min}$ of serum aldosterone levels after the IV administration of 250 µg ACTH on Day 57. Also analyzed was the incidence of subjects with the following: unstimulated (basal) cortisol levels less than 3 µg/dL, peak ACTH-stimulated cortisol levels less than 19 g/dL, peak ACTH-stimulated cortisol levels that were 7 µg/dL or less above basal cortisol levels, and peak ACTH-stimulated aldosterone levels that were less than 5 ng/dL above basal aldosterone levels.

Basal ACTH level: Basal levels of ACTH at baseline were similar for all three treatment groups with a slightly higher mean value for the nebivolol treatment group. All three treatment groups were associated with small increase in basal ACTH levels on Day 57 of the study with slightly greater changes in the placebo-treated group. However, there were no differences in the mean basal ACTH levels at study end for the nebivolol-treated group relative to placebo treatment. LS mean difference (90% CI) for nebivolol compared with placebo was -0.08 (-0.84, 0.67) ng/dL (see Table 6 below). No important differences in mean basal ACTH levels at study end were observed for the comparison of atenolol treatment relative to placebo treatment.

Table 6. Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Basal Adrenocorticotropic Hormone Levels at Day 57 – Intent-to-Treat Population (Reproduced from Sponsor, NEB-PK-03, Table 11.1.1.3.2-1., page 79 of 5947)

Basal adrenocorticotropic hormone levels, ng/dL	*Placebo (N=48)*	*Atenolol (N=29)*	*Nebivolol (N=42)*
Mean (SD)			
Day 8 (baseline)	3.41 (1.772)	3.42 (1.449)	3.74 (1.624)
Day 57	3.70 (2.241)	3.51 (1.800)	3.92 (3.177)
LSM[a] (SE)	3.70 (0.53)	3.53 (0.58)	3.61 (0.49)
LSMD[a,b] (90% CI)	—	–0.16 (–1.00, 0.68)	–0.08 (–0.84, 0.67)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.
b Active minus placebo (expressed as ng/dL).
N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 57; LSM = least squares mean; LSMD = least squares mean differences.

Basal cortisol level: Baseline mean basal levels of cortisol for all three treatment groups were similar; however, the nebivolol group had a slightly greater mean value (13.44 µg/dL) relative to the other two treatment groups (placebo 12.40 µg/dL; atenolol 12.76 µg/dL). As outlined in Table 7, all three treatment groups were associated with slight increases in mean basal cortisol levels from baseline to the study end with greater increases seen in placebo and atenolol-treated subjects than in nebivolol-treated subjects. There were no important differences observed in mean basal cortisol levels at study end for the comparison of nebivolol relative to placebo.

Table 7. Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Basal Cortisol Levels at Day 57 – Intent-to-Treat Population (Reproduced from Sponsor, NEB-PK-03, Table 11.1.1.3.3-1., page 80 of 5947)

Basal cortisol levels, µg/dL	*Placebo (N=48)*	*Atenolol (N=29)*	*Nebivolol (N=42)*
Mean (SD)			
Day 8 (baseline)	12.40 (3.593)	12.76 (3.473)	13.44 (4.227)
Day 57	13.76 (4.556)	13.86 (4.019)	13.52 (3.831)
LSM[a] (SE)	13.23 (0.99)	13.63 (1.08)	12.84 (0.92)
LSMD[a,b] (90% CI)	—	0.40 (–1.16, 1.96)	–0.40 (–1.81, 1.02)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.
b Active minus placebo (expressed as µg/dL x hour).
N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 57; LSM = least squares mean; LSMD = least squares mean differences.

Basal aldosterone level: At baseline, mean levels of basal aldosterone were nearly equivalent for all three treatment groups with the mean value slightly higher for the nebivolol subject group (15.97 ng/dL). All subjects were placed on a 4 g/d sodium diet during the study to minimize the impact of varying sodium intake on aldosterone levels. As outlined in Table 8, no changes from baseline mean values occurred in the three

treatment groups at EOS (Day 57). Nebivolol-treated subjects had essentially unchanged mean basal levels after 49 days of treatment. There were no differences noted in basal aldosterone levels in either the nebivolol or atenolol groups relative to placebo-treated subjects. The LS mean difference (90% CI) for nebivolol relative to placebo was -0.42 (-1.73, 0.88) ng/dL.

Table 8. Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Basal Aldosterone Levels at Day 57 – Intent-to-Treat Population (Reproduced from Sponsor, NEB-PK-03, Table 11.1.1.3.7-1., page 81 of 5947)

Basal aldosterone levels, ng/dL	***Placebo (N=48)***	***Atenolol (N=29)***	***Nebivolol (N=42)***
Mean (SD)			
Day 8 (baseline)	**14.84 (6.564)**	**14.29 (5.655)**	**15.97 (8.006)**
Day 57	**15.78 (6.539)**	**13.92 (5.622)**	**15.99 (6.912)**
LSM[a] (SE)	**14.68 (0.92)**	**13.61 (1.00)**	**14.25 (0.85)**
LSMD[a,b] (90% CI)	—	**–1.06 (–2.51, 0.38)**	**–0.42 (–1.73, 0.88)**

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.
b Active minus placebo (expressed as ng/dL).
N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 57; LSM = least squares mean; LSMD = least squares mean differences.

ACTH-stimulated serum aldosterone $AUC_{0\text{-}120\ min}$: Mean ACTH-stimulated aldosterone AUC values at baseline were similar for the three treatment groups. There were no changes in mean ACTH-stimulated AUC values from baseline to EOS for any of the treatment groups (see Table 9). Furthermore, there were no differences between nebivolol relative to placebo for ACTH-stimulated serum aldosterone $AUC_{0\text{-}120\ min}$ at EOS (LSMD = -1.13 ng/dL x h; 90% CI = -2.99, 0.73 ng/dL x h). No differences in ACTH-stimulated aldosterone $AUC_{0\text{-}120\ min}$ were noted at study end when atenolol was compared with placebo-treated subjects.

Table 9. Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Adrenocorticotropic Hormone-Stimulated $AUC_{0\text{-}120\ min}$ of Serum Aldosterone Levels at Day 57 – Intent-to-Treat Population (Reproduced from Sponsor, NEB-PK-03, Table 11.1.1.3.8-1., page 82 of 5947)

Serum aldosterone levels, ng/dL x h	***Placebo (N=48)***	***Atenolol (N=29)***	***Nebivolol (N=42)***
Mean $AUC_{0\text{-}120\ min}$ (SD)			
Day 8 (baseline)	43.99 (14.505)	41.47 (11.672)	45.89 (16.952)
Day 57	45.01 (13.935)	42.38 (13.515)	45.31 (14.033)
LSM[a] (SE)	44.92 (1.31)	44.99 (1.43)	43.79 (1.22)
LSMD[a,b] (90% CI)	—	0.07 (–2.00, 2.14)	–1.13 (–2.99, 0.73)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.
b Active minus placebo (expressed as ng dL x hour).
N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 57; LSM = least squares mean; LSMD = least squares mean differences.

Incidence of abnormal cortisol levels: There were no subjects in any of the groups who had unstimulated basal levels of cortisol < 3 µg/dL or peak ACTH-stimulated cortisol levels < 19 µg/dL at study end. One subjects in the placebo group had peak ACTH-stimulated cortisol level that was ≤ 7 µg/dL above unstimulated basal cortisol levels. However, given the values reported, it appears as if samples may have been incorrectly labeled.

Table 10: Patient with Abnormal Cortisol Level												
Patient	Group	Day	Cortisol (µg/dL)					Aldosterone (ng/mL)				
			0	30	60	90	120	0	30	60	90	120
0049042	Placebo	57	29.2	8.3	22.6	32.2	33.2	13	7.3	10.7	12.3	14.2

Incidence of abnormal aldosterone levels: There were 113 subjects in the three treatment groups on Day 8 (baseline) who had peak ACTH-stimulated aldosterone levels that exceeded 5 ng/dL above unstimulated basal aldosterone level. Six subjects (placebo n = 2/48; nebivolol n = 3/42; atenolol n = 1/29) had aldosterone responses to ACTH stimulation that were less than 5 ng/dL above basal unstimulated aldosterone level. No subjects in any group had a cortisol level less than 19 µg/dL following ACTH stimulation at baseline.

At study end on Day 57, there were nine subjects (placebo n = 4/48; nebivolol n = 3/43; atenolol n = 2/29) who had aldosterone levels equal to or less than 5 ng/dL above basal aldosterone levels in response to ACTH stimulation. As outlined in Table 11, compared with placebo, nebivolol treatment was associated with a 14% reduction in the incidence rate (odds ratio = 0.853; 90% CI – 0.228, 3.194) of this occurrence. Atenolol treatment was associated with a 17% reduction in incidence of occurrence relative to placebo-treated subjects having an odds ratio of 0.790 (90% CI = 0.179, 3.485).

Table 11. Incidence of Peak ACTH-Stimulated Aldosterone Levels that are < 5 ng/dL above Unstimulated (Basal) Aldosterone Level on Day 57 – Intent-to-Treat Population (Reproduced from Sponsor, NEB-PK-03, Table 14.4.3.9, page 147 of 5947)

	Placebo (n=48)	Atenolol (n=29)	Nebivolol (n=42)
Subjects (%)	**4 (8.33)**	**2 (6.90)**	**3 (7.14)**
Odds Ratio (90% CI)		**0.790 (0.179, 3.485)**	**0.853 (0.228, 3.194)**

Subjects with a post-ACTH aldosterone level < 5 ng/dL on Day 57 were scheduled to return for repeat ACTH-stimulation testing approximately 4 weeks (±2 days) after the last dose of study drug. Poststudy ACTH stimulation testing resulted in 3 of 4 placebo subjects, 2 of 3 nebivolol subjects, and both atenolol subjects having ACTH-stimulated aldosterone levels ≥ 5 ng/dL above basal aldosterone levels. As outlined in Table 12 below, there is no consistent pattern of changes in aldosterone levels post ACTH. Most patients with abnormal aldosterone levels had a normal cortisol response.

Table 12: Patients with Abnormal Aldosterone Levels												
Patient	**Group**	**Day**	**Cortisol (µg/dL)**					**Aldosterone (ng/mL)**				
			0	**30**	**60**	**90**	**120**	**0**	**30**	**60**	**90**	**120**
0019028	Placebo	1	26.4	31.8	32.5	34.3	34.1					
		8	9.8	24.3	28.6	31.2	32.8	14.1	22.6	17.2	21.9	21.2
		57	9.2	23.4	27.6	30.6	32	14.6	17.9	15.1	17	19.1
0029041	Placebo	1	19.6	26.1	30.2	32.1	33.9					
		8	16.5	23.8	26.7	31.5	33.4	15.3	17.7	19.4	19.6	17.7
		57	18.6	25.4	26.9	30.3	31.5	13.2	17.8	21.1	21.6	21.9
0039016	Placebo	1	20.8	25.4	29.5	31.8	33.3					
		8	10.4	23.8	27.7	30.2	32.2	37	36.1	29	39.4	40.1
		57	14	23	26.7	28.8	30.9	24.5	27.2	35.6	39.9	28.2
0039053	Placebo	1	8.3	22.9	25.3	28	28.8					
		8	11.7	23.8	27.2	29.6	32.6	7.4	14.4	14.3	16	15.7
		57	17.5	25.1	29.4	31.7	33.4	8.2	11.5	9.4	10.9	12.9
0049042	Placebo	1	8.4	22.6	26.2	28.1	29.8					
		8	9.9	25	29.5	30.6	33	6.7	9.9	9.8	8.2	12.6
		57	29.2	8.3	22.6	32.2	33.2	13	7.3	10.7	12.3	14.2
0059007	Placebo	1	15.2	23.5	26	27.9	29.1					
		8	11.1	24.9	27.6	29.6	30.9	19.8	37	29.7	32.4	28
		57	20.1	26.4	29.8	30.5	33.8	28.7	32.9	31.6	28	26.8
		PS	20.9	28.6	30.3	31.5	32.8	21.1	24.1	22.6	21.2	18.6
0019137	Atenolol	1	13.2	28.5	30.9	33.6	34.7					
		8	13.3	29	32.2	34	34.6	10.5	15.9	16.7	17	17.1
		57	13.9	30.1	33.3	35.9	38.5	13.9	15.6	13.5	14.4	11.3
0029026	Atenolol	1	13.8	28.7	34.1	35.9	37.9					
		8	11.3	26.4	29.3	33.4	34.2	16.6	27.9	24	27.9	21.8
		57	21.6	27.2	31.6	35.3	36.5	19.7	24.4	21.5	22.2	24
0049081	Atenolol	1	10.1	20.9	26.1	26.8	29.9					
		8	16.6	25.1	29.3	30.7	32.5	11	15.9	14.2	14.4	14
		57	14.3	26.4	30.4	33.4	36.1	7.9	14.6	15.9	15.1	14
0019075	Nebivolol	1	11.5	24.8	26.5	30.5	32.1					
		8	12.1	26.9	31.3	32.7	36	11.7	17.9	15.5	17.1	18.5
		57	18.2	28.3	29.4	33.7	34.9	16.7	15.7	14.5	19	17.2
0019118	Nebivolol	1	18	31.1	34	35.2	36.5					
		8	14.9	31.3	34.4	36.5	38.8	13.5	17	18.4	16.2	17.5
		57	20.8	33.9	37.9	41.7	41.6	14.4	17.3	23.5	20.4	21.7
0029074	Nebivolol	1	14.4	25	28.7	31.8	32.9					
		8	21.6	27.9	31	33.9	34.3	18.7	25.1	25.6	25.2	24.2
		57	26.7	31.6	34.5	36.7	36	22	26.2	22.3	18.1	19.6
			0	**30**	**60**	**90**	**120**	**0**	**30**	**60**	**90**	**120**
0039024	Nebivolol	1	11.1	25	29.5	31.7	34.2					
		8	12.9	25.1	30.9	33.1	36	9.1	12.6	16.1	17.9	14.6
		57	14.2	25.1	29.5	32.2	31.7	11.7	13.8	13.4	15.8	13.2
		PS	14.3	22.9	27.7	28.4	30.3	11.1	14.2	14.8	13.5	12.9
0069023	Nebivolol	1	19.4	32.9	36.5	39	41.1					
		8	23	30.9	30.8	25.9	21.8	11.1	13.7	15.9	12.9	9.6
		57	13.4	27.5	30.6	33	36.2	7.2	12.9	15.1	15.8	15.1
0069034	Nebivolol	1	12.5	26.2	30	32.2	33.8					
		8	22.7	28.9	30.4	30.2	26.6	17.8	20.1	22.2	21.6	20.8
		57	11.8	24.1	27.8	29.9	31.7	10	23.2	18.9	17.8	15.4
PS = Post-study repeat ACTH-stimulation test 4 weeks ((±2 days) after the last dose of study drug												

Discussion of Adrenal Function Findings: All three treatment groups were associated with slight increases in mean basal cortisol levels from baseline to the study end. There were no important differences observed in mean basal cortisol levels at study end for the comparison of nebivolol relative to placebo. No subjects in any of the groups had unstimulated basal levels of cortisol < 3 µg/dL or peak ACTH-stimulated cortisol levels < 19 µg/dL at study end. Based upon cortisol results, nebivolol does not result in adrenal insufficiency.

Regarding the unexpected aldosterone results, it must first be stated that patients were not on prior or concomitant medications, such as angiotensin-converting enzyme inhibitors, which may have influenced the data.

The aldosterone reference range for this study was 2.5 – 31.5 ng/dL. On Day 8, one (placebo group) of the six subjects whose stimulated aldosterone was < 5 above basal had a basal aldosterone of 37 ng/dL. This patient may have been maximally stimulated at the start of the study or results may have been incorrectly reported. (This patient's lowest aldosterone measurement was 29 ng/dL at time 60 minutes.)

Six of the 15 patients with ACTH-stimulated aldosterone < 5 ng/dL had elevated basal cortisol levels, as defined by cortisol > 19 mcg/dL (day 8: n = 2/6 [2 nebivolol]; day 57 n = 4/9 [2 placebo, 1 atenolol, 1 nebivolol]; poststudy n = 1/2 [placebo]). One placebo patient had elevated basal cortisols at two of the three time points (day 57 = 28.7 ng/dL; poststudy = 21.1 ng/dL). This same patient was one of two, whose aldosterone failed to stimulate poststudy.

The ACTH-stimulated aldosterone test, as described by Dluhy in 1974, "can be useful in differential diagnosis when adrenal hypofunction is suggested by a subnormal cortisol response."[1] Because these subjects had normal adrenal function, the test may not be informative. Dluhy's diagnostic criteria were developed based on the observations from 5 subjects with primary adrenal insufficiency and 12 patients with secondary adrenal insufficiency. As the sponsor acknowledges, the validity of this test has not be assessed in either a larger number of patients or in normal human subjects.

Since the cortisol results were normal and aldosterone is mainly regulated by the renin/angiotensin pathway, the aldosterone results are not clearly interpretable. For these reasons, the Division does not place much emphasis on the peak ACTH stimulated aldosterone level < 5 ng/dl above basal level on Day 57 in 4 placebo, 2 atenolol, and 3 nebivolol subjects; the abnormal ACTH stimulated aldosterone level on Day 8 (baseline) in 2 placebo, 1 atenolol, and 3 nebivolol subject; and the peak ACTH-stimulated aldosterone level < 5 ng/dl above unstimulated basal aldosterone level post-study in 1 placebo and 1 nebivolol subject.

Gonadotropins and Sex Hormones

Luteinizing hormone: At baseline, similar mean levels of LH were observed in all three treatment groups. On Day 56, there were no important differences between nebivolol and placebo-treated subjects in mean LH levels. The LS mean difference (90% CI) for nebivolol subjects was 0.08 (-0.36, 0.52) IU/L. Similarly, there were no important differences noted in mean LH levels for the atenolol-treated group relative to placebo-treated subjects (see Table 13).

Table 13. Effects of Nebivolol, Atenolol, and Placebo Administration on mean LH Levels at Day 56 – Intent-to-Treat Population (Reproduced from Sponsor, Study NEB-PK-03, Table 11.1.1.2.1-1., page 76 of 5947)

Luteinizing hormone levels, IU/L	*Placebo (N=48)*	*Atenolol (N=29)*	*Nebivolol (N=42)*
Mean (SD)			
Day 7 (baseline)	4.40 (1.386)	4.29 (1.513)	4.72 (1.828)
Day 56	4.52 (1.428)	4.31 (1.352)	4.76 (1.965)
LSM[a] (SE)	4.24 (0.31)	4.09 (0.34)	4.32 (0.29)
LSMD[a,b] (90% CI)	—	-0.15 (-0.63, 0.34)	0.08 (-0.36, 0.52)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.

b Active minus placebo (expressed as IU/L).

N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 56; LSM = least squares mean; LSMD = least squares mean differences.

Total testosterone: Baseline mean levels of total testosterone for all three treatment groups were similar. Small decreases in mean levels of total testosterone were seen in placebo and atenolol-treated subjects on Day 56 whereas; a small increase was seen in nebivolol-treated subjects. On Day 56, there were no significant differences noted in mean total testosterone levels in nebivolol-treated subjects compared with placebo-treated subjects. The LS mean difference (90% CI) for nebivolol subjects was 27.08 (-9.41, 63.58) ng/dL. Similarly, there were no differences noted in mean total testosterone levels at Day 56 for atenolol-treated subjects relative to placebo-treated subjects (see Table 14).

Table 14. Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Total Testosterone Levels at Day 56 – Intent-to-Treat Population (Reproduced from Sponsor, Study NEB-PK-03, Table 11.1.1.2.2-1., page 76 of 5947)

Total testosterone levels, ng/dL	*Placebo (N=48)*	*Atenolol (N=29)*	*Nebivolol (N=42)*
Mean (SD)			
Day 7 (baseline)	551.9 (138.59)	542.6 (125.50)	561.7 (156.21)
Day 56	549.0 (130.51)	516.1 (173.88)	588.4 (167.08)
LSM[a] (SE)	578.92 (25.71)	553.06 (28.13)	606.00 (23.78)
LSMD[a,b] (90% CI)	—	-25.85 (-66.31, 14.61)	27.08 (-9.41, 63.58)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status and study center as factors and the corresponding baseline value as a covariate.

b Active minus placebo (expressed as ng/dL).

N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 56; LSM = least squares mean; LSMD = least squares mean differences

Incidence of abnormal testosterone levels: Using the laboratory reference range given (normal = 280 – 800 ng/dL), three subjects had low testosterone levels (1 atenolol, 2 nebivolol) and 16 subjects had high testosterone (6 placebo, 2 atenolol, 7 nebivolol) at some point during the study. The Division of Reproductive and Urologic Products considers 300 – 1000 ng/dL to be the normal range. Using this range, two nebivolol subjects had low testosterone on Day 7, after placebo run-in. One atenolol subject had low testosterone on Day 56. Two atenolol and one nebivolol patients had elevated testosterone on Days 7, 56, and 56, respectively. The clinical significance of this is not clear, although likely insignificant. More atenolol patients had elevated testosterone than nebivolol patients, at the end of study with the data provided.

Table 15. Subjects with Abnormal Total Testosterone (Normal = 280 – 800 ng/dL)

Patient	Group	Total Testosterone ng/dL (% change from Day 1)		
		Day 1	Day 7	Day 56
0019043	Placebo	855	830 (-3%)	818 (-4%)
0029041	Placebo	938	878 (-6%)	883 (-6%)
0049177	Placebo	993	683 (-31%)	747 (-25%)
0059040	Placebo	801	727 (-9%)	701 (-12%)
0059041	Placebo	837	752 (-10%)	683 (-18%)
0069008	Placebo	551	655 (19%)	804 (46%)
0029038	Atenolol	891	1071 (20%)	
0039009	Atenolol	924	679 (-27%)	764 (-17%)
0039094	Atenolol	829	781 (-6%)	1104 (33%)
0049018	Atenolol	426	425 (0%)	134 (-69%)
0019075	Nebivolol	481	244 (-49%)	388 (-19%)
0029052	Nebivolol	834	796 (-5%)	
0029077	Nebivolol	826	685 (-17%)	584 (-29%)
0039101	Nebivolol	805	769 (-4%)	724 (-10%)
0049117	Nebivolol	359	252 (-30%)	371 (3%)
0059013	Nebivolol	762	901 (18%)	918 (20%)
0059038	Nebivolol	614	661 (8%)	1138 (85%)
0069005	Nebivolol	729	822 (13%)	922 (26%)
0069038	Nebivolol	712	898 (26%)	830 (17%)

Free testosterone: Baseline levels of mean free testosterone were similar quantitatively for all three treatment groups. On Day 56, after 48 days of treatment, small decreases in mean values for placebo and atenolol-treatment groups were observed. Nebivolol treatment was associated with a small increase in mean levels of free testosterone relative to the baseline value (14.58 vs. 13.58 ng/dL). There was no significant difference between nebivolol- and placebo-treated groups in Day 56 for free testosterone levels. LSMD (90% CI) for nebivolol compared with placebo was 1.003 (-0.082, 2.089) ng/dL. Similarly, there were no important differences in mean free testosterone levels between atenolol and placebo treatment groups in Day 56 (see Table 16).

Table 16. Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Free Testosterone Levels at Day 56 – Intent-to-Treat Population (Reproduced from Sponsor, Study NEB-PK-03, Table 11.1.1.3.1-1., page 78 of 5947)

Free testosterone levels, ng/dL	*Placebo (N=48)*	*Atenolol (N=29)*	*Nebivolol (N=42)*
Mean (SD)			
Day 7 (baseline)	13.92 (3.664)	13.86 (3.308)	13.58 (3.269)
Day 56	13.68 (3.499)	13.02 (4.117)	14.58 (4.316)
LSM[a] (SE)	14.735 (0.768)	14.158 (0.838)	15.738 (0.706)
LSMD[a,b] (90% CI)	—	–0.577 (–1.775, 0.621)	1.003 (–0.082, 2.089)

a Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate.
b Active minus placebo (expressed as ng/dL).
N = number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 56; LSM = least squares mean; LSMD = least squares mean differences.

Safety

Events Rates: As outlined in Table 16, a total of 38.2% (21/55) of subjects treated with nebivolol experienced one or more TEAEs during the study; 40.0% (20/50) of subjects in the atenolol group and 57.7% (30/52) of subjects in the placebo group reported one or more TEAEs. There were no SAEs and no deaths during the study. Four subjects discontinued from the study because of an AE (2/55 [3.6%] nebivolol subjects, 2/50 [4.0%] atenolol subjects, and no placebo subjects).

Table 17. Summary of Adverse Events – Safety Population (Reproduced from Sponsor, NEB-PK-03, Table 12.1.-1., page 87 of 5947)

	No. (%) of Patients		
	Placebo (N=52)	*Atenolol (N=50)*	*Nebivolol (N=55)*
Subjects with ≥ 1 TEAE[a]	30 (57.7)	20 (40.0)	21 (38.2)
Serious adverse events	0	0	0
AE resulting in premature discontinuation	0	2 (4.0)	2 (3.6)

a Subjects are counted once for "one or more" treatment-emergent adverse events.
TEAE = treatment-emergent adverse event; AE = adverse event.

A summary of TEAEs that occurred at an incidence rate of at least 5% of subjects in any treatment group is presented by decreasing frequency of occurrence in the nebivolol treatment group in Table 17.

TEAEs were reported in 38.2% (21/55) of subjects in the nebivolol group, 40.0% (20/50) in the atenolol group, and 57.7% (30/52) in the placebo group. Headache nebivolol-treated subjects, 16.0% (8/50) of atenolol-treated subjects, and 17.3% (9/52) of placebo-treated subjects. Pharyngolaryngeal pain occurred in at least 5% (5.5%) of nebivolol-treated subjects and with an incidence at least twice that of placebo-treated subjects

(1.9%). No TEAE occurred in at least 5% of nebivolol-treated subjects and with an incidence at least twice that of the atenolol-treated subjects. TEAEs that occurred in at least 5% of placebo-treated subjects and with an incidence at least twice that of the nebivolol-treated subjects included dizziness (placebo 7.7%, nebivolol 0), nausea (placebo 5.8%, nebivolol 0), and fatigue (placebo 5.8%, nebivolol 1.8%). Dizziness occurred in at least 5% of atenolol-treated subjects and with an incidence at least twice that of nebivolol-treated subjects (atenolol 8.0%, nebivolol 0).

Table 18. Summary of Adverse Events Reported in ≥ 5% of Subjects in Any Treatment Group - Safety Population (Reproduced from Sponsor, NEB-PK-03, Table 12.1.2-1., page 88 of 5947)

	No. (%) of Patients		
Adverse Event (Preferred Term)	*Placebo (N=52)*	*Atenolol (N=50)*	*Nebivolol (N=55)*
Subjects with ≥ 1 TEAE[a]	30 (57.7)	20 (40.0)	21 (38.2)
Headache	9 (17.3)	8 (16.0)	9 (16.4)
Pharyngolaryngeal pain	1 (1.9)	2 (4.0)	3 (5.5)
Fatigue	3 (5.8)	1 (2.0)	1 (1.8)
Dizziness	4 (7.7)	4 (8.0)	0
Nausea	3 (5.8)	1 (2.0)	0

a Subjects are counted once for "one or more" treatment-emergent adverse events.
TEAE = treatment-emergent adverse event.

Deaths: The were no deaths during the study.

Serious Adverse Events: There were no SAEs during the study.

Adverse Events Leading to Withdrawal: A total of 2.5% (4/157) of subjects discontinued the study because of AEs: 2 of 55 (3.6%) nebivolol-treated subjects and 2 of 50 (4.0%) atenolol-treated subjects. No placebo-treated subjects discontinued the study because of an AE. In the nebivolol group, a 45 year old male was discontinued from the study on Day 56 due to hypotension and a 28 year old male was discontinued from the study on Day 57 due to a low heart rate. In the atenolol group, a 45 year old male was discontinued from the study on Day 57 due to asymptomatic low blood pressure and a 42 year old male was discontinued from the study on Day 56 due to asymptomatic bradycardia. The episode began on Day 52 at which time study drug was discontinued. Screening and end of study vital signs for these subjects are shown in Table 19. All four subjects were CYP2D6 extensive metabolizers and had normal ACTH stimulation tests at baseline (Day 1). No ACTH stimulation testing was performed on Day 57 and therefore, data is not available for these patients at other study time points. It would have been informative to know if cortisol levels were changed at the time the change in vital signs were noted. It is possible, even likely, that these four patients' symptoms are due to the effect of nebivolol as a β-blocker.

Table 19. Screening and End of Study Blood Pressure and Pulse Measurements for Subjects Withdrawn Due to Adverse Events				
Subject	Screening		End of Study	
	Blood Pressure (mm Hg)	Blood Pressure (mm Hg)	Pulse (bpm)	Pulse (bpm)
0049009	114/82	67	97/60	71
0049034	106/75	64	92/59	65
0049048	139/85	67	116/63	55
0049053	122/86	62	119/73	55

COMMENT: The goal, for statistical purposes, was to obtain 30 subjects in each treatment and control group. Only the positive control (atenolol) group failed to meet this goal by obtaining 29 subjects. As shown in the table below, the randomized population and the intent-to-treat (ITT) population were very comparable. Except for race, other baseline demographics were well balanced among the three treatment groups for both populations. There were, however, a greater number of non-white individuals in the placebo group compared to the two other groups. Baseline levels of stimulated cortisol were also very similar in the randomized and ITT populations. The lack of differences between the two populations for measured attributes suggests that the loss of patients did not materially affect the balance between treatment groups achieved by randomization.

Table 20. Summary of Baseline Demographics (Reproduced from Mylan Bertek Pharmaceutics Inc.'s Response to the Agency's May 18, 2007 Correspondence, Table 1, page 3 of 5)

Table1. Summary of Baseline Demographics			
Intent-to-Treat Population			
Baseline Demographics	*Placebo (N=48)*	*Atenolol (N=29)*	*Nebivolol (N=42)*
Race			
White	58.3%	72.4%	81.0%
Non-White	41.7%	27.6%	19.0%
Mean Age (year)	30.4	27.8	28.4
Mean Weight (kg)	80.82	80.18	77.31
Mean Height (cm)	176.10	177.05	176.54
Randomized Population			
Baseline Demographics	*Placebo (N=52)*	*Atenolol (N=50)*	*Nebivolol (N=55)*
Race			
White	59.6%	76.0%	85.5%
Non-White	40.4%	24.0%	14.5%
Mean Age (year)	30.3	29.3	28.3
Mean Weight (kg)	80.98	79.42	78.66
Mean Height (cm)	176.58	175.73	176.88

COMMENT ON ADVERSE EVENTS OF SPECIAL INTEREST: As clinical pharmacologist Dr. Yaning Wang illustrated at an agency meeting on August 20, 2007, the peak post-ACTH cortisol, peak post-ACTH aldosterone, total and free testosterone, sex hormone binding globulin, and mean luteinizing hormone levels fall in a random distribution when plotted against the plasma concentration of l-nebivolol, even on a logarithmic scale. This led him to conclude that there was no drug effect on these hormones or that the drug was not studied long enough. (Please refer to Dr. Wang's review for full details.) As stated in previous DMEP nebivolol consultations, the Division feels that the six weeks of high-dose nebivolol therapy in study NEB-PK-03 should be adequate to assess endocrine pathways. After that length of time, even poor metabolizers did not experience lower hormone values. Therefore, given the data that we have been presented, the Division agrees that nebivolol and atenolol did not demonstrate any significant changes in adrenal function and nebivolol is unlikely to cause adrenal insufficiency with long-term use at the 10 mg dose.

Laboratory

Adverse Events: There were no clinically relevant differences between nebivolol and placebo, nebivolol and atenolol, or atenolol and placebo treatment groups in the mean change from baseline to EOS for any of the clinical laboratory parameters evaluated in this study.

Marked Laboratory Abnormalities: The incidence of potentially clinically significant (PCS) abnormalities was low for all treatment groups. Potentially clinically significant laboratory values that occurred during the study included low neutrophil levels (1 nebivolol subject), high total bilirubin levels (2 nebivolol and 2 placebo subjects), and high uric acid levels (2 placebo subjects). No subject withdrew from the study because of a laboratory abnormality.

Vital Signs: The mean change at EOS in SBP was -3.59 mm Hg in the nebivolol group, -2.85 mm Hg in the atenolol group, and 0.47 mm Hg in the placebo group. The mean change in DBP from baseline to EOS was -4.42 mm Hg in the nebivolol group, -2.56 mm Hg in the atenolol group, and 0.04 mm Hg in the placebo group. The mean changes in pulse rate from baseline to EOS were -4.62 bpm, -1.38 bpm, and 7.10 bpm for the nebivolol, atenolol, and placebo treatment groups. As expected, subjects in the nebivolol and atenolol treatment groups had decreases in mean SBP, DBP, and pulse rate at EOS. Subjects in the placebo group had little change in SBP and DBP and a slight increase in pulse rate at EOS.

Four nebivolol-treated subjects had postbaseline PCS vital sign values: one subject with PCS decreased DBP and pulse, one subject with PCS decreased pulse rate, and two subjects with PCS weight gain. One atenolol-treated subject had a PCS decreased pulse. None of the subjects with a PCS vital sign value had a TEAE potentially associated with the PCS value. One subject in the nebivolol treatment group (0049059) with a PCS value

for pulse rate was withdrawn from the study due to a protocol violation (dosed in error on Day 15 with an exclusionary pulse rate).

ECG: No clinically relevant differences were observed in mean change from baseline to EOS ECG findings among the three treatment groups.

Physical Examination: One subject in the nebivolol group and two subjects in the atenolol group had normal to abnormal shifts in physical examination results. In the "cardiovascular" body system, one nebivolol subject developed a systolic ejection murmur and one atenolol subject developed sinus bradycardia. There was one abnormality in both the "eyes, ears, nose, throat" and "head and neck, including thyroid" groups, both in one subject in the atenolol group.

No subjects had a breast mass or testicular mass at screening or at any time during the study.

Safety Conclusions: Nebivolol was well tolerated at a dosage of 10 mg/d. The percentage of subjects with at least one TEAE was similar for subjects receiving nebivolol (21/55, 38.2%) and atenolol (20/50, 40.0%). Thirty subjects receiving placebo (30/52, 57.7%) had at least one TEAE. The most frequent TEAE during the study was headache.

Two subjects in the nebivolol group and two subjects in the atenolol group discontinued the study because of an AE. Adverse events leading to discontinuation were: hypotension (1 nebivolol, 1 atenolol), decreased pulse rate (1 nebivolol), and bradycardia (1 atenolol). No subjects in the placebo group withdrew from the study because of an AE.

There were no clinically relevant differences among the three treatment groups in laboratory, vital sign, and ECG values. The incidences of potentially clinically significant laboratory, vital sign, and ECG values were low and similar between the three groups. Physical examination findings were not remarkable.

Discussion and Conclusions: The primary objective of this study was to evaluate the effects of nebivolol 10 mg on adrenal function, luteinizing hormone, and testosterone levels in healthy male volunteers including CYP2D6 EMs and PMs. Placebo and atenolol treatments were controls. In this double-blind, randomized comparator study, the primary pharmacodynamic end point of adrenal function was the change from baseline in $AUC_{0\text{-}120\ min}$ of serum cortisol following intravenous administration of 250 µg ACTH at EOS (Day 57). Study results demonstrated that after 49 days of treatment with nebivolol, of which 42 days were at 10 mg, there were no significant changes in adrenal function, as evidenced by no significant difference in ACTH-stimulated mean serum cortisol $AUC_{0\text{-}120\ min}$ LSMD with 90% CI expressed as a percentage of placebo when nebivolol and atenolol were compared with placebo at EOS.

Based upon early morning and ACTH-stimulated cortisol levels, none of the nebivolol subjects demonstrated clinically relevant laboratory abnormalities of the HPA axis. At the end of the treatment period, neither nebivolol nor atenolol elicited important changes from baseline in mean LH and total testosterone levels. None of the nebivolol subjects demonstrated clinically relevant laboratory abnormalities of the HPG axis.

At study end, there were no significant differences in mean free testosterone, basal ACTH, basal cortisol, basal aldosterone, or ACTH-stimulated $AUC_{0\text{-}120\ min}$ for aldosterone levels in nebivolol- and atenolol-treated groups relative to placebo. ACTH stimulation at study end produced no cortisol responses < 19 µg/dL, suggesting that all subjects were adrenally sufficient. Aldosterone responses less than 5 ng/dL above unstimulated basal levels occurred in a total of nine subjects among the three treatment groups. Poststudy evaluation indicated that seven of these nine subjects had aldosterone responses to ACTH stimulation that were greater than or equal to 5 ng/dL. Because, the ACTH-stimulated aldosterone test, as described by Dluhy in 1974, may be useful in the differential diagnosis of adrenal hypofunction, its utility in the setting of adrenal sufficiency is unclear. As a result, DMEP does not place much emphasis on these results.

There were no SAEs and no deaths during the study. Overall, the percentages of AEs were similar for the nebivolol and atenolol treatment groups. Headache was the most frequent AE in all three treatment groups. Two subjects each in the nebivolol and atenolol group discontinued from the study for AEs (3.6% and 4.0%, respectively). There were no significant differences between the three treatment groups in any of the other safety measures.

RESPONSE TO QUESTIONS FROM CARDIO-RENAL

1. Do you find the methods of hormone sampling in this study to be acceptable and the results to be reliable?

Yes, the methods of hormone sampling and processing, as described above and in study NEB-PK-03, are appropriate and should yield reliable results.

2. Do the significant number of drop-outs in this study make the results uninterpretable?

No. Of the 157 subjects who received double-blind treatment, 119 (76%) completed the study. More subjects in the placebo group (48/52, 92%) than in the nebivolol (42/55, 76%) or atenolol (29/50, 58%) groups completed the study. The goal, for statistical purposes, was to obtain 30 subjects in each treatment and control group. Only the positive control (atenolol) group failed to meet this goal by obtaining 29 subjects. The randomized population and the intent-to-treat (ITT) population were comparable. Baseline levels of stimulated cortisol were also similar in the randomized and ITT populations. The lack of differences between the two

populations for measured attributes suggests that the loss of patients did not materially affect the balance between treatment groups achieved by randomization.

3. What do you make of the peak ACTH stimulated aldosterone level < 5 ng/dl above basal level on Day 57 in 4 placebo, 2 atenolol, and 3 nebivolol subjects? On Day 8 (baseline), there were 2 placebo, 1 atenolol, and 3 nebivolol subjects who had an abnormal ACTH stimulated aldosterone level. Post-study, only 1 subject in the placebo group and 1 subject in the nebivolol group still had a peak ACTH-stimulated aldosterone level < 5 ng/dl above unstimulated basal aldosterone level.

Aldosterone-response to ACTH was not evaluated at baseline. On treatment Day 8, 113 subjects in the three treatment groups had peak ACTH-stimulated aldosterone levels greater than 5 ng/dL the basal aldosterone level. Six subjects (placebo n = 2/48; nebivolol n = 3/42; atenolol n = 1/29) had aldosterone responses less than 5 ng/dL above basal unstimulated aldosterone level. None of these subjects had a cortisol level less than 19 µg/dL following ACTH stimulation at baseline, suggesting adequate adrenal reserve. At Day 57, 9 subjects (placebo n = 4/48; nebivolol n = 3/43; atenolol n = 2/29) had aldosterone levels equal to or less than 5 ng/dL above basal aldosterone levels in response to ACTH stimulation. Compared with placebo, nebivolol treatment was associated with a 14% reduction in the incidence rate (odds ratio = 0.853; 90% CI – 0.228, 3.194) of this occurrence. Atenolol treatment was associated with a 17% reduction in incidence of occurrence relative to placebo-treated subjects having an odds ratio of 0.790 (90% CI = 0.179, 3.485).

Based upon cortisol results, there is no evidence that treatment with nebivolol results in adrenal insufficiency. Given that the cortisol response was normal and aldosterone is mainly regulated by the renin/angiotensin pathway, the aldosterone results are not clearly interpretable. The ACTH-stimulated aldosterone test, as described by Dluhy in 1974, "can be useful in differential diagnosis when adrenal hypofunction is suggested by a subnormal cortisol response."[1] However, in the setting of a normal cortisol response, the ACTH-stimulated aldosterone test may not be informative. For these reasons, the Division does not place much emphasis on the peak ACTH stimulated aldosterone level < 5 ng/dl above basal level on Day 57 in 4 placebo, 2 atenolol, and 3 nebivolol subjects; the abnormal ACTH stimulated aldosterone level on Day 8 (baseline) in 2 placebo, 1 atenolol, and 3 nebivolol subject; and the peak ACTH-stimulated aldosterone level < 5 ng/dl above unstimulated basal aldosterone level post-study in one placebo and one nebivolol subject.

4. Do you agree with the sponsor's conclusions that nebivolol and atenolol did not demonstrate any significant changes in adrenal function? Do you think nebivolol is unlikely to cause adrenal insufficiency with long-term use at the 10 mg dose?

Yes, DMEP agrees that in Study NEB-PK-03, nebivolol and atenolol did not demonstrate significant alterations in adrenal function. Given these results,

nebivolol is unlikely to cause clinically significant adrenal insufficiency with long-term use at the 10 mg dose in patients with baseline normal adrenal function.

5. Do you feel that the population size was sufficient to capture the effects of nebivolol on the adrenal gland? (Question arose at the 10/1/2007 nebivolol team meeting)

Yes. NEB-PK-03 was designed to enroll approximately 120 healthy men ages 18 – 50 years. The Sponsor anticipated that 90 subjects (30/treatment group) would complete the study. This plan was accepted by the Division in the consult dated June 7, 2006. Previously, a smaller study of 12 subjects suggested a possible signal after exposure to lower doses of nebivolol. As outlined in the June 2006 consult, a study size of 30 subjects per treatment group would be sufficient to determine if this was a true signal. Although the ITT atenolol population was 29 at study completion, the nebivolol ITT sample size was 42.

As described above, study NEB-PK-03 suggests that there is no effect of nebivolol on the adrenal. Utilizing the rule of three, adrenal insufficiency would have been detected in this population with 95% confidence if it occurred with a frequency ≥7%.

References:

1. Vermeulen A, Verdonck L, Kaufman JM: A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endcrinol Metab*: 84:3666-72, 1999.

2. Dluhy RG, Himathongkam T, Greenfield M: Rapid ACTH test with plasma aldosterone levels. *Ann Int Med* 80:693-696, 1974.

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/s/

Valerie Pratt
10/10/2007 09:30:53 AM
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10/19/07

CLINICAL REVIEW

Application Type	NDA 21,742
Submission Number	N(000)
Submission Code	505(b)(1)
Letter Date	May 30, 2007
Stamp Date	May 31, 2007
PDUFA Goal Date	October 31, 2007
Reviewer Name	Karen A. Hicks, M.D.
Review Completion Date	October 19, 2007
Established Name	Nebivolol
(Proposed) Trade Name	----------
Therapeutic Class	Selective β1 blockade
Applicant	Mylan Bertek
Priority Designation	2nd cycle review (Standard)
Formulation	PO
Dosing Regimen	2.5 mg, 5 mg, 10 mg
Indication	Hypertension
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of nebivolol for the treatment of mild to moderate hypertension.

Nebivolol is a selective β1 receptor antagonist and a new molecular entity. The efficacy of nebivolol as an antihypertensive agent was established during the first cycle review. However, preclinical studies demonstrated nebivolol was associated with statistically significant and dose-related increases in benign and malignant Leydig cell tumors in male mice, and there were possible endocrinologically-mediated observations in the rodent chronic and reproductive/developmental toxicity studies. Additionally, BEL-52, which was an open-label study in 12 healthy male and premenopausal women volunteers who received nebivolol 5 mg daily for 7 days, showed changes in the hypothalamic-pituitary axis, including slightly lower basal adrenocorticotropic hormone (ACTH) levels post- vs. pre-treatment with nebivolol, lower basal cortisol levels post-nebivolol treatment, a statistically significant reduction in 24-hour urinary cortisol levels post-nebivolol, and a lower post-nebivolol ACTH peak during the insulin test.

The Agency's May 31, 2005 Action Letter and correspondences dated July 11 and July 28, 2005 indicated nebivolol was "Approvable" if the sponsor could establish the mechanism by which nebivolol was responsible for these findings in male mice, prove that the findings were not relevant in humans, and demonstrate nebivolol treatment did not alter adrenal function, LH, or testosterone levels in human males.

The sponsor completed Studies NEB-TX-02 and NEB-PK-03 which were designed with input from the Agency. Study NEB-TX-02 evaluated the effect of subcutaneous dihydrotestosterone (DHT) administration on serum luteinizing hormone (LH) levels and Leydig cell proliferation in male mice following gavage administration of nebivolol for 28 days. NEB-TX-02 demonstrated nebivolol significantly suppressed circulating testosterone levels ($p < 0.0005$) and increased LH at both 4 hours and 6 hours on Day 28 which was accompanied by an increased incidence of Leydig cell hyperplasia. However, if hormonal pulses were removed, there was no difference between the LH values in the control and nebivolol groups. Furthermore, the administration of DHT, alone or in combination with nebivolol, decreased LH levels and resulted in Leydig cell atrophy, compared to control and nebivolol-treated animals. Therefore, NEB-TX-02 supports an indirect effect of nebivolol on LH secretion.

NEB-PK-03 was a randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. The primary pharmacodynamic endpoint was the area under the curve from time zero to 120 minutes ($AUC_{0\text{-}120\ min}$) of ACTH-stimulated (IV dose of 250 μg) serum cortisol levels at end of study. Secondary pharmacodynamic endpoints were the mean levels of three basal LH measurements on Day 56 (20 minutes apart as scheduled) and the mean serum levels of total testosterone on Day 56. The study consisted of 1 week of single-blind matching-placebo run-in, followed by 1 week of double-blind low-dose treatment (nebivolol 5 mg/d, atenolol 50 mg/d, or placebo), followed by 6 weeks of double-blind high-dose treatment (nebivolol 10 mg/d, atenolol 100 mg/d, or placebo). NEB-PK-03 demonstrated nebivolol had no significant effect on ACTH-stimulated mean serum cortisol $AUC_{0\text{-}120\ min}$, serum LH, or serum total testosterone. There were also no significant differences in mean free testosterone, basal ACTH, basal cortisol, basal aldosterone, or ACTH-stimulated $AUC_{0\text{-}120\ min}$ aldosterone levels in nebivolol- and atenolol-treated groups relative to placebo. ACTH stimulation at end of study produced no cortisol responses < 19 μg/dL, suggesting that all subjects were adrenally sufficient. Therefore, after 49 days of daily nebivolol treatment, including 7 days at the 5 mg dosage and 42 days at the 10 mg dosage, nebivolol did not demonstrate any significant changes in adrenal or gonadal function. These findings suggest that the Leydig cell tumors in male mice are species specific.

NEB-PK-03 was adequately powered to detect a clinically meaningful difference between treatment groups. Per the Division of Metabolism and Endocrinology Products, utilizing the rule of three, adrenal insufficiency in NEB-PK-03 "would have been detected in this population with 95% confidence if it occurred with a frequency ≥ 7%." Furthermore, Dr. Sonia Castillo's statistical review states "NEB-PK-03 had 99% power to detect a reduction in [serum] total testosterone of 20% or greater in the nebivolol group compared to the placebo group." Based on Dr. Castillo's analysis, only 16 subjects per group were required to detect a ≥ 20% reduction in serum total testosterone in the nebivolol group compared to the placebo group."

An analysis of the nine safety endpoints from NEB-PK-03 was performed by Dr. Yaning Wang from the Office of Clinical Pharmacology. His analysis included results from 4 poor metabolizers of cytochrome P4502D6 who achieved significantly higher exposure of l-nebivolol or d-nebivolol. His analysis found no significant difference between placebo and nebivolol groups in terms of change from baseline for 7 out of the 9 endpoints, including $AUC_{0\text{-}120\ min}$ aldosterone, $AUC_{0\text{-}120\ min}$ cortisol, mean luteinizing hormone, peak post-ACTH aldosterone above basal level, peak post-ACTH cortisol, peak post-ACTH cortisol above basal, and sex hormone binding globulin (SHBG). However, the other two endpoints, free testosterone and total testosterone, suggested a possible relationship with nebivolol. With free testosterone, there were "marginal significant p-values in both regression analysis ($p = 0.03$) and t-test ($p=0.07$). However, the direction of this relationship [was] opposite of hormone suppression, which [was] highly influenced by one outlier observation in [the] nebivolol group (patient 59038 with [an] 18 unit increase in free testosterone level at the end of study). The same influence was also observed for total testosterone level." He concluded that "overall, these results do not support the observation from animal data which suggested suppression of male hormone by nebivolol."

When the Division of Reproductive and Urologic Products (DRUP) was asked if the increase in free and total testosterone levels at the end of study could become clinically significant over a longer period of time, DRUP did not think the approximately 8% increase in testosterone levels would approach a level of concern since other agents had been approved with greater increases. Per DRUP, the only expected adverse events related to breast or testicles would be breast tenderness and/or gynecomastia. Although breast tenderness was reported in the nebivolol safety database, the rate of this adverse event was not substantially increased in patients receiving nebivolol compared to placebo. As for gynecomastia, twelve patients receiving nebivolol reported this adverse event. Eleven of these patients were also receiving spironolactone, known to cause gynecomastia, and the other patient had a prior history of gynecomastia. Furthermore, there were no cases of testicular cancer or Leydig cell tumors in the nebivolol development program and the incidence of breast cancer was low.

Since the safety review does not provide definitive evidence of hormonally mediated adverse events, it appears the preclinical findings are not likely to be relevant in humans. Per the Division of Metabolism and Endocrinology Products, based on the results of NEB-PK-03, "nebivolol is unlikely to cause clinically significant adrenal insufficiency with long-term use at the 10 mg dose in patients with baseline normal adrenal function." However, per DRUP, "without data from long-term studies, significant effects or lack of effects on gonadal function remain conjectural."

1.2 Recommendation on Postmarketing Actions

There are no required Phase 4 Commitments. However, the sponsor has 2 studies, NEB-310 and NEB-324, which are currently in progress. Unlike Study NEB-323, which the sponsor planned to terminate with FDA approval of nebivolol during the first cycle review, the sponsor should ensure that the following studies are completed and the Clinical Study Reports submitted for review. Both NEB-310 and NEB-324 incorporate special safety measures including Male and Female Health Questionnaires, breast examinations in males and females, and testicular examinations in males to help determine whether or not nebivolol is associated with any hormonally-mediated adverse events.

NEB-310, entitled, "A Double-Blind, Randomized, Placebo- and Active-Controlled, Force Titration Study Evaluating the Effects of Nebivolol on Blood Pressure and Heart Rate in African American Patients with Hypertension," had randomized approximately 651 patients as of August 6, 2007 and is expected to be completed in October 2007. NEB-310 is still a blinded study. The sponsor is targeting database lock for November 2007, top-line results for December 2007, and the clinical study report for January 2008. NEB-310 studies doses of nebivolol up to 20 mg. The planned duration of the study is up to 162 days.

NEB-324, entitled, "An Open-Label, Randomized Study Evaluating the Long-Term Effects of Metoprolol versus Nebivolol as Monotherapy or in Combination with Amlodipine or Hydrochlorothiazide for the Treatment of Patients with Hypertension," had enrolled 332 patients as of July 26, 2007. Patients who completed a previous nebivolol study within 5 days of Visit 1 for NEB-324 were eligible for enrollment. The targeted completion date of this open-label long-term trial will be after the last patient is enrolled in the study at the close of NEB-310. In NEB-310, the

sponsor plans to enroll up to 1,000 patients and ≥ 500 patients will be exposed to nebivolol for at least one year. NEB-324 studies doses of nebivolol up to 10 mg. The planned duration of the study is up to 560 days.

1.2.1 Risk Management Activity N/A

1.2.2 Required Phase 4 Commitments N/A

1.2.3 Other Phase 4 Requests N/A

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Please see my prior reviews dated January 31, 2005 and April 22, 2005 for full details. The original NDA submission dated April 29, 2004 included four primary randomized, placebo-controlled clinical trials (NEB-202, -302, -305, -321), one active-controlled study (NEB-203) and two primary uncontrolled clinical trials (NEB-306, -323). In these studies, a total of 2,468 patients were treated with nebivolol at doses ranging from 1.25 mg to 40 mg and nebivolol was found to significantly reduce trough sitting diastolic blood pressure in patients with mild to moderate hypertension. In the original NDA, the sponsor also submitted 151 supportive studies.

The US nebivolol hypertension clinical development program represents 1014 person-years of nebivolol use with over 130 patients exposed to nebivolol for over 360 days.

The current submission includes Clinical Study Reports for NEB-PK-03, NEB-323 and two clinical pharmacology studies (NEBI-0398 and NEBI-0438). NEB-PK-03 was designed to evaluate the effect of nebivolol on $AUC_{0\text{-}120\ min}$ of ACTH-stimulated serum cortisol levels, LH, and total testosterone. NEB-323 was an open-label study to assess the long-term safety and efficacy of nebivolol exposure in patients with mild to moderate hypertension. NEB-0398 was conducted to determine the pharmacokinetic and pharmacodynamic effects of co-administration of nebivolol hydrochloride and Viagra® in healthy adult male extensive metabolizer volunteers, and NEBI-0438 was performed to investigate the bioequivalence of Mylan's nebivolol 5 mg tablets to Menarini's Nebivolol 5 mg tablets.

The submission also includes summaries of 4 in vitro studies evaluating nitric oxide and peroxynitrite release from human endothelial cells following incubation with nebivolol and various metabolites. Please see Section 3.2 for a description of these studies and Section 7 for the reviews of each individual study.

1.3.2 Efficacy

The sponsor did not make any efficacy claims in this second cycle review.

1.3.3 Safety (Please see Section 1.1)

There are no new safety issues.

After 49 days of nebivolol treatment, including 7 days at the 5 mg/day dosage and 42 days at the 10 mg/day dosage, NEB-PK-03 demonstrated nebivolol had no significant effects on mean adrenocorticotropic hormone (ACTH)-stimulated $AUC_{0\text{-}120\ min}$ of serum cortisol, mean luteinizing hormone levels, and mean total testosterone levels, as displayed in Tables 1 through 3.

Table 1. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Adrenocorticotropic Hormone-Stimulated $AUC_{0\text{-}120\ min}$ of Serum Cortisol Levels at End of Study--Intent-to-Treat Population (NEB-PK-03)

Serum cortisol levels, µg/dL x h	Placebo (n=48)	Atenolol (n=29)	Nebivolol (n=42)
Mean $AUC_{0\text{-}120\ min}$ (SD)			
Day 8 (baseline)	55.04 (6.337)	56.71 (5.629)	55.70 (5.802)
Day 57	55.80 (7.096)	57.98 (6.374)	56.13 (5.645)
LSM[a] (SE)	55.895 (1.01)	57.188 (1.11)	55.887 (0.94)
LSMD[a,b] (90% CI)	-	1.29 (-0.31, 2.90)	-0.01 (-1.45, 1.43)
LSMD[a,c] (90% CI)	-	2.31 (-0.55, 5.18)	-0.01 (-2.59, 2.56)

[a]Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate
[b]Active minus placebo (expressed as µg/dL x hour)
[c]Active minus placebo (expressed as a percentage of placebo least squares mean)
AUC=area under the plasma concentration versus time curve; N=number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 57; LSM=least squares mean; LSMD=least squares mean differences.
Cross reference: Table 14.4.1.1.
Reproduced from Sponsor, Clinical Study Report, Table 11.1.1.1-1, page 74 of 5947.

Table 2. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Luteinizing Hormone Levels at Day 56--Intent-to-Treat Population (NEB-PK-03)

Luteinizing Hormone Levels, IU/L	Placebo (n=48)	Atenolol (n=29)	Nebivolol (n=42)
Mean (SD)			
Day 7 (baseline)	4.40 (1.386)	4.29 (1.513)	4.72 (1.828)
Day 56	4.52 (1.428)	4.31 (1.352)	4.76 (1.965)
LSM[a] (SE)	4.24 (0.31)	4.09 (0.34)	4.32 (0.29)
LSMD[a,b] (90% CI)	-	-0.15 (-0.63, 0.34)	0.08 (-0.36, 0.52)

[a]Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate
[b]Active minus placebo (expressed as IU/L)
N=number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 56; LSM=least squares mean; LSMD=least squares mean differences.
Cross reference: Table 14.4.2.1.
Reproduced from Sponsor, Clinical Study Report, Table 11.1.1.2-1, page 76 of 5947.

Table 3. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Total Testosterone Levels at Day 56--Intent-to-Treat Population (NEB-PK-03)

Total Testosterone Levels, ng/dL	Placebo (n=48)	Atenolol (n=29)	Nebivolol (n=42)
Mean (SD)			
Day 7 (baseline)	551.9 (138.59)	542.6 (125.50)	561.7 (156.21)
Day 56	549.0 (130.51)	516.1 (173.88)	588.4 (167.08)
LSM[a] (SE)	578.92 (25.71)	553.06 (28.13)	606.00 (23.78)
LSMD[a,b] (90% CI)		-25.85 (-66.31, 14.61)	27.08 (-9.41, 63.58)

[a]Analyses are based on an analysis-of-covariance model with the treatment group, CYP 2D6 metabolic status, and study center as factors and the corresponding baseline value as a covariate
[b]Active minus placebo (expressed as ng/dL)
N=number of subjects in the Intent-to-Treat Population with available analysis value at both baseline and Day 56; LSM=least squares mean; LSMD=least squares mean differences.
Cross reference: Table 14.4.2.2.
Reproduced from Sponsor, Clinical Study Report, Table 11.1.2.2-1, page 77 of 5947.

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. NEB-PK-03 used a nebivolol dose of 10 mg. The sponsor plans to market the 2.5, 5.0, and 10.0 mg tablets. The sponsor's recommended maximum dose is 10 mg daily.

1.3.5 Drug-Drug Interactions

Study NEBI-0398 was a Phase I open-label pharmacokinetic and pharmacodynamic assessment of the effects of co-administration of nebivolol hydrochloride and Viagra® in healthy adult male volunteers. NEBI-0398 demonstrated

that coadministration of sildenafil citrate with steady-state levels of nebivolol resulted in a statistically significant ($p < 0.01$) depression in average systolic and diastolic blood pressure over a 24-hour dosing interval, relative to either moiety being administered alone.

Steady-state nebivolol alone resulted in decreases in average and peak systolic blood pressures of -12.92 and -22.70 mm Hg, respectively, as well as decreases in average and peak diastolic blood pressures of -8.97 and -15.86 mm Hg, respectively.

Single dose sildenafil produced decreases in average and peak systolic blood pressure of -3.57 and -13.55 mm Hg, respectively, and decreases in average and peak diastolic blood pressure of -2.28 and -9.57 mm Hg.

However, coadministration of sildenafil in the setting of steady-state nebivolol resulted in decreases in average and peak systolic blood pressures of -15.89 and -26.55 mm Hg, respectively, as well as decreases in average and peak diastolic blood pressures of -11.53 and -18.81 mm Hg, respectively. For combination dosing of nebivolol at steady state and sildenafil citrate on Day 10, the time to peak decrease in SBP was 5.5 hours and the time to peak decrease in DBP was 7.15 hours. These results are displayed in Table 4.

Table 4. Mean (%CV) Pharmacodynamic Parameters (after pre-dose profile adjustment) in Thirty-Four Subjects Following a Single, Oral 100 mg (1x100 mg) Dose of Sildenafil citrate, a Steady-State Concentration of 10 mg Oral Nebivolol Hydrochloride (1 x 10 mg) Tablets, or Both (NEBI-0398)

Parameter	Single-dose Sildenafil (Day 1)	Steady-State Nebivolol (Day 9)	Steady-State Nebivolol + Single-dose Sildenafil (Day 10)	Least Squares Mean Ratio (%)		90% Confidence Interval (%)	
				Day 10 vs Day 1	Day 10 vs Day 9	Day 10 vs Day 1	Day 10 vs Day 9
HRTavg* (beats/minute)	3.06 (-169.0)	-11.64 (44.09)	-9.31 (53.86)	-303.9	79.9	-262 to -346	69 to 91
HRTpeak* (beats/minute)	-6.60 (88.19)	-19.03 (30.03)	-18.68 (31.58)	283.1	98.2	261 to 305	91 to 106
THRTpeak (hr)	-7.32 (107.7)	-7.27 (95.69)	-6.32 (104.5)	86.4	87.0	56 to 117	56 to 118
AUCHRT* (bpm*hr)	73.48 (-169.0)	-279.5 (44.09)	-223.3 (53.86)	-303.9	79.9	-262 to -346	69 to 91
DBPavg* (mmHg)	-2.28 (140.3)	-8.97 (45.06)	-11.53 (36.85)	505.8	128.4	471 – 541	120 – 137
DBPpeak* (mmHg)	-9.57 (38.58)	-15.86 (31.84)	-18.81 (32.15)	196.6	118.6	185 – 208	112 – 126
TDBPpeak (hr)	-6.97 (98.10)	-12.38 (76.69)	-7.15 (105.9)	102.5	57.7	67 – 138	38 – 78
AUCDBP* (mmHg*hr)	-54.68 (140.3)	-215.3 (45.06)	-276.6 (36.85)	505.8	128.4	471 – 541	120 – 137
SBPavg* (mmHg)	-3.57 (117.3)	-12.92 (36.67)	-15.89 (37.73)	445.6	123.1	415 – 476	115 – 131
SBPpeak* (mmHg)	-13.55 (41.11)	-22.70 (35.10)	-26.55 (31.90)	196.0	117.0	185 – 207	110 – 124
TSBPpeak (hr)	-6.68 (90.68)	-8.41 (85.68)	-5.50 (99.71)	82.4	65.4	52 – 113	41 – 90
AUCSBP* (mmHg*hr)	-85.59 (117.3)	-310.0 (36.67)	-381.4 (37.73)	445.6	123.1	415 – 476	115 – 131

* A negative sign (-) in front of a value represents a decrease or depression in that parameters value over baseline levels. No negative sign in front represents an increase in that parameters value from baseline levels. These signs are opposite of that reported in the statistical output which was assessing the depression of that pharmacodynamic parameter from the baseline level.

Source: Section 14.11 – Attachment 3 and Section 14.12 – Attachment 4.

(Reproduced from Sponsor, Clinical Study Report, page 16 of 129)

Therefore, I recommend including information about blood pressure reduction in the "Warnings" section of the label when sildenafil is coadministered with steady-state nebivolol.

1.3.6 Special Populations

The SENIORS study was a randomized, prospective, multi-national, multi-centre, parallel group, placebo-controlled, double-blind phase III study to evaluate the effects of nebivolol on mortality and hospitalizations in clinically stable elderly patients (≥ 70 years) with chronic heart failure. The study was conducted in 11 European countries from September 12, 2000 to March 12, 2004. In SENIORS, patients with NYHA Class I-IV chronic heart failure were randomized to nebivolol (titrated from 1.25 to 10 mg daily) or placebo and followed for up to 39 months. In terms of treatment emergent adverse events, 118 patients (118/1070 or 11.0%) in the nebivolol treatment group experienced bradycardia, compared to 28 patients (28/1064 or 2.6%) in the placebo treatment group. In the

nebivolol treatment group, 16 patients (1.5%) with "bradycardia NOS" and 1 patient (0.1%) with "bradyarrhythmia" had to be discontinued from the trial, compared to 4 patients (0.4%) with "bradycardia NOS" and 0 patients with "bradyarrhythmia" in the placebo treatment group. Based on these results, I recommend that geriatric patients receive a nebivolol starting dose of 2.5 mg, instead of 5.0 mg.

2 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

2.1 CMC (and Product Microbiology, if Applicable)

No chemistry, manufacturing, and/or control issues were identified at the time I completed this review. Please refer to the CMC review which will be completed at a later date.

2.2 Animal Pharmacology/Toxicology

Please see the Executive Summary for the findings from Study NEB-TX-02, entitled, "Effect of Subcutaneous Dihydrotestosterone (DHT) Administration on Serum Luteinizing Hormone (LH) Levels and Leydig Cell Proliferation Following Gavage Administration of Nebivolol for 28 days to Mice."

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

The sponsor submitted an electronic NDA which can be found at the following link: \\CDSESUB1\N21742\N 000\2007-05-30.

3.2 Tables of Clinical Studies

The current submission includes Clinical Study Reports for NEB-PK-03, NEB-323 and two clinical pharmacology studies (NEBI-0398 and NEBI-0438). The submission also includes summaries of 4 in vitro studies evaluating nitric oxide and peroxynitrite release from human endothelial cells following incubation with nebivolol and various metabolites. The clinical studies in this submission are summarized in Table 5.

Table 5. Summary of Clinical Studies

Study ID (Total Randomized)	Study Title	Study Dates	# Subjects Randomized to Each Study Arm	Sex (F=female M=male)
NEB-PK-03 (n=157)	Effects of Nebivolol on Adrenal Function, Luteinizing Hormone, and Testosterone Levels in Healthy Male Volunteers	September 6, 2006-February 28, 2007	Placebo: 52 Atenolol: 50 Nebivolol: 55	All males
NEB-323 (n=85) (open-label)	A Multi-Center, Open-Label Study to Assess the Long-Term Safety and Efficacy of Nebivolol Exposure in Patients with Mild to Moderate Hypertension	October 1, 2003-September 22, 2004	Nebivolol: 85 Nebivolol + Adjunct Therapy: 71/85 or 83.5%	F: 39 M: 46
NEBI-0398 (n=34) (open-label)	A Phase I Open-Label Pharmacokinetic and Pharmacodynamic Assessment of the Effects of Co-Administration of Nebivolol Hydrochloride and Viagra® in Healthy Adult Male Volunteers	Subjects 1-17: June 20-July 2, 2004 Subjects 18-26: 1 August 1-13, 2004	Treatment Regimen: (n=34) Treatment A: 100 mg Viagra on Day 1 Treatment B: 10 mg nebivolol on Days 3 through 9, and Day 11 Treatment C: 100 mg Viagra co-administered with 10 mg nebivolol on Day 10	All males
NEBI-0438 (n=48)	Single-Dose Fasting In Vivo Bioequivalence Study of Nebivolol Tablets (5 mg; Mylan) to Nebivolol Tablets (5 mg; Menarini) in Healthy Volunteers	Period 1: December 3-7, 2005 Period 2: December 17-21, 2005	Treatment A: Mylan Nebivolol Tablets, 5 mg; Treatment B: Menarini Nebivolol Tablets 5 mg Sequence AB: 24 Sequence BA: 24	F: 20 M: 28

3.3 Review Strategy

Please see reviews for each individual study.

3.4 Data Quality and Integrity

Data quality and integrity were acceptable.

3.5 Compliance with Good Clinical Practices

NEB-PK-03, NEB-323, NEBI-0398, and NEBI-0438 were conducted in accordance with the ICH consolidated guidelines for Good Clinical Practice (GCP) and the Code of Federal Regulations which originates from the ethical principles laid down in the Declaration of Helsinki. Written informed consent was to be obtained in all study subjects.

3.6 Financial Disclosures

The sponsor submitted financial disclosure information for studies NEB-PK-03, NEB-323, NEBI-0398, and NEBI-0438. A sponsor representative signed FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and checked Box 1 of the form. The sponsor provided categorical assurance there were no financial arrangements with the clinical investigators, and I am in agreement with this assessment.

4 CLINICAL PHARMACOLOGY

For full details, please see individual study reviews for NEBI-0398 and NEBI-0438. Conclusions from these studies are summarized here:

Study NEBI-0398

1. The steady-state pharmacokinetic disposition of nebivolol hydrochloride tablets is not affected following coadministration with a single dose of sildenafil tablets.
2. However, under steady-state nebivolol conditions, sildenafil citrate tablets are approximately 21% less bioavailable when administered simultaneously with nebivolol hydrochloride.
3. Coadministration of sildenafil citrate with steady-state levels of nebivolol resulted in a statistically significant ($p < 0.01$) depression in average systolic and diastolic blood pressure over a 24 hour dosing interval, relative to either moiety being administered alone.
4. Coadministration of sildenafil with nebivolol resulted in a statistically significant "less than nebivolol alone" reduction of the average heart rate over the 24 hour dosing interval.
5. Extensive metabolizers were studied in NEBI-0398 only. It is likely that poor metabolizers may experience more profound pharmacodynamic effects following coadministration of sildenafil citrate with nebivolol.
6. There were no clinically significant changes in laboratory results or ECG parameters during this study.
7. Labeling should describe blood pressure reduction in the "Warnings" section of the label when sildenafil is coadministered with steady-state nebivolol. Furthermore, if a patient has underlying coronary artery disease and is on nebivolol as well as a nitrate, coadministration of sildenafil with this medical regimen could be hazardous and possibly deadly.

Study NEBI-0438

Mylan's nebivolol tablets are bioequivalent to Menarini's Nebivolol tablets following a single, oral 10 mg (2 x 5 mg) dose under fasting conditions.

5 INTEGRATED REVIEW OF EFFICACY

Please see Section 1.1.

6 INTEGRATED REVIEW OF SAFETY

6.1 Deaths

6.1.1 Studies NEB-PK-03, NEB-323, NEBI-0398, NEBI-0438, NEB-310, and NEB-324

Study populations for NEB-PK-03 and NEB-323 were healthy males ages 18 to 50 years and healthy males and females ≥ 18 years of age, respectively. NEBI-0398 studied healthy nonsmoking males ≥ 18 years of age, and NEBI-0438 evaluated healthy nonsmoking males and females between the ages of 18 and 55.

In Studies NEB-PK-03, NEB-323, NEBI-0398, and NEBI-0438, there were no deaths.

NEB-310 is an ongoing trial (still blinded) studying Black men and women ages ≥ 18 years with mild to moderate hypertension. As of October 18, 2006, there have been no deaths reported in 439 randomized patients.

NEB-324 is an ongoing study in hypertensive men and women ages ≥ 18 years. As of March 1, 2007, there were 9 serious adverse events, including 3 deaths in the nebivolol treatment group and two serious adverse events in the metoprolol treatment group as of March 1, 2007. The deaths on nebivolol therapy are summarized in Table 6.

Table 6. Deaths in the Nebivolol Treatment Group (NEB-324) as of March 1, 2007

Patient (Case)	Age/Sex M: Male F: Female	Cause of Death	Comments
#018180003 (Case #2006G1000098)	75/M	Left cerebral artery infarct with brain death. Mechanical support withdrawn. Patient died ———	The patient began nebivolol 5 mg once daily on 7/19/2006. Sitting blood pressures averaged 152/89 mm Hg at entry into NEB-324. HCTZ 12.5 mg once daily was added to the hypertensive regimen on 8/16/2006 at Visit 2 when sitting blood pressures averaged 163/71 mm Hg. At Visit 3 (9/13/2006), BP was 138/81 mm Hg. On ———, the patient was found obtunded with right upper and lower extremity flaccid paralysis and was hospitalized. Head CT was remarkable for a left cerebral artery infarct. A radioisotope study demonstrated the absence of cerebral blood flow. A decision was made to withdraw support.
#0089800018 (Case #2006G1000126)	34/M	Ventricular fibrillation arrest/asystole/death on ———	The patient was assigned to treatment with nebivolol 5 mg daily on 6/28/2006. The dose was increased to nebivolol 10 mg daily on 7/26/2006. Amlodipine 5 mg daily was added on 8/26/2006. Patient had hypertension since 2003. Family history was significant for the sudden death of 2 sisters, ages 27 and 33, as well as 2 uncles. The patient's father died of cardiovascular disease before the age of 55. QTcB 425 msec on ——ECG.
#008360001 (Case #2007G1000015)	51/M	Unknown (death on ———	The patient began nebivolol 5 mg daily on 2/1/2006. Norvasc 5 mg daily was added in May 2006. Patient had HIV infection since 1993.

6.1.2 SENIORS Trial (MEN199-001)

6.1.2.1 Patient Demographics (SENIORS)

The SENIORS study was a randomized, prospective, multi-national, multi-centre, parallel group, placebo-controlled, double-blind phase III study to evaluate the effects of nebivolol on mortality and hospitalizations in clinically stable elderly patients (≥ 70 years) with chronic heart failure. The study was conducted in 11 European countries from September 12, 2000 to March 12, 2004. In SENIORS, patients with NYHA Class I-IV chronic heart failure were randomized to nebivolol (titrated from 1.25 to 10 mg daily) or placebo and followed for up to 39 months. Approximately 75% of patients in each treatment group were followed for longer than 1 year, with a mean duration of follow-up of 21 months.

Baseline demographics for the SENIORS trial are presented in Table 7. The treatment groups appeared to be fairly well balanced, although the placebo treatment group had a greater percentage of patients with NYHA Class IV

congestive heart failure. Approximately 75% of patients in each treatment group were followed for longer than 1 year (mean duration of follow-up: 21 months).

Table 7. Demographics (Safety Population) (SENIORS)

Parameter		Nebivolol (n=1070)	Placebo (n=1064)
Age (years)	N	**1070**	**1064**
	Mean (SD)	76.1 (4.76)	76.1 (4.56)
	Median	75.1	75.3
	Min-Max	69.7-92.7	69.4-94.7
Sex	Male (%)	658 (61.5)	687 (64.6)
Race	White (%)	1034 (96.6)	1031 96.9)
	Black	3 (0.3)	0
	Oriental	2 (0.2)	0
	Other	2 (0.2)	2 (0.2)
	Missing	29 (2.7)	31 (2.9)
Diabetes	Yes (%)	288 (26.9)	269 (25.3)
Etiology of CHF	Ischemic (%)	798 (74.6)	786 (73.9)
	Ischemic + idiopathic dilated cardiomyopathy	3 (0.3)	7 (0.7)
	Ischemic + other	12 (1.1)	17 (1.6)
	Idiopathic dilated cardiomyopathy	163 (15.2)	157 (14.8)
	Idiopathic dilated cardiomyopathy + other	1 (0.1)	3 (0.3)
	Other	92 (8.6)	94 (8.8)
	Missing	1 (0.1)	0
NYHA Category	I (%)	32 (3.0)	29 (2.7)
	II	605 (56.5)	599 (56.3)
	III	414 (38.7)	412 (38.7)
	IV	19 (1.8)	24 (2.3)
Exposure	≤ 180 Days	177 (16.5)	160 (15.0)
	181 - ≤ 360 Days	99 (9.3)	100 (9.4)
	361 - ≤ 540 Days	228 (21.3)	230 (21.6)
	541 - ≤ 720 Days	211 (19.7)	211 (19.8)
	721 - ≤ 900 Days	138 (12.9)	135 (12.7)
	901 - ≤ 1080 Days	149 (13.9)	154 (14.5)
	1081 to ≤ 1260 Days	68 (6.4)	74 (7.0)
	Patient Years	1667.8	1682.2
Reproduced from Sponsor, Summary of SENIORS Safety Data, Table 2, page 17of 73)			

6.1.2.2 Patient Disposition (SENIORS)

Patient disposition for the SENIORS trial is presented in Table 8.

Table 8. Patient Disposition (Safety Population) (SENIORS)

Disposition	Nebivolol (n=1070)	Placebo (n=1064)
Completer	782 (73.1%)	756 (71.1%)
Early Withdrawal at Patient Request	76 (7.1%)	79 (7.4%)
Lost to Follow-Up	24 (2.2%)	19 (1.8%)
Adverse Event	13 (1.2%)	14 (1.3%)
Death	160 (15.0%)	178 (16.7%)
Other	15 (1.4%)	18 (1.7%)
Reproduced from Sponsor, Summary of SENIORS Safety Data, Table 1, page 16of 73)		

6.1.2.3 Treatment Emergent Adverse Events Leading to Death (SENIORS)

Selected treatment emergent adverse events (TEAEs) leading to death are displayed in Table 9.

Table 9. Reviewer-Selected Treatment Emergent Adverse Events Leading to Death (SENIORS)

SOC Preferred Term	Nebivolol (n=1070)	Placebo (n=1064)
All Cause Mortality	**188 (17.6%)**	**214 (20.1%)**
Any Adverse Event	**165 (15.4%)**	**182 (17.1%)**
Cardiac Disorders	**70 (6.5%)**	**85 (8.0%)**
Acute myocardial infarction	10 (0.9%)	7 (0.7%)
Acute pulmonary oedema	0	2 (0.2%)
Angina unstable	2 (0.2%)	2 (0.2%)
Arrhythmia NOS	2 (0.2%)	1 (0.1%)
Atrial fibrillation	1 (0.1%)	1 (0.1%)
Atrioventricular block complete	0	1 (0.1%)
Cardiac arrest	7 (0.7%)	6 (0.6%)
Cardiac asthma	0	2 (0.2%)
Cardiac failure aggravated	33 (3.1%)	30 (2.8%)
Cardiac failure congestive	1 (0.1%)	2 (0.2%)
Cardiac failure NOS	1 (0.1%)	6 (0.6%)
Cardio-respiratory arrest	2 (0.2%)	6 (0.6%)
Cardio-respiratory distress	0	1 (0.1%)
Cardiogenic shock	3 (0.3%)	4 (0.4%)
Coronary artery disease aggravated	0	2 (0.2%)
Coronary artery disease NOS	1 (0.1%)	0
Coronary artery occlusion	0	1 (0.1%)
Dilatation ventricular	0	1 (0.1%)
Myocardial infarction	3 (0.3%)	2 (0.2%)
Myocardial ischemia	0	3 (0.3%)
Myocardial Reinfarction	2 (0.2%)	1 (0.1%)
Pulmonary oedema NOS	2 (0.2%)	4 (0.4%)
Ventricular arrhythmia NOS	1 (0.1%)	0
Ventricular fibrillation	2 (0.2%)	3 (0.3%)
General Disorders and Administration Site Conditions	**44 (4.1%)**	**58 (5.5%)**
Asthenia	1 (0.1%)	0
Cardiac death	1 (0.1%)	0
Chest pain	0	1 (0.1%)
Death NOS	1 (0.1%)	1 (0.1%)
Malaise	1 (0.1%)	1 (0.1%)
Multi-organ failure	3 (0.3%)	0
Oedema aggravated	1 (0.1%)	0
Pyrexia	0	1 (0.1%)
Sudden cardiac death	2 (0.2%)	14 (1.3%)
Sudden death unexplained	34 (3.2%)	40 (3.8%)
Infections and Infestations	**12 (1.1%)**	**7 (0.7%)**
Vascular Disorders	**16 (1.5%)**	**15 (1.4%)**
Cerebrovascular accident NOS	11 (1.0%)	7 (0.7%)
Reproduced from Summary of SENIORS Safety Data, Table 3.4, Treatment Emergent Adverse Events Leading to Death, pages 70-73..		

6.2 Other Serious Adverse Events

6.2.1 Studies NEB-PK-03, NEB-323, NEBI-0398, NEBI-0438, NEB-310, and NEB-324

In Studies NEB-PK-03, NEBI-0398, and NEBI-0438, there were no serious adverse events.

In Study NEB-323, there was one serious adverse event of left breast cancer in Patient 2652000370, a 67 year-old Caucasian female who previously completed both NEB-305 and NEB-306. She was enrolled in NEB-323 on

10/10/2003 and initiated on nebivolol for hypertension the same day. On ——— her mammogram revealed a left upper quadrant density. Breast biopsy on ——— was remarkable for ductal carcinoma in situ, involving multiple cores of mammary tissue.; she underwent a partial mastectomy on ———, and additional surgery on ———. No action was taken with nebivolol. Total nebivolol exposure is summarized in Table 10.

Table 10. Nebivolol Exposure for Patient #26520000370, Site 265 (NEB-323)

Study	Nebivolol Duration	Nebivolol Dose	Dates	Concomitant Therapy
NEB-305	84 Days	5 mg	9/26/2002-12/20/2002	
NEB-306	215 Days	10 mg	12/21/2002-1/15/2003	Chlorthalidone 25 mg (added 01/12/2003)
		5 mg	01/16/2003-06/22/2003	Amlodipine (added 03/19/2003)
		10 mg	06/23/2003-08/25/2003	
NEB-323	297 Days	5 mg	10/10/2003-10/26/2003	Chlorthalidone continued from NEB-306
		10 mg	10/27/2003-11/11/2003	
		20 mg	11/26/2003-08/02/2004	Amlodipine (added 12/11/2003) Olmesartan (added 12/31/2003)

In NEB-310, there were 8 patients with treatment emergent serious adverse events (TESAEs) as of the data lock for the safety update. These cases remain blinded. In NEB-324, there were 6 TESAEs in addition to the three deaths. TESAEs for NEB-310 and NEB-324 are summarized in Table 11.

Table 11. Treatment Emergent SAEs (NEB-310 and NEB-324)

Patient #	Case #	Age/Sex M: Male; F: Female	Serious TEAE
NEB-310			
0004100012	2005G1000091	77/F	Bilateral headache with visual changes
0102100002	2005G1000082	57/M	Stomach pain/heartburn/blood in stool
0004000011	2005G1000086	50/F	Chest pain and shortness of breath. Patient was discontinued from the study.
0016900014	2005G1000096	39/M	Appendicitis requiring appendectomy
01015000005	2006G1000015	45/M	New onset diabetes with diabetic ketoacidosis (weakness, dizziness, blurred vision)
0063800013	2006G1000018	45/M	Hospitalized for hypertension, headache, and arteriovenous malformation. Double-blind medication was discontinued.
0015800042	2006G1000056	39/F	Miscarriage post 21 days of 2.5 mg nebivolol.
012900003	2006G1000082	42/M	Motor vehicle accident on 1/10/2006. Double-blind study medication was initiated on 10/6/2005.
NEB-324			
0096100001	2005G1000094	61/F	Hospitalized for acute fever and headache
0081700001	2005G1000115	39/M	Hospitalized for fevers, headache, nausea, vomiting, diarrhea, myalgias, and arthralgias 5 days after starting nebivolol 5 mg daily. Patient found to have a tender prostate. Laboratory tests revealed HIV + and mild elevation of ALT (53), AST (92), and total bilirubin (1.8). Treated with Ofloxacin.
0119700010	2006G1000017	70/F	Hospitalized for acute dyspnea, pneumonia, and chronic sinusitis 12 days post initiating nebivolol 5 mg daily.
0154800003	2006G1000042	56/M	Hospitalized for exacerbation of Type II diabetes
0003000012	2006G1000052	40/F	Hospitalized for worsening anemia 31 days after starting nebivolol 5 mg daily. Hematocrit 25.3. Patient was transfused with two units of packed red blood cells
0057100001	2006G1000127	57/F	Hospitalized for a syncopal episode/fall due to transient ischemic attack. In hospital, patient was found to have new onset rate-controlled atrial fibrillation.
0057100001	2007G1000001	57/F	Patient rehospitalized for a pseudoseizure hours after she had been discharged after recovering from a transient ischemic attack that occurred one week earlier. Physical exam remarkable for mild left facial droop/weakness. EEG and Head CT were normal.

ALT: alanine aminotransferase or serum glutamic pyruvic transaminases (SGPT); AST: aspartate aminotransferase or serum glutamic oxaloacetic transaminase(SGOT). No units for labs were specified.
Compiled by Karen A. Hicks, M.D. from Sponsor's Safety Update, pages 19-25.

6.2.2 SENIORS Trial

Selected treatment emergent SAEs for the SENIORS trial are displayed in Table 12.

Table 12. Selected Treatment Emergent SAEs (SENIORS)

SOC Preferred Term	Nebivolol (n=1070)	Placebo (n=1064)
Any Serious Adverse Event	**432 (40.4%)**	**470 (44.2%)**
Cardiac Disorders	**234 (21.9%)**	**277 (26.0%)**
Acute coronary syndrome	2 (0.2%)	1 (0.1%)
Acute myocardial infarction	23 (2.1%)	14 (1.3%)
Acute pulmonary oedema	7 (0.7%)	11 (1.0%)
Age indeterminate myocardial infarction	2 (0.2%)	0
Angina pectoris	7 (0.7%)	14 (1.3%)
Angina pectoris aggravated	1 (0.1%)	6 (0.6%)
Angina unstable	25 (2.3%)	36 (3.4%)
Arrhythmia NOS	5 (0.5%)	6 (0.6%)
Atrial fibrillation	12 (1.1%)	21 (2.0%)
Atrial flutter	3 (0.3%)	3 (0.3%)
Atrioventricular block complete	3 (0.3%)	6 (0.6%)
Atrioventricular block NOS	0	1 (0.1%)
Atrioventricular block second degree	1 (0.1%)	1 (0.1%)
Bradyarrhythmia	1 (0.1%)	0
Bradycardia NOS	**6 (0.6%)**	**6 (0.6%)**
Bundle branch block, right	0	1 (0.1%)
Cardiac arrest	8 (0.7%)	6 (0.6%)
Cardiac asthma	4 (0.4%)	4 (0.4%)0
Cardiac failure aggravated	124 (11.6%)	132 (12.4%)
Cardiac failure chronic	0	1 (0.1%)
Cardiac failure congestive	3 (0.3%)	5 (0.5%)
Cardiac failure NOS	20 (1.9%)	17 (1.6%)
Cardio-respiratory arrest	2 (0.2%)	6 (0.6%)
Cardio-respiratory distress	0	1 (0.1%)
Cardiogenic shock	3 (0.3%)	4 (0.4%)
Cardiopulmonary failure	0	1 (0.1%)
Congestive cardiac failure aggravated	2 (0.2%)	7 (0.7%)
Coronary artery disease aggravated	0	2 (0.2%)
Coronary artery disease NOS	1 (0.1%)	1 (0.1%)
Coronary artery insufficiency	0	1 (0.1%)
Coronary artery occlusion	0	1 (0.1%)
Dilatation ventricular	0	1 (0.1%)
Left ventricular failure	1 (0.1%)	8 (0.8%)
Myocardial infarction	9 (0.8%)	12 (1.1%)
Myocardial ischemia	2 (0.2%)	4 (0.4%)
Myocardial reinfarction	2 (0.2%)	2 (0.2%)
Pericarditis	0	1 (0.1%)
Pulmonary oedema NOS	10 (0.9%)	14 (1.3%)
Sick sinus syndrome	0	1 (0.1%)
Sinus bradycardia	2 (0.2%)	0
Supraventricular arrhythmia NOS	0	1 (0.1%)
Supraventricular tachycardia	1 (0.1%)	1 (0.1%)
Tachyarrhythmia	1 (0.1%)	2 (0.2%)
Tachycardia NOS	0	1 (0.1%)
Ventricular arrhythmia NOS	1 (0.1%)	1 (0.1%)
Ventricular bigeminy	0	1 (0.1%)
Ventricular extrasystoles	1 (0.1%)	3 (0.3%)
Ventricular fibrillation	5 (0.5%)	3 (0.3%)
Ventricular hypokinesia	1 (0.1%)	1 (0.1%)
Ventricular tachycardia	5 (0.5%)	3 (0.3%)
General Disorders and Administration Site Conditions	**68 (6.4%)**	**81 (7.6%)**
Asthenia	2 (0.2%)	1 (0.1%)
Cardiac death	1 (0.1%)	0
Chest pain	11 (1.0%)	12 (1.1%)
Chest pain aggravated	1 (0.1%)	1 (0.1%)
Chest tightness	0	1 (0.1%)
Death NOS	1 (0.1%)	1 (0.1%)
Exercise tolerance decreased	1 (0.1%)	0

SOC Preferred Term	Nebivolol (n=1070)	Placebo (n=1064)
Fall	3 (0.3%)	7 (0.7%)
Fatigue	1 (0.1%)	0
Fatigue, aggravated	1 (0.1%)	0
General physical health deterioration	0	1 (0.1%)
Granuloma NOS	1 (0.1%)	0
Hernia NOS	0	1 (0.1%)
Hyperpryexia	0	1 (0.1%)
Malaise	3 (0.3%)	6 (0.6%)
Multi-organ failure	3 (0.3%)	0
Oedema aggravated	1 (0.1%)	0
Oedema lower limb	2 (0.2%)	0
Oedema NOS	0	1 (0.1%)
Oedema peripheral	2 (0.2%)	0
Pyrexia	2 (0.2%)	3 (0.3%)
Sudden cardiac death	2 (0.2%)	14 (1.3%)
Sudden death unexplained	34 (3.2%)	40 (3.8%)
Weakness	2 (0.2%)	0
Infections and Infestations	**69 (6.4%)**	**53 (5.0%)**
Vascular Disorders	**72 (6.7%)**	**67 (6.3%)**
Cerebrovascular accident NOS	34 (3.2%)	23 (2.2%)
Reproduced from Summary of SENIORS Safety Data, Table 3.4, Treatment Emergent Adverse Events Leading to Death, pages 70-73..		

6.3 Discontinuations due to Adverse Events

6.3.1 Studies NEB-PK-03, NEB-323, NEBI-0398, NEBI-0438, NEB-310, and NEB-324

In NEB-323, NEBI-0398, and NEBI-0438, there were no discontinuations due to adverse events.

In NEB-PK-03, there were 4 discontinuations due to adverse events, including 2 subjects receiving atenolol and 2 subjects receiving nebivolol, as shown in Table 13.

Table 13. Discontinuations Due to Adverse Events (NEB-PK-03)

Subject ID (Age, Race, Sex)	Study Center	Treatment group	Number of Days on Double-Blind Drug	Number of Days in Double-Blind Phase	Specified Reason for Discontinuation (AEs by Preferred Term/Investigator Term)
0049009 (45/C/M)	004	Atenolol	48	49	"Dyspepsia/Indigestion." Date of AE Start/Stop: 6. "Hypotension/Asymptomatic low blood pressure." Date of AE Start/Stop: 49/49.
0049048 (42/AI/M)	004	Atenolol	45	48	"Bradycardia/Asymptomatic Bradycardia." Date of AE Start/Stop: 12/9-12/11/2006. Study drug discontinued.
0049034 (45/C/M)	004	Nebivolol	45	49	"Hypotension." 12/9-12/13/2006. Study drug discontinued.
0049053 (28/C/M)	004	Nebivolol	48	49	"Heart Rate Decreased/Low Heart Rate." 12/12-12/14/2006. Study drug discontinued.
AI: American Indian; C: Caucasian; M: Male **Compiled by Karen A. Hicks, M.D.**					

In NEB-PK-03, 26 other patients were thought to meet the criteria for potentially clinically significant vital signs and were also discontinued from the trial.

In regard to discontinuations due to adverse events, information from NEB-310 and NEB-324 is not available at the time of this review.

6.3.2 SENIORS Trial

Treatment emergent adverse events ≥ 1% leading to discontinuation are summarized in Table 14. Compared to the placebo treatment group, thirteen more patients in the nebivolol treatment group experienced bradycardia or bradyarrhthmia requiring discontinuation.

Table 14. Treatment Emergent Adverse Events ≥ 1% Leading to Discontinuation (SENIORS)

SOC Preferred Term	Nebivolol (n=1070)	Placebo (n=1064)
Any Adverse Event	**165 (15.4%)**	**136 (12.8%)**
Cardiac Disorders	**77 (7.2%)**	**79 (7.4%)**
Bradyarrhythmia	**1 (0.1%)**	0
Bradycardia NOS	**16 (1.5%)**	**4 (0.4%)**
Cardiac failure aggravated	**26 (2.4%)**	**20 (1.9%)**
Cardiac failure congestive	1 (0.1%)	1 (0.1%)
Cardiac failure NOS	3 (0.3%)	1 (0.1%)
Nervous System Disorders	**19 (1.8%)**	**9 (0.8%)**
Dizziness (excluding vertigo)	12 (1.1%)	4 (0.4%)
Reproduced from Summary of SENIORS Safety Data, Table 3.4, Treatment Emergent Adverse Events Leading to Death, pages 70-73..		

6.4 Common Adverse Events

6.4.1 Studies NEB-PK-03, NEB-323, NEBI-0398, NEBI-0438, NEB-310, and NEB-324

Frequent adverse events included headache, fatigue, dizziness, and pharyngolaryngeal pain.

In NEB-PK-03, there were no clinically important adverse events in any of the treatment groups, with the exception of Subject 0029050, a 36 year old Caucasian man in the nebivolol treatment group who experienced three episodes of chest discomfort and Subject 0059025, a 44 year old Asian man in the nebivolol treatment group who experienced two episodes of chest discomfort. For Subject 0029050, no serial 12-lead electrocardiograms (ECGs) or cardiac enzymes were obtained during 2 out of the 3 episodes of chest discomfort. A subsequent ECG demonstrated nonspecific ST-T waves but no obvious Q waves. For Subject 0059025, no serial 12-lead ECGs or cardiac enzymes were obtained during either episode of discomfort. A subsequent ECG was unremarkable. The investigators should have checked serial cardiac enzymes and 12-lead ECGs in these subjects during symptoms to determine if they had experienced myocardial infarctions.

Adverse events reported in ≥ 5% of subjects in any treatment group in NEB-PK-03 are summarized in Table 15.

Table 15. Sponsor's Analysis: Adverse Events Reported in >= 5% of Subjects in Any Treatment Group (Safety Population) (NEB-PK-03)

	No. (%) of Patients		
Adverse Event *(Preferred Term)*	*Placebo* *(N=52)*	*Atenolol* *(N=50)*	*Nebivolol* *(N=55)*
Subjects with ≥ 1 TEAE[a]	30 (57.7)	20 (40.0)	21 (38.2)
Headache	9 (17.3)	8 (16.0)	9 (16.4)
Pharyngolaryngeal pain	1 (1.9)	2 (4.0)	3 (5.5)
Fatigue	3 (5.8)	1 (2.0)	1 (1.8)
Dizziness	4 (7.7)	4 (8.0)	0
Nausea	3 (5.8)	1 (2.0)	0

a Subjects are counted once for "one or more" treatment-emergent adverse events
TEAE = treatment-emergent adverse event
Cross-reference: Table 14.5.1.2.

(Reproduced from Sponsor, Table 12.1.2-1, page 88 of 5947)

Similar adverse events were found in NEB-323, NEBI-0398, and NEBI-0438.

Table 16. Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2.0% of Patients (ITT Population) (NEB-323)

MedDRA Term	Nebivolol (N=85) n (%)
Dizziness	7 (8.2)
Arthralgia	6 (7.1)
Headache NOS	6 (7.1)
Nasopharyngitis	5 (5.9)
Insomnia	4 (4.7)
Arthritis NOS	3 (3.5)
Back pain	3 (3.5)
Cough	3 (3.5)
Diarrhea NOS	3 (3.5)
Hypokalemia	3 (3.5)
Rash NOS	3 (3.5)
Upper respiratory tract infection NOS	3 (3.5)
Back injury NOS	2 (2.4)
Bursitis	2 (2.4)
Constipation	2 (2.4)
Dermatitis contact	2 (2.4)
Fatigue	2 (2.4)
Hypercholesterolemia	2 (2.4)
Hypoesthesia	2 (2.4)
Muscle fatigue	2 (2.4)
Myalgia	2 (2.4)
Nausea	2 (2.4)
Paresthesia	2 (2.4)
Sinus congestion	2 (2.4)
Sinus headache	2 (2.4)
Sinusitis NOS	2 (2.4)
Skin lesion NOS	2 (2.4)
Viral infection NOS	2 (2.4)
Weakness	2 (2.4)

NOS, not otherwise specified
Data Source: Table 3.6.1

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 12.2-01, page 45)

6.4.2 SENIORS Trial

Common treatment emergent adverse events for the SENIORS trial are summarized in Table 17. Approximately 11.0% of patients in the nebivolol treatment group experienced bradycardia, compared to 2.6% in the placebo group.

Table 17. Treatment Emergent Adverse Events ≥ 1% (SENIORS)

SOC Preferred Term	Nebivolol (n=1070)	Placebo (n=1064)
Any Adverse Event	**913 (85.3%)**	**903 (84.9%)**
Blood and Lymphatic System Disorders	**59 (5.5%)**	**56 (5.3%)**
Anaemia NOS	37 (3.5%)	38 (3.6%)
Cardiac Disorders	**568 (53.1%)**	**561 (52.7%)**
Acute myocardial infarction	23 (2.1%)	16 (1.5%)
Acute pulmonary edema	7 (0.7%)	11 (1.0%)
Angina pectoris	52 (4.9%)	72 (6.8%)
Angina pectoris, aggravated	21 (2.0%)	23 (2.2%)
Angina, unstable	31 (2.9%)	45 (4.2%)
Atrial fibrillation	78 (7.3%)	74 (7.0%)
Atrioventricular block, first degree	21 (2.0%)	16 (1.5%)
Bradyarrhythmia	**1 (0.1%)**	**0**
Bradycardia NOS	**118 (11.0%)**	**28 (2.6%)**
Bundle branch block left	6 (0.6%)	11 (1.0%)
Cardiac failure aggravated	256 (23.9%)	265 (24.9%)

SOC Preferred Term	Nebivolol (n=1070)	Placebo (n=1064)
Cardiac failure NOS	34 (3.2%)	30 (2.8%)
Congestive cardiac failure aggravated	5 (0.5%)	11 (1.0%)
Myocardial infarction	9 (0.8%)	12 (1.1%)
Extrasystoles NOS	7 (0.7%)	13 (1.2%)
Myocardial ischemia	34 (3.2%)	33 (3.1%)
Palpitations	15 (1.4%)	23 (2.2%)
Pulmonary edema NOS	18 (1.7%)	20 (1.9%)
Sinus bradycardia	26 (2.4%)	3 (0.3%)
Sinus tachycardia	7 (0.7%)	11 (1.0%)
Supraventricular extrasystoles	15 (1.4%)	17 (1.6%)
Ventricular extrasystoles	30 (2.8%)	44 (4.1%)
Ear and Labyrinth Disorders	**23 (2.1%)**	**19 (1.8%)**
Vertigo	13 (1.2%)	14 (1.3%)
Endocrine Disorders	**18 (1.7%)**	**19 (1.8%)**
Eye Disorders	**29 (2.7%)**	**27 (2.5%)**
Gastrointestinal Disorders	**195 (18.2%)**	**157 (14.8%)**
Abdominal pain upper	22 (2.1%)	10 (0.9%)
Constipation	27 (2.5%)	24 (2.3%)
Diarrhea NOS	33 (3.1%)	21 (2.0%)
Dyspepsia	17 (1.6%)	16 (1.5%)
Nausea	37 (3.5%)	22 (2.1%)
Vomiting NOS	15 (1.4%)	15 (1.4%)
General Disorders and Administration Site Conditions	**297 (27.8%)**	**254 (23.9%)**
Asthenia	18 (1.7%)	9 (0.8%)
Chest pain	45 (4.2%)	26 (2.4%)
Chest pain aggravated	2 (0.2%)	1 (0.1%)
Chest tightness	0	2 (0.2%)
Drug intolerance NOS	19 (1.8%)	9 (0.8%)
Fall	15 (1.4%)	19 (1.8%)
Fatigue	72 (6.7%)	63 (5.9%)
Fatigue aggravated	10 (0.9%)	11 (1.0%)
Lethargy	12 (1.1%)	6 (0.6%)
Malaise	16 (1.5%)	14 (1.3%)
Edema lower limb	55 (5.1%)	24 (2.3%)
Edema peripheral	42 (3.9%)	24 (2.3%)
Sudden cardiac death	2 (0.2%)	14 (1.3%)
Sudden death unexplained	34 (3.2%)	40 (3.8%)
Weakness	16 (1.5%)	11 (1.0%)
Hepatobiliary Disorders	**46 (4.3%)**	**38 (3.6%)**
Infections and Infestations	**284 (26.5%)**	**272 (25.6%)**
Bronchitis acute NOS	27 (2.5%)	32 (3.0%)
Bronchitis NOS	23 (2.1%)	27 (2.5%)
Cystitis NOS	8 (0.7%)	19 (1.8%)
Influenza	35 (3.3%)	31 (2.9%)
Lower respiratory tract infection NOS	14 (1.3%)	12 (1.1%)
Nasopharyngitis	43 (4.0%)	34 (3.2%)
Pneumonia NOS	34 (3.2%)	31 (2.9%)
Respiratory tract infection NOS	16 (1.5%)	13 (1.2%)
Upper respiratory tract infection NOS	10 (0.9%)	12 (1.1%)
Urinary tract infection NOS	35 (3.3%)	19 (1.8%)
Injury, Poisoning and Procedural Complications	**48 (4.5%)**	**57 (5.4%)**
Investigations	**208 (19.4%)**	**182 (17.1%)**
Blood creatinine increased	26 (2.4%)	12 (1.1%)
Blood glucose increased	7 (0.7%)	11 (1.0%)

SOC Preferred Term	Nebivolol (n=1070)	Placebo (n=1064)
Blood pressure decreased	16 (1.5%)	9 (0.8%)
Blood pressure increased	34 (3.2%)	29 (2.7%)
Blood urea increased	26 (2.4%)	20 (1.9%)
Blood uric acid increased	18 (1.7%)	8 (0.8%)
Heart rate decreased	17 (1.6%)	8 (0.8%)
Heart rate increased	11 (1.0%)	15 (1.4%)
Weight decreased	10 (0.9%)	21 (2.0%)
Weight increased	18 (1.7%)	12 (1.1%)
Metabolism and Nutrition Disorders	**176 (16.4%)**	**132 (12.4%)**
Diabetes mellitus aggravated	15 (1.4%)	10 (0.9%)
Diabetes mellitus NOS	15 (1.4%)	19 (1.8%)
Gout	27 (2.5%)	14 (1.3%)
Hypercholesterolaemia	28 (2.6%)	19 (1.8%)
Hyperkalemia	14 (1.3%)	9 (0.8%)
Hyperlipidemia NOS	23 (2.1%)	16 (1.5%)
Hyperuricemia	32 (3.0%)	14 (1.3%)
Musculoskeletal and Connective Tissue Disorders	**124 (11.6%)**	**115 (10.8%)**
Arthralgia	21 (2.0%)	22 (2.1%)
Back pain	29 (2.7%)	20 (1.9%)
Localized osteoarthritis	11 (1.0%)	9 (0.8%)
Pain in limb	23 (2.1%)	20 (1.9%)
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)	**41 (3.8%)**	**40 (3.8%)**
Nervous System Disorders	**279 (26.1%)**	**253 (23.8%)**
Dizziness (excluding vertigo)	166 (15.5%)	142 (13.3%)
Dizziness postural	12 (1.1%)	9 (0.8%)
Headache NOS	62 (5.8%)	52 (4.9%)
Syncope	17 (1.6%)	14 (1.3%)
Transient ischaemic attack	7 (0.7%)	15 (1.4%)
Psychiatric Disorders	**46 (4.3%)**	**52 (4.9%)**
Insomnia	16 (1.5%)	30 (2.8%)
Insomnia exacerbated	2 (0.2%)	0
Renal and Urinary Disorders	**124 (11.6%)**	**108 (10.2%)**
Haematuria	8 (0.7%)	11 (1.0%)
Renal failure acute	3 (0.3%)	1 (0.1%)
Renal failure aggravated	6 (0.6%)	3 (0.3%)
Renal failure chronic	5 (0.5%)	2 (0.2%)
Renal failure chronic aggravated	2 (0.2%)	1 (0.1%)
Renal failure NOS	23 (2.1%)	26 (2.4%)
Respiratory, Thoracic and Mediastinal Disorders	**201 (18.8%)**	**221 (20.8%)**
Cough	22 (2.1%)	30 (2.8%)
Dyspnoea exacerbated	66 (6.2%)	72 (6.8%)
Epistaxis	12 (1.1%)	4 (0.4%)
Skin and Subcutaneous Tissue Disorders	**59 (5.5%)**	**62 (5.8%)**
Pruritus NOS	11 (1.0%)	13 (1.2%)
Surgical and Medical Procedures	**63 (5.9%)**	**62 (5.8%)**
Cataract extraction	8 (0.7%)	17 (1.6%)
Vascular Disorders	**294 (27.5%)**	**268 (25.2%)**
Cerebrovascular accident NOS	36 (3.4%)	23 (2.2%)
Hypertension aggravated	26 (2.4%)	19 (1.8%)
Hypertension NOS	55 (5.1%)	62 (5.8%)
Hypertensive crisis	23 (2.1%)	16 (1.5%)
Hypotension NOS	82 (7.7%)	76 (7.1%)

SOC Preferred Term	Nebivolol (n=1070)	Placebo (n=1064)
Orthostatic hypotension	15 (1.4%)	14 (1.3%)
Postural hypotension	29 (2.7%)	13 (1.2%)
Reproduced from Sponsor, Summary of SENIORS Safety Data, Table 3.1, pages 19-49.		

6.5 Laboratory Findings, Vital Signs, and Electrocardiograms

There are no new safety issues.

6.6 Breast Cancer, Breast Tenderness, Testicular Masses, and Gynecomastia

In the nebivolol development program and in worldwide post-marketing pharmacovigilance, approximately 5 cases of breast cancer, 5 cases of breast pain, 1 case of breast tenderness, 2 cases of nipple pain, and 12 cases of gynecomastia were reported. There has also been 1 case of breast mass NOS, 1 case of breast disorder NOS, and 4 cases of breast lump.

In the Safety Review by Dr. Salma Lemtouni dated February 9, 2005, the following less common adverse events in the Phase 2/3 trials of the primary program were noted:

> "**Reproductive system and breast disorders:** Erectile dysfunction in 10 (0.4%); dysmenorrhea in 5 (0.2%); prostatitis in 4 (0.2%); breast cyst in 2; sexual dysfunction NOS in 1; amenorrhea in 1; breast mass NOS in 1; breast pain and breast tenderness in 1 each; dysfunctional uterine bleeding in 1; galactorrhea in 1; menopausal symptoms in 1; menorrhagia in 1; nipple pain in 1; post-menopausal bleeding in 1; vaginal discharge in 1.
>
> **Neoplasm:** Breast lump in 4 (0.2%); lipoma in 3; solar keratosis in 3; colon cancer in 2; bladder cancer, **breast cancer**, lung squamous cell carcinoma, small cell lung cancer, throat cancer, peripheral nervous system neoplasm NOS, and skin papillomas in 1 each."
>
> Dr. Lemtouni also noted that there were **2** adverse events of **malignant breast cancer** that led to patients being discontinued from the secondary program.

In NEB-323, there was 1 **breast cancer** which was previously described. NEB-323 also had (1) each of erectile dysfunction NOS, intermenstrual bleeding, menopausal symptoms, prostatitis, and sexual dysfunction NOS.

In SENIORS, there was (1) **breast cancer** NOS each in the nebivolol (Patient #1585, 82 year old Caucasian woman receiving nebivolol up to 10 mg daily from 2/14/2003-7/22/2003) and placebo treatment groups. The placebo group also had (1) "breast lump NOS" and (1) "breast neoplasm NOS." Under Reproductive System and Breast Disorders, in the **nebivolol** treatment group there were 10 benign prostatic hyperplasia, **1 breast disorder NOS, 3 breast pain, 9 gynecomastia (0.8%), 1 gynecomastia aggravated (0.1%)**, 2 orchitis NOS, 1 prostatitis, and 1 scrotal oedema. In the **placebo** group, there were 6 benign prostatic hyperplasia, 1 breast pain, **5 gynecomastia (0.5%),** 1 hydrocele, 1 penile pain, 1 prostatic disorder NOS, and 2 prostatitis. All 10 nebivolol patients with gynecomastia were receiving spironolactone, and 2 of these patients also had preexisting gynecomastia.

In NEB-310, blinded data demonstrated the following emergent adverse events: 1 breast mass, 3 breast tenderness, 3 erectile dysfunction, 1 menorrhagia, 1 metrorrhagia, 1 ovarian cyst, 1 ovarian cyst ruptured, 1 scrotal pain, 1 prostatic hypertrophy, **2 alpha fetoprotein increased**, and **1 testicular mass**. Neither Patient 0102100002 (nebivolol) nor Patient #0102900028 (atenolol in NEB-310 and nebivolol in NEB-324) with elevated alpha fetoprotein levels developed testicular cancer or a Leydig cell tumor. As for the testicular mass, Patient #0097300002, a 56 year old man, was found to have a testicular mass [redacted] during the routine physical examination. He began double-blind medication on 8/27/2005. A testicular ultrasound on [redacted] showed bilateral prominent rete testes with bilateral cystic lesions, and a separate less well-defined right lateral testicle hypoechoic area. Alpha fetoprotein levels were normal. A follow-up testicular ultrasound [redacted] was unchanged, but a urologist could not palpate a mass. The patient was discontinued from the study on 12/30/2005 due to the event. Upon FDA request, the patient's treatment group was unblinded, and he had received placebo.

As of 3/1/2007, **2 cases of gynecomastia** have been reported in Worldwide Post-Marketing Pharmacovigilance. One case (2006G1000101) was associated with spironolactone use and 1 case (2005G1000095) was in an elderly patient with a prior history of gynecomastia. Pharmacovigilance also demonstrated 1 amenorrhoea, 1 breast enlargement, 1 breast pain, 37 erectile dysfunction, 1 metrorrhagia, 1 nipple pain, and 1 sexual dysfunction.

6.7 Worldwide Post-Marketing Pharmacovigilance

6.7.1 Deaths

There have been 14 deaths reported during postmarketing use of nebivolol.

Table 18. Post-Marketing Deaths (From Investigator's Brochure, 8/18/2006: N(241) IM) and Postmarketing Reports

Case ID	Age/Sex M: Male F: Female	Cause of Death	Narrative
2004S1000051	75/F	Sudden death	Treated with nebivolol 5 mg/day for hypertension. Six days later, the patient was **found dead at home** with froth in her mouth. Medical history: coronary artery disease, gout, dementia. Concomitant medications: triamterene/hydrochlorothiazide, memantine.
2005G1000092, 051R-MENIR-064	57/M	Sudden death	Patient had been receiving nebivolol 30 mg/day for approximately 1 week. The patient had also been receiving amiodarone, but the dates were not specified. The patient experienced **cardiac failure and sudden death.** Medical history unknown. Concomitant medications: OxyContin.
2004S1000097, U2001-643	81/F	Myocardial infarction	Patient suddenly collapsed in front of her house. She had been treated with nebivolol 2.5 mg/day for 3.5 weeks. The emergency physician found her with gasping breath and made a diagnosis of **myocardial infarction.** She died the same day. Medical history: heart failure, coronary artery disease, peripheral occlusive disease, atrial fibrillation, glaucoma, left ventricular hypertrophy, multiple occlusion of left popliteal artery with embolectomy, aortic valve sclerosis with aortic valve insufficiency grade II. Concomitant medications: furosemide, warfarin, isosorbide, hypericum extract (St. John's Wort), Vertigoheel®.
MENIT43883	71/	Sudden death	This patient received 3 days of nebivolol for severe hypertension and **died suddenly**. Medical history: adiposis, diabetes, coronary atherosclerosis. Concomitant medications: hydrochlorothiazide/enalapril, candesartan, amitriptyline, gliclazide, aloxiprin, pravastatin.
2004S1000113, CSM 420617	70/M	Sudden death	Patient had been taking nebivolol for about 7 months and **died suddenly**. No autopsy was performed. There was no history of ischemic heart disease or hyperlipidemia. However, he had mildly impaired glucose tolerance. Medical history: unknown. Concomitant medication: bendroflumethiazide.
2004S1000179, U2004294	93/F	Pulmonary edema/death	Patient suffered from pulmonary edema due to digitalis intoxication. She was hospitalized and digitalis was discontinued. Nitrendipine and nebivolol were initiated, and she recovered. She was discharged to a nursing home where the dose of nitrendipine was decreased. Four weeks after the start of nebivolol, the patient again developed **pulmonary edema and died**. Medical history and concomitant medications unknown.
JATCH16260	63/F	Sudden death	Patient was receiving nebivolol 5 mg/day as compassionate use for heart failure, after completing neb-tch-9004 trial. She **suddenly died.** Congestive heart failure was diagnosed. Medical history: hepatomegaly. Concomitant medications: amiloride, codeine, aminophylline.
JRFBEL1999001191	Late 80s/M	Death in setting of known congestive heart failure	Patient **died** after 63 days of nebivolol therapy for heart failure.
JRFBEL1999001193	54/F	Death due to Unspecified Accident	Patient **died due to an unspecified accident**, 1 month after starting nebivolol for hypertension. Medical history and concomitant medications unknown.
JRFBEL1999001194	68/M	Probable cardiac failure	Patient died 2 weeks after his last intake of nebivolol due to cardiac failure. The patient had received nebivolol for 36 days. Medical history: disturbed metabolism. Concomitant medications: unknown.
JRFBEL1999001195 (0)	70/M	Bronchial carcinoma	Patient received nebivolol 5 mg/day for an unknown period of time. He had a history of hypertension and **bronchial carcinoma**. He died due to his preexisting carcinoma.

Case ID	Age/Sex M: Male F: Female	Cause of Death	Narrative
MENIT42429	74/F	Suspected cerebral embolism	Patient was on nebivolol 5 mg/day for an unspecified time and digitoxin. She developed sudden syncope with nausea, emesis, paleness, and sweating. ECG showed bradyarrhythmia (HR of 35/min); also suspected stroke was diagnosed. At the hospital, digitoxin and nebivolol were discontinued. A temporary pacemaker was placed, and she was heparinized. The patient died 2 days later due to a **suspected cerebral embolism**. Medical history: unknown. Concomitant medications: isosorbide, valsartan, thiamazole, glibenclamide, xipamide, nisoldipine.
MENIT42431	78/F	Pneumonia	Patient was on nebivolol 5 mg/day for hypertension. She was hospitalized due to stroke. While hospitalized, she developed **pneumonia** and died, 25 days after starting nebivolol. Medical history: arrhythmia, coronary artery disease, chronic hepatic disease. Concomitant medications: unknown.
2007G1000047, FR-MEN-1103(1)	61/M	Pulmonary fibrosis and interstitial pneumonia	Patient was treated with nebivolol 5 mg x 6 weeks (+ hydrochlorothiazide) prior to event. The patient died of hemodynamic failure. The physician thought the patient had experienced an immunoallergical reaction to nebivolol.

6.7.2 Other Postmarketing Adverse Events of Interest

Other postmarketing adverse events of interest with nebivolol are described in Table 19.

Table 19. Other Adverse Events of Interest (Postmarketing)

Case ID	Age/Sex M: Male F: Female	Adverse Event	Narrative
2005G1000062, 05-FR-MenFR-002	75/M	Cardiac failure leading to cardiogenic shock	Patient had a history of heart failure, chronic renal insufficiency, and aortic valvular disorder. Event occurred post nebivolol 5 mg for 12 days to treat hypertension. Concomitant medications: felodipine, ramipril, and furosemide.
2006G1000132, FR-MEN-10664 (1)	37/F	Cardiac arrest x 2	Occurred 2 weeks after initiating nebivolol for hypertension. Patient underwent stent placement x 3 in the right coronary artery which was totally occluded.
2005G1000116, FR-MEN-10001	62/M	Bradycardia	Event occurred while patient received amiodarone for atrial fibrillation in addition to his previous therapy of nebivolol 5 mg/day.
2005G1000118, ES-MEN-10007	54/F	Thoracic pain and dizziness; nodal arrhythmia	Event occurred following concomitant administration of nebivolol and diltiazem and required hospitalization. Both drugs were withdrawn.
2006S1000005, FR-MEN-10032	88/F	Repeated falls, bradycardia	Patient had a history of hypertension, diabetes, and atrial fibrillation and flutter. She was hospitalized for a work-up of repeated falls over a few weeks. On admission, heart rate was **45 bpm**. The patient had been receiving nebivolol 5 mg/day, digoxin 0.125 mg/day, and flecainide 25 mg/day. Nebivolol and digoxin were discontinued, and flecainide was decreased to 12.5 mg/day. Treatment with acebutolol was started. Heart rate stabilized around 60-65 bpm.
2006G1000008, FR-MEN-10044	92/M	Asthenia, abnormal lab tests, and bradycardia	Patient was hospitalized. Laboratory tests were remarkable for urea 20.8 mmol/L (normal range 1.66-8.33), creatinine 231 µmol/L (normal range 60-120), and potassium 5.5 mmol/L (normal range 3.8-5.2). ECG showed bradycardia at 40 bpm. Patient had been receiving nebivolol 2.5 mg/day, spironolactone 50 mg, furosemide 20 mg/day, nicardipine prolonged release 50 mg BID, and budesonide/formoterol. All causative drugs were removed. Two days later, patient had a brain natriuretic peptide of 883 pg/ml (normal range < 100), suggesting congestive heart failure. One week later, laboratory values were improved (urea 12.2 mmol/L, creatinine 180 µmol/L, and potassium 4.7 mmol/L). Patient was discharged.
2006G1000120, IE-MEN-10575	56/M	Face edema	Event occurred while patient was receiving nebivolol and atenolol. The drugs were withdrawn, but the event did not resolve.

Case ID	Age/Sex M: Male F: Female	Adverse Event	Narrative
2006G1000054, FR-MEN-10307	93/M	Bradycardia and asthenia	Patient had been receiving nebivolol 5 mg daily and donepezil 10 mg daily as well as candesartan, zopiclone, acetylsalicylate acid, and magnesium. Donepezil, nebivolol, acetylsalicylate acid, and magnesium were discontinued, and the patient recovered.
2005G1000080, 2005.0074	83/F	Thrombocytopenic Purpura	Event occurred approximately 74 days after beginning treatment with nebivolol. The patient also experienced bradycardia and asthenia without anorexia. Concomitant medications: anastrozole, diosmin, morphine sulfate, paracetamol, metoclopramide, macrogol 4000 and verapamil/trandolapril.
2005G1000102, 05FR-MenFR-119	72F	Malaise, fall	Led to hospitalization 2 days after initiating nebivolol and paroxetine. Work-up revealed hyponatremia at 118 mmol/l (normal range 136-146).
2007G1000024, FR-MEN-10807 (1)	79/F	Amaurosis fugax, photophobia, headache, visual disturbance	Patient started nebivolol 5 mg orally on 1/8/2007. On 1/8/2007, she developed left eye blindness lasting 3 to 4 hours with pulsatile cephalgia and photophobia. She had a second episode with similar symptoms. Nebivolol was withdrawn and she had no recurrence of the events. CT scan showed past small cortico-subcortical hypodensities. She had taken 2 doses of nebivolol only, experiencing visual symptoms following each dose.
2004S1000102, CSM422974	71/F	Angioedema of the tongue	Event occurred approximately 1 month after starting nebivolol for hypertension. The event was treated with intravenous hydrocortisone 200 mg and intravenous chlorpheniramine. The patient had previously had angioedema/perioral edema about 4 weeks after starting other unspecified anti-hypertensives.
2007G1000023, FR-MEN-10809 (1)	63/M	Febrile inflammatory syndrome and Raynaud's syndrome	Patient was started on nebivolol 1.25 mg per day for an unspecified indication in 11/2006. The following day, he developed a febrile inflammatory syndrome.
2005G1000039, 2005.0038	39/M	Icterus, microlithiasis, and enlargement of biliary ducts	Patient had a history of aortic coarctation and hepatic cirrhosis due to alcohol abuse. He developed icterus after 2 days of nebivolol 5 mg/day. Concomitant medications included cholestyramine for pruritus and ursodeoxycholic acid for biliary lithiasis. After 2 weeks of nebivolol therapy, patient was hospitalized for treatment of jaundice and released. After 1 month of nebivolol therapy (3 days after hospital discharge), he developed hypochondrial pain and was rehospitalized. Patient was found to have microlithiasis and enlargement of biliary ducts. Nebivolol was discontinued.
2006G1000006, FR-MEN-10035	50/F	Increased transaminases at 400 U/L (normal range < 25)	Event occurred 6 months after starting nebivolol 2.5 mg/day for essential hypertension. Concomitant medications: methotrexate for 3 months, and aceclofenac, paracetamol, and fenofibrate. The nebivolol dose was decreased to 1.25 mg daily while other drugs were withdrawn. Outcome was unknown.
2005G1000002, 04-FR-MENFR-136	48/F	Nausea and stomachache 7 days after starting ibuprofen and 3 days before starting nebivolol; elevated LFTs	Patient was also receiving Sulpiride and Gestodene + ethinyl estradiol. Six days after starting nebivolol, patient developed marked increases in total bilirubin (151 µmol/L, normal: 7-32 µmol/L), conjugated bilirubin (120 µmol/L, normal: 0-45 µmol/L), ASAT (1173 U/L, normal 7-32 U/L), and ALAT (2055 U/L, normal: 6-311 U/L). Nebivolol and ibuprofen were withdrawn. Values were still elevated one week later.
2006G1000025, HU-MEN-10111	50/F	Allergic reaction (lip edema, tongue numbness, and skin itching	Event occurred 30 minutes after ingesting the first dose of nebivolol 1.25 mg.
2006G1000087, FR-MEN-10409	80/F	Urticaria, fever, leukocytoclastic vasculitis, cryoglobulinemia	Cryoglobulinemia was thought to be of neoplastic origin.
2006G1000129, DE-MEN-10644 (1)	/F	Anaphylactic shock	Patient reported severe anaphylactic shock with urinary and fecal incontinence, vomiting, and circulatory failure 2 hours after taking nebivolol 5 mg by mouth. Patient stated she was unconscious for approximately 20-30 minutes in her home, where she lived alone. Eight hours later, she developed hyperesthesia on her whole body which lasted for 2 days.
2006G1000031, GB-MEN-10165	64/M	Diabetes mellitus	Patient is an English physician. He developed diabetes following 3 years of treatment with nebivolol.

Case ID	Age/Sex M: Male F: Female	Adverse Event	Narrative
2005G1000074, 05-FR-MenFR-067	49/M	Cerebrovascular accident	Event occurred after 3 months of nebivolol. Concomitant medication: atorvastatin.
2004G1000074, U2004953	55/M	Syncope	Event occurred 3 weeks after starting nebivolol 5 mg/day. Patient was hospitalized for 2 days, and nebivolol was withdrawn. Patient recovered.
2006G1000004, GB-MEN-10030(1)	69/F	Bradycardia (HR of 55 bpm) and syncope	Patient was on nebivolol 5 mg daily at the time of the event. Nebivolol dose was reduced to 2.5 mg.
2006G1000036, GB-MEN-10184	/F	Depression and suicidal thoughts	Patient had been on nebivolol for an unspecified period of time.
2006G1000022, FR-MEN-10098 (1)	76/F	Renal failure aggravated	Patient was HIV-positive and also receiving antiretroviral therapy. Patient was hospitalized for bradycardia, hypotension, and acute renal failure after beginning nebivolol 5 mg daily. Following withdrawal of nebivolol and antiretroviral therapy, the bradycardia and renal failure resolved.
2005G1000072, 05-FR-MenFR-086	51/M	Acute renal insufficiency	Patient complained of diarrhea and vomiting with the addition of nebivolol 5 mg. Three weeks later, he developed hypotension, malaise, and acute renal insufficiency (serum creatinine 1080 µmol/L (normal: 62-115) and BUN 32.8 mmol/L (normal: 2.1-7.1). Concomitant medications: gliclazide, candesartan, and quinapril/hydrochlorothiazide. Antihypertensive and antidiabetic drugs were withdrawn. Patient recovered after fluid infusion and vasopressor administration.
2005G1000031, 2005.0023	54/F	Exertional dyspnea and bronchospasm/ankle edema	Event occurred after 1 week of nebivolol 5 mg/day for hypertension. Nebivolol was withdrawn, and the patient recovered 2 days later.
2005G1000075, 05PT-MENPT001	60/F	Dyspnea and cough	Event occurred 15 days after beginning nebivolol 5 mg. Concomitant medications: cilazapril (ACE inhibitor).
2006G1000021, FR-MEN-10093	82/M	Acute pulmonary edema	Event required hospitalization and occurred post nebivolol 2.5 mg daily x 1 week, clopidogrel, and spironolactone. Nebivolol was withdrawn, and the event resolved..
2006G1000051, GB-MEN-10278	/F	Worsening of asthma and palpitations	Event occurred 2 weeks after starting nebivolol. She had a history of worsening asthma during prior beta blocker therapy.
2006G1000117, BE-MEN-10563	58/M	Pulmonary fibrosis	Event occurred one year after starting nebivolol. Resolved in 4 months with the discontinuation of nebivolol.
2005G1000104, 2005.0128	70/F	Angioedema (edema of face and ankle edema)	Event occurred during treatment with nebivolol 5 mg/day and ezetimibe. Ezetimibe was withdrawn with resolution of the events. Nebivolol was continued without further events.
2006G1000043, FR-MEN-10232	66/F	Angioedema (swelling of tongue, jaw, and inferior lip)	Patient was a 66 year old retired physician. Two months prior to nebivolol therapy, she developed jaw and inferior lip edema while treated with enalapril/HCTZ and nifedipine/atenolol for 5 years. The event was thought to be due to enalapril. The treatments were discontinued, and she was started on nebivolol 5 mg/day and manidipine hydrochloride 10 mg/day, a dihydropyridine calcium channel blocker. The angioedema was not fully recovered at the time of nebivolol initiation. Several weeks later, the jaw and lip edema reappeared with a progressive burning sensation of the mouth and the tongue that increased in the evening and after meals. Nebivolol and manidipine were withdrawn, and the symptoms resolved. Manidipine was restarted, and the event did not reappear.
2006G1000037, IT-MEN-10207	43/F	Erythema Dyschromicum Perstans	After 18 days of nebivolol 5 mg/day, she developed a skin eruption on face, neck, trunk, arms, and legs. The patient began antihistamines 13 days before the event. Both drugs were withdrawn, and although the symptoms improved, they did not resolve.

Case ID	Age/Sex M: Male F: Female	Adverse Event	Narrative
2006G1000084, FR-MEN-10402	84/F	Cutaneous eruption; Ischemia of the right index finger requiring amputation	Patient had a history of diabetes, hypertension, and renal failure. Twenty-five days after starting nebivolol, she developed a cutaneous eruption. Patient was also receiving allopurinol, lercanidipine, and fluvastatin. All medications were withdrawn. One week later, the patient developed ischaemia of the right index finger, and she was hospitalized for fever and inflammatory syndrome. She was treated with corticosteroid therapy and iloprost. The rash improved, but the ischemia and renal failure persisted. Necrosis of the right index finger required amputation. Rash was thought to be of **toxodermic** etiology.
2005G1000090, 05CH-MenCH001	62/F	Focal lichenoid dermatitis	Patient developed pruritic, erythematous skin lesions on her arms and legs 5 weeks after beginning nebivolol 2.5 mg/day.
2005G1000081, 20050076	80/M	Maculopapular skin eruption (exanthema) and allergic vascular (Henoch-Schönlein) purpura	Event occurred after 32 days of nebivolol 5 mg/day and required hospitalization.
2007G1000013, FR-MEN-10760 (1)	49/F	Erythema polymorphe	Event occurred after 5-6 weeks of nebivolol therapy.
2007G1000059, FR-MEN-11170 (1)	54/M	Rash generalized and Toxic Epidermal Necrolysis	Patient received nebivolol for cardiac insufficiency from 4/27/2007 and ciprofloxacin from 6/2/2007. The patient developed a diffuse necrotizing cutaneous rash starting on 6/14/2007. Both drugs were discontinued, and the symptoms were improving.
2007G1000061, PT-MEN-11170 (1)	68/F	Face edema and a photosensitivity reaction	After 7 days of nebivolol 5 mg/daily, patient developed face edema and an unspecified skin disorder on sun-exposed areas (arms). Concomitant medication: atorvastatin. Nebivolol was withdrawn.
2006G1000038, FR-MEN-10208	42/F	Peripheral ischemia	Event occurred 18 months after starting nebivolol 5 mg/day for hypertension.
2006G1000050, FR-MEN-10035	56/F	Leg edema, dyspnea, dizziness, peripheral occlusive disease, exhaustion, and hypertensive crisis	Patient was a physician. Symptoms occurred following 1 year of nebivolol therapy.
2007G1000056, FR:MEN-11118 (1)	64/F	Systemic Lupus Erythematosus	On an unknown date, patient switched from losartan + HCTZ 50/12.5 and propranolol to nebivolol and losartan + HCTZ 100/25. Three weeks later, the patient presented with polyarthralgia with inflammation. Antinuclear antibody, anticardiolipin antibodies, and antiphospholipid antibodies were positive. Current medical regimen was discontinued, and she was started on losartan + HCTZ 50/12.5. She was treated with cortisone and recovered.
2006G1000045, DE-MEN-10245	34/M	Exacerbated cutaneous lupus	Event occurred after a year of treatment with nebivolol.
From Sponsor's Safety Update and Reviewer's Tables of Postmarketing adverse events.			

6.8 Literature[1]

From the literature, there is one case of torsade de pointes occurring in a 62 year old man with reduced left ventricular systolic function (ejection fraction of 29%) and nonobstructive heart disease, in the setting of atrial fibrillation and multiple concomitant medications. The patient was hospitalized for progressive dyspnea due to atrial fibrillation with a ventricular response of 100 bpm. The patient had received acetyl-digoxin 0.2 mg with reportedly normal plasma levels, and nebivolol 2.5 mg daily. The patient had bilateral pleural effusions and was treated with intravenous furosemide. He developed hypokalemia (2.8 mmol/L, reference: 3.5-5.3 mmol/L), and ventricular fibrillation developed. The patient was resuscitated and defibrillated successfully. After correction of the potassium level (4.3 mmol/L) and with normal electrolytes (sodium: 137 mmol/L, reference 135-153 mmol/L;

[1]**Schrickel JW. JO Schwab, A Yang, A Bitzen, B Lüderitz, T Lewalter, 2006, "Torsade de Pointes" in Patients with Structural Heart Disease and Atrial Fibrillation Treated with Amiodarone, β-blockers, and Digitalis, Pace, 29:363-366.**

magnesium 0.8 mmol/L, ref: 0.7-1.05 mmol/L), the patient continued to experience atrial fibrillation with a rapid ventricular response. The patient was loaded with amiodarone (1,050 mg in 50 ml; 3 ml per hour IV). Approximately 3 hours later, following infusion of 190 mg of amiodarone, the patient developed torsade de pointes. The surface ECG prior to this event demonstrated sinus rhythm at 68 bpm with a prolonged QTc of 527 ms. Prior to the amiodarone, the QTc was 491 ms. Amiodarone was discontinued, and intravenous magnesium was administered. The patient underwent prophylactic dual chamber internal cardioverter defibrillator (ICD) implantation for his severely reduced left ventricular ejection fraction. The patient was continued on nebivolol 2.5 mg daily and digitoxin 0.1 mg daily, but not amiodarone. There was no further QTc prolongation, and 12-month ICD follow-up showed no further episodes of ventricular tachycardia.

7 REVIEW OF INDIVIDUAL STUDY REPORTS

7.1 Study NEB-PK-03, "Effects of Nebivolol on Adrenal Function, Luteinizing Hormone, and Testosterone Levels in Healthy Male Volunteers" (September 6, 2006 – February 28, 2007) (Report Date: May 18, 2007)

7.1.1 Protocol, Amendment, and Post Hoc Changes

The study description was based on the original protocol dated July 7, 2006 (Version 1.0 dated May 18, 2007) and 5 Protocol Amendments dated August 16, 2006, September 14, 2006, September 25, 2006, November 1, 2006, and November 21, 2006, respectively.

Amendment 1 (August 16, 2006)

- changed primary outcome measure from ACTH-stimulated AUC (0-120 min) of plasma cortisol levels to ACTH-stimulated AUC (0-120 min) of **serum** cortisol levels
- clarified secondary endpoints to include mean levels of luteinizing hormone and total testosterone
- added free testosterone (calculated from total testosterone and SHBG levels) on Days 7 and 56 to the outcome measures
- clarified additional samples were to be collected on Days 7 and 56 for future analysis if indicated (i.e. estradiol, dihydrotestosterone, prolactin, and follicle stimulating hormone)
- changed inclusion criterion #6 to require triplicate reading to calculate the average pulse rate. Also, the inclusion criteria was changed from a sitting pulse rate of not greater than 100 bpm or not less than 60 bpm by vital signs assessment to not greater than 100 bpm or not less than 62 bpm
- modified exclusion criterion #17 so that subjects would also agree to abstain from taking nonsteroidal anti-inflammatory drugs (NSAIDs)
- added exclusion criteria #23 and #24:
    - 23. Subjects who demonstrate adrenal insufficiency, defined as subjects who on Day 1 fail to have at least one post ACTH-stimulation cortisol level of $\geq$ 19 µg/dl
    - 24. Subjects who are hypogonadal, defined as subjects who on Day 1 have a total testosterone level of < 350 ng/dl
- extended the double-blind high-dose study period from 4 weeks to 6 weeks and increased the total duration of the study from 6 weeks to 8 weeks
- clarified subjects would receive standard diets with no added salt (limit of 4 grams/day)
- clarified secondary and all additional pharmacodynamic parameters would be analyzed using a similar ANCOVA model as used for the primary pharmacodynamic parameter
- clarified subjects with an abnormal ACTH-stimulated cortisol or aldosterone levels on Day 57 would undergo a repeat ACTH stimulation test approximately 4 weeks after their last dose of study drug
- per FDA recommendation, provided a justification for the coefficient of variability used in the protocol for the power calculation and included in the amended protocol criteria provided by the Agency to compare the proportion of subjects in each treatment group with clinical abnormal ACTH-stimulation test results
- included language in the protocol to ensure the review of a subject's medication compliance was performed and documented properly

Amendment 2 (September 14, 2006)

- modified Inclusion Criterion #6 from a sitting pulse rate of not less than 62 bpm to not less than **60 bpm.**
- clarified Exclusion Criterion #7 by stating subjects with a blood pressure equal to 140/90 mm Hg would be excluded from the study
- extended the screening window from 21 to **28 days** of study initiation
- clarified subjects would be admitted at approximately 13:00 on Day -1 and at 18:00 on Day 50
- clarified ECGs would be performed at any other time during the course of the study on subjects who either
  - had an irregular pulse rate; or
  - were symptomatic with light-headedness, dizziness, palpitations, diaphoresis, or nausea
  - had a sitting pulse rate of less than or equal to 52 bpm and an ECG was considered medically indicated by the investigator

  If the subjects were considered clinically stable, they would continue the study.
- revised the Safety Criteria for Discontinuation of Subjects from the Study to the following:
  - Subjects who on Days 15 or 16 had an average sitting pulse rate of less than or equal to 52 beats per minutes would not be dosed and must be discontinued from the study
  - Subjects who at any time during the course of the study demonstrated any of the following conditions must be discontinued from the study at that time. Additionally, these subjects were to be evaluated by the Investigator, and, as deemed medically appropriate, treated by the on-site physician or at the nearest Emergency Room:
    - Sitting pulse rate $\leq$ 46 bpm
    - SBP < 95 mm Hg or a DBP < 55 mm Hg recorded on two separate measurements taken 5 minutes apart; or
    - Persistent dizziness, lightheadedness, or other clinically significant symptom(s); or
    - A clinically significant arrhythmia on ECG; or
    - A PR interval $\geq$ 0.22 seconds on ECG; or
    - Evidence of second or third degree heart block on ECG

Amendment 3 (September 25, 2006)

- added a Principal Investigator and fourth study site
- modified Section 11.3, Vital Signs/Safety/Adverse Event Assessment so that if considered medically indicated by the investigator, subjects having a sitting pulse rate of less than or equal to 52 bpm or greater than or equal to 100 bpm would under an ECG
- clarified the sponsor would also determine the proportion of subjects with peak ACTH-stimulated aldosterone levels that were < 5 µg/dl (and not $\leq$ 5 µg/dl) above time zero aldosterone levels.

Amendment 4 (November 1, 2006)

- added two Principle Investigators and clinical sites
- changed the ITT Population from all subjects in the Safety Population with post-baseline series of cortisol levels after ACTH administration to all subjects in the Safety Population with post-Baseline series of cortisol levels after ACTH administration **who have taken the double-blind study drug as assigned during the study**.

Amendment 5 (November 21, 2006)

- added activities for subjects required to have a repeat ACTH-stimulation test
- revised the volume of blood to be collected during the study
- corrected the unit of measure for aldosterone levels per comments from the FDA
- made various administrative changes

7.1.2 Study Design

This was a randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers ages 18 to 50 years.

7.1.3 Objectives

The primary objective was to evaluate the effects of nebivolol 10 mg on adrenal function, LH levels, and total testosterone levels in healthy males.

7.1.4 Inclusion and Exclusion Criteria

Inclusion Criteria (Must be present)

1. Written informed consent
2. Healthy male, 18 to 50 years of age
3. Normal vital signs, physical examination findings, serum chemistry, hematology, and urinalysis results, and negative anti-HIV 1, anti-HIV 2, HbsAg, anti-HCV antibody, and RPR/VDRL
4. Nonsmoker (having never smoked or not smoked within the prior year)
5. Body mass index in the range of 18.0 to 29.9. kg/m^2
6. Sitting pulse rate of $\geq$ 60 bpm and $\leq$ 100 bpm by vital sign assessment (triplicate readings)

Exclusion Criteria (Cannot be present)

1. Known hypersensitivity to nebivolol, atenolol, other β-blocking agents, ACTH-stimulation test, or any excipient in the investigational formulations
2. Significant history of cardiovascular, hepatic, endocrine, renal, pulmonary, hematologic, gastrointestinal, urologic (including infertility), immunologic, dermatologic, or neurologic disease
3. Known hereditary endocrine dysfunction in family
4. History of asthma, hyperglycemia, hypoglycemia, or abnormal glucose tolerance testing
5. History of cancer (other than nonmelanoma skin cancer) or testicular mass
6. Clinically significant disease state in any body system, in the opinion of the examining physician
7. After a 5-minute resting period, an average sitting systolic blood pressure (SBP) greater than 140 mm Hg or less than 105 mm Hg or a sitting diastolic blood pressure (DBP) greater than 90 mm Hg or less than 65 mm Hg at Screening or on Day -1. Triplicate readings were taken to calculate the average. Note: Subjects with a blood pressure equal to 140/90 mm Hg were also excluded
8. Clinically significant ECG abnormalities, including a PR interval greater than or equal to 200 ms or less than or equal to 100 ms, QT prolongation (QT or QTc $\geq$ 430 ms), sick sinus syndrome, second- or third-degree atrioventricular block, any type of tachycardia, greater than 1 PVC on a 12-lead ECG, incomplete left-bundle branch block or complete left- or right-bundle branch block, nonsinus rhythm, or evidence of myocardial ischemia/infarction (either changes suggesting acute ischemia/infarction or changes from previous tracings compatible with an infarction during the preceding 6 months)
9. History of alcohol or substance abuse within the prior 5 years
10. Positive test results for drugs of abuse (including alcohol) or cotinine
11. Recent (within 1 month) significant change in diet or exercise habits
12. Consumption of caffeine- or xanthine-containing food or beverages or of any grapefruit-containing products within 48 hours or alcohol within 72 hours before the start of the study (Day 1)
13. Unwillingness to adhere to a standard diet with no added sodium (limited to 4 g/d) throughout the duration of the study or unwillingness to abstain from alcohol, caffeine- and xanthine-containing foods and beverages, and grapefruit-containing juices or foods throughout the duration of the study
14. Unwillingness to forego strenuous or rigorous exercise activities (such as jogging or weight lifting) for the duration of the study
15. Sexually active and unwilling to use an approved form of birth control while in the study
16. Any clinical condition that might affect the absorption, distribution, biotransformation, or excretion of nebivolol or atenolol
17. Taken within 14 days before Day 1 (study drug administration), any medications, including prescription medications, prescription eye drops, over-the-counter medications, vitamins, nutritional supplements, or herbal remedies. Subjects must have agreed to abstain from taking medications, including nonsteroidal anti-inflammatory drugs, vitamins, nutritional supplements, and herbal remedies throughout the duration of the study, except as medically necessary
18. Taken within 60 days before Day 1, any hormone treatment or steroid therapy, including topical steroids and ophthalmic steroid drops. Note: hormonal therapies and steroid treatment were prohibited throughout the study
19. Previous ingestion of nebivolol or prior participation in an investigational study of nebivolol

20. Participation in any other clinical investigation using an experimental drug requiring repeated blood draws within 30 days of the start of this study or participation in a blood donation program within the prior 60 days
21. Employment by, or family members employed by, the clinical research organization at which the study was conducted
22. Employment as a shift worker or a lifestyle that may have affected diurnal hormone pattern
23. Demonstration of adrenal insufficiency, defined as subjects who failed to have at least one post-ACTH stimulation cortisol level of 19 µg/dl or greater on Day 1
24. Hypogonadal, defined as subjects who had a total testosterone level of less than 350 ng/dl on Day 1

7.1.5 Study Plan

The study consisted of 1 week of single-blind matching-placebo run-in, followed by 1 week of double-blind low-dose treatment (nebivolol 5 mg/d, atenolol 50 mg/d, or placebo) and 6 weeks of double-blind high-dose treatment (nebivolol 10 mg/d, atenolol 100 mg/d, or placebo).

Following the lead-in period, all qualifying subjects were randomized in a 1:1:1 manner to one of three double-blind treatment sequences within each CYP 2D6 phenotype stratum, as displayed in Table 21.

On Day 1, prior to the administration of single-blind treatment, a screening ACTH-stimulation test was performed and a screening total testosterone level was obtained to exclude subjects who were adrenally insufficient or hypogonadal. ACTH-stimulation tests were also performed on Day 8, after 7 days of single-blind placebo treatment and before double-blind low-dose treatment, and on Day 57, after 7 weeks of double-blind nebivolol, atenolol, or placebo treatment. Samples for LH, total testosterone, and SHBG were collected on Day 7 of single-blind placebo treatment and during double-blind treatment on Day 56.

On Days 55, 56, and 57, all subjects had trough blood samples drawn for nebivolol and atenolol plasma concentration analysis.

The maximum study duration was approximately 58 days (Days -1 through 57).

For subjects who failed to demonstrate a normal cortisol and a normal aldosterone response to ACTH stimulation during the double-blind treatment period, a follow-up ACTH-stimulation test was conducted 4 weeks (± 2 days) after the End of Study.

Safety measurements included adverse event monitoring, clinical laboratory parameters, vital sign values, ECGs, and physical examinations.

The schedule of procedures/events is summarized in Table 20.

Table 20. Study Flow Chart (NEB-PK-03)

Table 9.5.1–1. Study Flow Chart of Procedures and Determinations

Period	*Screening*[a]		*Placebo Run-in*			*Low Dose*			*High Dose*											*EOS*[b]	*Post*[c]
Study Day	*−28 to −1*	*−1*	*1*	*2 to 6*	*7*	*8*	*9*	*10 to 14*	*15*	*16*	*17 to 24*	*25*	*26 to 42*	*43*	*44 to 49*	*50*	*51 to 54*	*55*	*56*	*57*		
Informed consent	X																					
Medical and surgical history	X																					
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Monitoring of adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratories (safety)	X	X														X					X	X
Vital signs																						
BP, PR, temperature, RR	X	X	X	X	X	X	X		X	X		X		X		X	X	X	X	X	X	X
Height, weight	X	X[d]																			X[d]	
Electrocardiogram	X																				X	
Physical examination	X																				X	
Tox-drug screen	X	X														X						X
Serology and genotype test (CYP 2D6)	X																					
PK samples[e]																		X	X	X		

Table 9.5.1–1. Study Flow Chart of Procedures and Determinations

Period	*Screening*[a]		*Placebo Run-in*			*Low Dose*			*High Dose*											*EOS*[b]	*Post*[c]
Study Day	*−28 to −1*	*−1*	*1*	*2 to 6*	*7*	*8*	*9*	*10 to 14*	*15*	*16*	*17 to 24*	*25*	*26 to 42*	*43*	*44 to 49*	*50*	*51 to 54*	*55*	*56*	*57*		
Basal cortisol, basal aldosterone, basal ACTH levels			X[f]			X														X		X
Basal LH, basal total testosterone levels			X[g]		X														X			
Cortisol and aldosterone levels post–ACTH-stimulation test			X[h]			X														X		X
Sample for SHBG					X														X			
Additional samples collected for future endocrine testing					X														X			
Randomization to treatment						X																
Dosing of medication			X[i]	X[i]	X[ij]	X[ij]	X[i]	X[k]	X[i]	X[i]	X[k]	X[i]	X[k]	X[i]	X[k]	X[k]	X[i]	X[i]	X[ij]			
Drug compliance									X			X		X		X						
Drug dispensing							X			X		X		X								
Admission to clinic[l]		X							X							X						X[m]
Outpatient visit	X											X		X								
Discharge from clinic[n]							X			X										X		X[o]

a Must be done within 28 days before Day 1.

b Must be within 7 days of Day 57 or at early termination.

c Subjects with an abnormal post–ACTH cortisol or aldosterone level on Day 57 will be scheduled to return for repeat ACTH-stimulation testing approximately 4 weeks (± 2 days) after the last dose of study drug.

Table 9.5.1–1. Study Flow Chart of Procedures and Determinations

Period	*Screening*[d]		*Placebo Run-in*			*Low Dose*			*High Dose*											*EOS*[k]	*Post*[l]
Study Day	*–28 to –1*	*–1*	*1*	*2 to 6*	*7*	*8*	*9*	*10 to 14*	*15*	*16*	*17 to 24*	*25*	*26 to 42*	*43*	*44 to 49*	*50*	*51 to 54*	*55*	*56*	*57*	

d Weight only.
e Samples will be drawn on Day 55 at predose, Day 56 at predose, and Day 57 at 24 hours post–last dose.
f Samples for basal cortisol and basal ACTH levels only.
g Sample for total testosterone only.
h Samples for posttest cortisol levels only.
i Dosing occurs in clinic.
j Dosing occurs after tests completed.
k Dosing occurs at home.
l Admission to clinic at 13:00 on Day –1, at 07:00 on Day 15 and at 18:00 on Day 50.
m Subject admitted to the clinic at 18:00 on the day before the repeat ACTH-stimulation test.
n Discharge occurs on Days 9, 16, 25, and 43 after 4 hours vital sign assessment and on Day 57 after end of study procedure.
o Subject discharge after the completion of the ACTH-stimulation test.

EOS = End of Study; BP = blood pressure; PR = pulse rate; RR = respiration rate; CYP 2D6 = 2D6 isozyme of cytochrome P-450; Tox = toxicology; PK = pharmacokinetic; ACTH = adrenocorticotropic hormone; LH = luteinizing hormone; SHBG = sex hormone–binding globulin.

(Reproduced from Sponsor, Clinical Study Report (NEB-PK-03), Table 9.5.1-1, pages 39-41 of 5947)

7.1.6 Dosage, Duration, and Adjustment of Therapy

The dosage treatment sequences are displayed in Table 21.

Table 21. Treatments (NEB-PK-03)

Treatment Sequence	*Description*	
	Days 8 Through 14	*Days 15 Through 56*
A	Nebivolol 5-mg tablet + atenolol-matching placebo capsule	Nebivolol 10-mg tablet + atenolol-matching placebo capsule
B	Nebivolol-matching placebo tablet + atenolol 50-mg capsule	Nebivolol-matching placebo tablet + encapsulated atenolol (two 50-mg) capsule
C	Nebivolol-matching placebo tablet + atenolol-matching placebo capsule	Nebivolol-matching placebo tablet + atenolol-matching placebo capsule

(Reproduced from Sponsor, Clinical Study Report, Table 9.4.1-1, page 32 of 5947)

Any subject who missed more than two doses of double-blind study medication between Days 8 and 56 would have been discontinued from the study for noncompliance (i.e. an overall study drug compliance < 96%).

7.1.7 Concomitant Therapy

No concomitant medications were allowed during the study. For treatment of headache, pain, or fever, only acetaminophen was permitted. If the subject required treatment of nausea, he was administered a total study maximum of two doses of trimethobenzamide hydrochloride (Tigan), provided it was not within 10 days of hormonal testing.

7.1.8 Endpoints

Primary Pharmacodynamic Endpoint: The primary pharmacodynamic endpoint was the area under the curve from time zero to 120 minutes ($AUC_{0\text{-}120\ min}$) of ACTH-stimulated (IV dose of 250 µg) serum cortisol levels at end of study (EOS) (Day 57). The $AUC_{0\text{-}120\ min}$ was calculated using the trapezoidal rule based on the pre- and post-ACTH-stimulation cortisol levels at 0 hour (pre-ACTH injection) and 0.5, 1.0, 1.5, and 2 hours post-ACTH injection.

Secondary Pharmacodynamic Endpoints: The secondary pharmacodynamic endpoints were the mean levels of three basal LH measurements on Day 56 (20 minutes apart as scheduled) and the mean serum levels of total testosterone on Day 56.

Additional Pharmacodynamic Endpoints: Additional endpoints included free testosterone levels (calculated from total testosterone and SHBG levels); basal ACTH, basal cortisol, and basal aldosterone levels; and $AUC_{0\text{-}120\ min}$ of serum aldosterone levels after the IV administration of ACTH (250 µg) at end of study. If the primary and secondary endpoints required additional explanation, sufficient plasma/serum samples were taken on Days 7 and 56 and frozen for possible measurements of estradiol, dihydrotestosterone, prolactin, and follicle-stimulating hormone.

7.1.9 Statistical Considerations

The primary analysis was the comparison between nebivolol and placebo in the intent-to-treat population and used an analysis-of-covariance (ANCOVA) model with treatment group, metabolic status (CYP 2D6 extensive metabolizers (EMs) vs poor metabolizers (PMs)), and study center as factors and the corresponding baseline (Day 8) $AUC_{0\text{-}120\ min}$ value as a covariate.

Least squares mean differences (LSMD) in the primary pharmacodynamic endpoint between active treatments and placebo expressed as a percentage of the placebo least squares mean (LSM) were presented along with the 90% CI.

The secondary pharmacodynamic endpoints were analyzed in a similar fashion to the primary endpoints.

Assuming the coefficient of variability (CV, defined as the pooled standard deviation divided by the placebo mean) was 26% (projected based on the estimated CV in Study NEB-BEL-55 and the relative length of treatment in the current study) and the true treatment difference between nebivolol and placebo was zero in the primary pharmacodynamic parameter, a sample size of 30 subjects per treatment group provided approximately 90% power at the significance level of 0.05 for one-sided test to rule out a 20% reduction in the primary pharmacodynamic parameter for nebivolol subjects relative to the placebo subjects. The sample size also provided 90% power to detect a 20% difference between nebivolol and placebo at the one-sided significance level of 0.05, if such a difference existed.

The intent-to-treat (ITT) population consisted of all subjects in the Safety Population who had a postbaseline series of cortisol levels after ACTH administration and took the double-blind study medication as assigned during the study.

The safety population consisted of all subjects in the Randomized Population who took at least one dose of double-blind study drug.

7.1.10 Results

7.1.10.1 Sites, Investigators, and Study Dates

The study was conducted from September 6, 2006 through February 28, 2007 at 6 study sites.

7.1.10.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices. There were 5 subjects at site 002 that received incorrect randomization kits for Days 43 through 56 of the study. Three of these subjects (002-9029, 002-9031, and 002-9052) terminated early on Days 52 through 53. The other two subjects (002-9041 and 002-9050) completed the study and were subsequently found to have received the correct treatment following unblinding after database lock.

7.1.10.3 Disposition of Subjects

A total of 596 subjects were screened and 157 subjects were randomized to double-blind treatment, including 55 subjects to nebivolol, 50 subjects to atenolol, and 52 subjects to placebo. A total of 119 (119/157 or 75.8%) subjects had postbaseline series of cortisol levels after ACTH administration, took the double-blind study drug as assigned,

and completed the study, including 42 subjects in the nebivolol group (42/55 or 76.4%), 29 subjects in the atenolol group (29/50 or 58.0%), and 48 subjects in the placebo group (48/52 or 92.3%). Subject populations for NEB-PK-03 are displayed in Table 22; there were 157 subjects in the Safety Population and 119 subjects in the ITT Population.

The screening failures included but were not limited to 8 subjects (1.3%) that did not meet criteria, 1 subject (0.2%) who experienced an adverse event, 52 subjects (8.7%) who had protocol violations, 1 subject (0.2%) who withdrew consent, and 47 subjects who had screening failures due to "other" causes.

Table 22. Sponsor's Analysis: Subject Populations (NEB-PK-03)

	Placebo	*Atenolol*	*Nebivolol*	*Total*
Subjects Randomized,[a] n	52	50	55	157
Did not receive study drug, n	0	0	0	0
Safety Population,[b] n	52	50	55	157
No postbaseline pharmacodynamic data, n	4	21	13	38
Intent-to-Treat Population,[c] n	48	29	42	119

a All subjects in the Screened Population who were randomized to a treatment group.
b All subjects in the Randomized Population who took at least one dose of double-blind study drug.
c All subjects in the Safety Population who had a postbaseline series of cortisol levels after ACTH administration and took the double-blind study drug as assigned.
Cross-reference: Table 14.1.1.

(Reproduced from Sponsor, Clinical Study Report, Table 10.1-1, page 66 of 5947)

There were numerous withdrawals in the atenolol and nebivolol treatment groups. Although one subject in the atenolol group was withdrawn due to Investigator discretion, the subjects who withdrew because of the "other" category were withdrawn for vital sign values outside the protocol-specified safety criteria. The number of subjects discontinued from NEB-PK-03 is displayed in Table 23.

Table 23. Sponsor's Analysis: Number (%) of Subjects Discontinued from the Study--Randomized Population (NEB-PK-03)

	Placebo (N=52) n (%)	*Atenolol (N=50) n (%)*	*Nebivolol (N=55) n (%)*	*Total (N=157) n (%)*
Completed study	48 (92.3)	29 (58.0)	42 (76.4)	119 (75.8)
Withdrawn from study	4 (7.7)	21 (42.0)	13 (23.6)	38 (24.2)
Reason for withdrawal				
Other	3[a] (5.8)	15[b] (30.0)	8[c] (14.5)	26 (16.6)
Protocol violation	1 (1.9)	4 (8.0)	2 (3.6)	7 (4.5)
Adverse event	0	2 (4.0)	2 (3.6)	4 (2.5)
Consent withdrawn	0	0	1 (1.8)	1 (0.6)
Lost to follow-up	0	0	0	0

a Three subjects were withdrawn because of protocol-specified safety criteria: 2 subjects because of low blood pressure (1 systolic and 1 diastolic) outside protocol parameters, and 1 subject because of low pulse rate outside protocol parameters.
b One subject was withdrawn because of Investigator's discretion. The remaining 14 subjects in this group were withdrawn because of protocol-specified safety criteria: 8 subjects because of low blood pressure outside protocol parameters (5 diastolic, 1 systolic and diastolic, and 2 unspecified) and 6 subjects because of low pulse rate outside protocol parameters.
c Eight subjects were withdrawn because of protocol-specified safety criteria: 4 subjects were withdrawn because of low blood pressure outside protocol parameters (1 diastolic, 2 systolic, and 1 systolic and diastolic) and 4 subjects were withdrawn because of low pulse rate outside protocol parameters.
Cross-reference: Tables 14.1.3 and 14.1.4

(Reproduced from Sponsor, Clinical Study Report, Table 10.2-1, page 67 of 5947)

7.1.10.4 Subjects who Prematurely Discontinued the Study

Subjects who prematurely discontinued the study are displayed in Table 25, along with the reasons for discontinuation. One of the protocol violations was due to a patient who was dosed in error with an exclusionary heart rate. According to the Clinical Study Report, all twenty-six of the discontinuations due to "other" were related to abnormalities in vitals signs. Per my review, three subjects in the atenolol group only did not meet vital sign criteria for discontinuation.

Criteria for potentially clinically significant vital signs are displayed in Table 24.

Table 24. Sponsor's Table: Criteria for Potentially Clinically Significant Vital Signs (NEB-PK-03)

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Systolic Blood Pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic Blood Pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	-	Increase of ≥ 7%
	Low	-	Decrease of ≥ 7%

[a]A postbaseline value was considered a potentially clinically significant value if it met both criteria for observed value and change from baseline. (Reproduced from Sponsor, Table 9.7.1.6.3-1, page 60 of 5947)

Table 25. Subjects who Prematurely Discontinued the Study (NEB-PK-03)

Subject ID	Study Center	Treatment Group	Number of Days on Double-Blind Drug	Number of Days in Double-Blind Phase	Reason for Discontinuation	Specified Reason for Discontinuation (AEs by Preferred Term/Investigator Term)	Reviewer Comments
0049009 (45 yo Caucasian man)	004	Atenolol	48	49	Adverse Event	"Dyspepsia/Indigestion." Date of AE Start/Stop: 6 "Hypotension/Asymptomatic low blood pressure." Date of AE Start/Stop: 49/49.	**Met criteria for potentially clinically significant vital signs.** At Screening on [redacted] BP ranged from 110-118/80-84 with a HR of 65-70 bpm. On Day -1 [redacted], Sitting, Supine, and Standing vital signs were BP 111/67, HR 70; BP 114/64, HR 67, and BP 121/66, HR 70, respectively. On [redacted] the subject experienced asymptomatic low blood pressure at a start time of 0659 hours **(BP 84/65, HR 60)**. Repeat BP at 07:04 the same day was **83/57**. The event resolved at 07:59 hours the same day. At end of study [redacted], vital signs were as follows: Sitting: BP 98/60, HR 70; Supine: BP 96/59, HR 70; Standing: BP 98/62, HR 72. Subject was discontinued from the study on 12/14/2006 due to the adverse event of asymptomatic low blood pressure on 12/13/2006.
0049048 42 yo American Indian man)	004	Atenolol	45	48	Adverse Event	"Bradycardia/Asymptomatic Bradycardia." Date of AE Start/Stop: 12/9-12/11/2006. Study drug discontinued.	**Met criteria for potentially clinically significant vital signs.** At Screening on [redacted] BP was 136-142/81-88 and HR was 66-69. On Day -1 [redacted] BP ranged from 112-129/70-79 with a HR of 67-74 bpm. Approximately 4 hours after dosing on 12/9/2006 (Day 52), the subject experienced asymptomatic bradycardia, with a start time of 1216 hours. HR at 08:16 (predose) on [redacted] was 54 bpm. HR at 12:36 on [redacted] was **45 bpm**. The event continued until 12/11/2006 at 20:16 hours (HR 61 bpm). The subject did not get dosed after 12/9/2006 (Day 52). Subsequent vital signs were monitored and returned to normal levels prior to discharge from the study. During the asymptomatic bradycardia, the subject also experienced dizziness from 09:50 to 20:00 on 12/10/2006 and from 11:25 to 06:30 on 12/11 and 12/12/2006. As a result of the asymptomatic bradycardia, the subject was discontinued from the study on 12/13/2006.

Subject ID	Study Center	Treatment Group	Number of Days on Double-Blind Drug	Number of Days in Double-Blind Phase	Reason for Discontinuation	Specified Reason for Discontinuation (AEs by Preferred Term/Investigator Term)	Reviewer Comments
0049034 (45 yo Caucasian man)	004	Nebivolol	45	49	Adverse Event	"Hypotension." 12/9 – 12/13/2006. Study drug discontinued.	**Met criteria for potentially clinically significant vital signs.** At screening on [redacted] sitting BP was 107/77 and HR was 67 bpm. On Day -1 [redacted], BP ranged from 106-114/69 with HR 82-83 bpm. An unscheduled 12-lead ECG was performed on [redacted] because of a SBP of 88. The patient was asymptomatic, and the ECG demonstrated normal intervals and a heart rate of 65 bpm. On [redacted] at 08:03, BP was 99/71 and HR was 67 bpm. Approximately 4 hours after dosing (start time of 12:08) on [redacted], he experienced hypotension, with a BP of 92/60 and HR of 54). BPs on [redacted] ranged from **85/62** to 103/64. The event continued until [redacted] at 0:703 hours when BP was 101/65 and HR was 60 bpm. The subject continued to be dosed until 12/12/2006, but he did not get dosed on 12/13/2006 (Day 56). Subsequent vital signs were closely monitored and returned to normal levels prior to discharge from the study. The subject was discontinued from the study on 12/13/2006 (BP 107/74, HR 62 bpm). Vital signs on 12/14/2006 ranged from 86/64 with a heart rate of 59 bpm to 101/67 with a heart rate of 63 bpm.
0049053 (28 yo Caucasian man)	004	Nebivolol	48	49	Adverse Event	"Heart rate decreased/Low heart Rate." 12/12-12/14/2006. Study drug discontinued.	**Met criteria for potentially clinically significant vital signs.** At Screening on [redacted] BP ranged from 115-130/84-88 and HR was 61-62 bpm. On Day -1, BP ranged from 127-128/77-82 with HR 64-65 bpm. Prior to dosing on [redacted] at 08:17, BP was 112/65 with HR 54. Approximately 4 hours after dosing on 12/12/2006 (Day 55), the subject experienced a low heart rate **(45 bpm)**, with a start time at 12:22 hours. The event continued until 12/14/2006 at 09:17 hours. The subject did not get dosed on 12/13/2006 (Day 56). At End of Study on [redacted] BP ranged from 117-121/69-78 with a HR of 51-59 bpm. As a result of the low heart rate, the subject was discontinued from the study on 12/14/2006.
0049164	004	Placebo	46	47	Protocol Violation	Positive drug screen	Patient experienced adverse event of abdominal pain, nausea, and vomiting on 12/12/2006. Drug screen on [redacted] was positive for opiates. Patient was discontinued from the study on 1/20/2007.
0039041	003	Atenolol	47	50	Protocol Violation	Positive urine drug screen on Day 50	Dosing was initiated on 10/19/2006. Urine drug screen was positive for cannabinoids on [redacted].
0049103	004	Atenolol	45	46	Protocol Violation	Subject left clinic	Subject was discontinued from the study on 12/18/2006 due to "noncompliance to inpatient stay" on same date.