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
0049146	004	Atenolol	44	44	Protocol Violation	Subject returned 18 tablets (capsules 0% compliance on Day 50)	Confirmed. On 12/22/2006, the subject returned 7 tablets each from Bottles A and B. Eighteen tablets were returned on 1/16/2007. Subject was discontinued from the study on 1/8/2007.
0059012	005	Atenolol	14	26	Protocol Violation	Subject did not self dose	Subject stopped taking drug. On 12/22/2006, subject returned 7 tablets each from Bottles A and B. Subject was discontinued from the study on 1/8/2007.
0049059	004	Nebivolol	9	10	Protocol Violation	Subject was dosed in error on Day 15 with an exclusionary heart rate	**Met criteria for potentially clinically significant vital signs.** At Screening on [redacted] BP ranged from 110-113/72-81 and HR ranged from 60-63 bpm. On Day -1 [redacted], BP ranged from 117-123/73-76 and HR ranged from 72-80 bpm. Predose (07:22) on [redacted] BP ranged from 127-130/82-84 with HR 69-71 bpm. On [redacted] at 12:02, four hours after dosing, BP was 116/73 with HR 49 bpm. Repeat vitals at 12:09 demonstrated BP of 116/72 with **HR 45 bpm**. From 12:11 on [redacted] to 08:26 on [redacted] BP ranged from 111-120/64-72 and HR ranged from 48-62. 12-lead ECG on [redacted] demonstrated a HR of 48 bpm. At End of Study on [redacted] BP ranged from 102-103/65-69 with HR 48-50 bpm. Subject was discontinued from the study on 11/4/2006.
0069031	006	Nebivolol	49	49	Protocol Violation	Positive drug screen at day 50	Subject was discontinued from the study on 2/9/2007. Drug screen was positive for amphetamines on [redacted]
0039026	003	Nebivolol	8	20	Consent Withdrawn		Subject was first dosed on 9/8/2006 and was discontinued from the study on 9/22/2006 due to withdrawn consent. Subject experienced mild nasal congestion as an adverse event from 9/20/2006 to 10/1/2006.
0019102	001	Placebo	8	9	Other	Systolic Blood Pressure (SBP) out of Protocol Parameters	**Met criteria for potentially clinically significant vital signs.** At Screening on [redacted] BP was 120/83-84 with a heart rate of 69 bpm. On Day -1 [redacted], BP ranged from 104-113/80-84 with a HR of 66-67. Predose (7:52) [redacted] BP ranged from 97-106/69-74 with HR 71-76 bpm. Two hours after dosing at 10:05, BP was **88/62** with HR of 74 bpm. At 10:11, BP was **89/65** with a HR of 68 bpm. [redacted] (End of Study), BP ranged from 105-107/74-76 with a heart rate of 82 bpm. Subject was discontinued from the study on 11/3/2006 due to SBP on Day 15. However, Discrepancy No. 3723 in the CRF states: "Subject was discontinued from Study on Day 7 due to total testosterone levels." This notation appeared to be subsequently corrected on the CRF.

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
0029031	002	Placebo	46	46	Other	Due to heart rate (HR) protocol safety requirement	**Met criteria for potentially clinically significant vital signs.** At Screening c [redacted] BP ranged from 121-127/84-87 and HR ranged from 60-71 bpm. On Day -1 [redacted], BP ranged from 120-137/69-79 and HR ranged from 51-86 bpm. On Day 50 ([redacted] BP ranged from 121-134/66-82 and HR ranged from 49-81. HR on 10/25/2006 ECG was 46 bpm. Predose (07:55) on [redacted] the subject experienced sitting BP of 133/74 with a HR of 52 bpm. Two hours post dosing (10:10), BP was 116/62 with a HR of 48 bpm. Four hours post-dosing (11:55), BP was 133/73 with a HR of **43** bpm. At 20:10 on [redacted] BP was 130/73 and HR was 48 bpm. Subject was discontinued from the study on 10/27/2006. This patient had a history of "sinus bradycardia" in 3/2006.
0029039	002	Placebo	8	14	Other	Protocol safety requirement of Diastolic Blood Pressure (DBP)	**Met criteria for potentially clinically significant vital signs.** According to the CRF, this subject experienced diastolic hypotension from 09:59 to 10:11 on 9/20/2006. At screening on [redacted], BP was 103-113/**68-76** and HR was 66-77 bpm. On Day -1 ([redacted], BP was 114-116/**52-63** and HR was 63-67 bpm. On [redacted] at 08:04 (previously documented as 12:03) (predose), BP was 105/**50** and heart rate was 62 bpm. On [redacted] at 09:59 (two hours post dosing), BP was 117/53 and HR was 61 bpm. At 10:11, BP was 117/58 and HR was 57 bpm, and at 12:03, BP was 105/**50** and HR was 62 bpm. At 15:13, BP was 107/57. End of study vital signs on 9/26/2006 included BP 109-118/61-67 and HR 58-63.
0019046	001	Atenolol	8	9	Other	Protocol requirements for DBP	**Met criteria for potentially clinically significant vital signs.** At screening on [redacted]. BP was 121-123/56-70 and HR was 57-60 bpm. On Day -1 ([redacted], BP was 101-107/61-64 and HR was 67-68 bpm. First dose of study drug was given on 9/14/2006. On 9/21/2006, patient complained of nausea (14:28-18:30), indigestion (15:00-18:00), and dizziness (15:00 to 07:00 on 9/22/2006). Predose vitals (07:53) demonstrated BP 122-130/56-65 and HR 61-64 bpm. Two hours post dosing (10:00), BP was 108-114/**53-54** and HR was 52 bpm. Four hours after dosing (11:52), BP was 117/58 with HR **42**

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
							bpm. Last study drug dose was administered on 9/21/2006. Subject was prematurely discontinued from the study on 9/22/2006 due to DBPs of "61 and 64 on Day -1 and SBP of 100 which should have excluded this subject from the study." However, these values were subsequently crossed out on the CRF. At end of study [redacted], BP ranged from 123-129/**53-54** and HR ranged from 59-65 bpm. The CRF stated "Subject dropped Day 15 due to protocol Requirements for Diastolic Blood Pressure."
0019056	001	Atenolol	2	6	Other	Protocol requirements for HR	**Did not meet criteria for potentially clinically significant vital signs.** At Screening (8/31/2006), BP was 111-114/68-76 and HR was 64-67 bpm. On Day -1 [redacted], BP was 121-126/74-80 and HR was 58-67 bpm. Predose (07:54) [redacted] BP was 111/65 and HR was 63 bpm. Four hours after dosing (12:00), BP was 105/60 with HR 49 bpm. At end of study [redacted] BP was 116-125/70-73 and HR was 64-66 bpm. Patient was discontinued from the study on 10/9/2006.
0019100	001	Atenolol	8	9	Other	Due to vitals on Day 15	**Did not meet criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 104-112/65-68 and HR was 71-74 bpm. On Day -1 [redacted] BP was 109-115/64-68 and HR was 74-80 bpm. On [redacted] at 07:50 (predose), BP was 112-120/58-63 with HR 62-70 bpm. Two hours post dosing (10:05), BP was 104/50 with HR 62 bpm. At end of study [redacted] BP was 103-105/49-57 and HR was 69-74 bpm. Patient was discontinued from the study on 11/3/2006.

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
0019108	001	Atenolol	47	48	Other	Protocol requirements for HR	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 128-139/80-88 with HR 82-85 bpm. On Day -1 [redacted], BP was 119-135/76-81 with HR 91-96 bpm. Predose on [redacted] (07:55), BP was 102/61 with HR 55 bpm. Four hours post dosing (12:10), BP was 99/62 and HR was **43** bpm. At end of study [redacted] BP was 105-111/57-65 and HR was 55-67. Patient was discontinued from the study on 12/12/2006.
0019130	001	Atenolol	36	36	Other	Protocol Requirements for HR	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 109-127/75-79 and HR was 69-74. On Day -1 [redacted], BP was 116-134/67-73 and HR was 56-72 bpm. On [redacted] at 07:46 (predose), BP was 119/72 with HR of 47 bpm. Four hours post-dose (12:00), BP was 112/78 and HR was 46 bpm. Patient also had low HRs of 48 and 47 on [redacted] respectively. At end of study [redacted], BP was 115-123/69-81 and HR was 49-53 bpm. Patient was discontinued from the study on 1/2/2007.
0019135	001	Atenolol	1	1	Other	Dropped per protocol requirements due to low DBP	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 101-111/61-71 with HR 56-64 bpm. On Day -1 [redacted], BP was 100-116/59-71 and HR was 65-73 bpm. Predose on [redacted] at 07:51. BP was 111-113/66-71, and HR was 61-64 bpm. At 13:05 on [redacted] BP was 98/**54** with HR of 64 bpm. At end of study [redacted] BP was 104-109/53-56 and HR was 63-67 bpm. Patient was discontinued from the study on 11/21/2006.
0029027	002	Atenolol	8	14	Other	Due to Investigator's discretion	Patient was discontinued from the study on 9/26/2006 due to patient experiencing a left arm abrasion from the intravenous phlebotomy (recorded as an adverse event).

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
0029038	002	Atenolol	8	9	Other	Due to diastolic protocol safety requirements	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 131-136/76-82 with HR 74-83 bpm. On Day -1, BP was 115-133/62-71 with HR 78-90 bpm. Predose (07:58) on [redacted] BP was 116-123/57-66 with HR 57-59 bpm. Two hours post-dosing (10:00), BP was 100/**49** with HR 52 bpm. At end of study [redacted], BP was 115-117/55-64 with HR 77-86 bpm. Patient was discontinued from the study on 9/21/2006.
0029047	002	Atenolol	18	21	Other	Due to protocol safety requirements of heart rate per medical investigator	**Met criteria for potentially clinically significant vital signs.** At Screening ([redacted] BP was 110-117/79-80 with HR 82-86 bpm. On Day -1, BP was 123-131/74-77 with HR 86-89 bpm. At predose (08:12) on [redacted] BP was 109/65 with HR 52 bpm. Four hours after dosing (12:07), BP was 105/68 with HR **45** bpm. At end of study [redacted], BP was 121-150/76-81 with HR 73-80 bpm. The patient was discontinued from the study on 10/3/2006.
0029075	002	Atenolol	44	46	Other	Due to systolic and diastolic blood pressure (BP) protocol safety requirements on Day 51 study hour 4 per Medical Investigator	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 110-117/68-76 with HR 58-66 bpm. On Day -1, BP was 123-137/68-69 with HR 59-64 bpm. Predose (08:02) [redacted] BP was 116/66 with HR 64 bpm. Four hours post dosing (12:00), BP was **86/53** with HR 55 bpm. At end of study [redacted] BP was 118-126/58-62 with HR 64-68 bpm. Patient was discontinued on 12/7/2006.
0029078	002	Atenolol	46	47	Other	Dropped per medical investigator due to diastolic blood pressure protocol safety requirements on Day 53 study hour 2	**Met criteria for potentially clinically significant vital signs (SBP).** At Screening [redacted], BP was 119-125/69-77 with HR 73-78 bpm. On Day -1, BP was 106-117/63-66 with HR 72-76 bpm. On Day 50 [redacted], BP was 98-108/53-56 with HR 61-63 bpm. On [redacted] at 07:59 (predose), BP was 107/59 with HR 59 bpm.

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
							Two hours post-dose (10:10), BP was **90/52** with HR 64 bpm. At end of study [redacted] BP was 112-118/55-69 and HR was 67-76 bpm. Patient was discontinued from the study on 12/9/2006.
0039042	003	Atenolol	7	9	Other	Pulse out of range	**Did not meet criteria for potentially clinically significant vital signs.** At Screening [redacted], BP was 122-125/76-82 with HR 62-65 bpm. On Day -1 [redacted], BP was 126-133/86 with HR 68-74 bpm. Predose (7:30) on [redacted] BP was 102-109/67-74 with HR 49-50 bpm. Four hours post dosing (11:50), BP was 119/78, with HR **49** bpm. At end of study [redacted] BP was 118-119/77-82 with HR of 60-65 bpm. Patient was discontinued from the study on 11/3/2006.
0039076	003	Atenolol	1	5	Other	BP was not within protocol requirements on Day 9	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 122-128/77-80 with HR 93-96 bpm. On Day -1, BP was 119-122/78-82 with HR 67-71 bpm. At predose (07:32) on [redacted] BP was **85/47** with HR 50 bpm. At end of study [redacted] BP was 119-131/76-81 with HR 72-82 bpm. Patient was discontinued from the study on 11/8/2006.
0059036	005	Atenolol	8	21	Other	Low BP	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 116-131/71-81 with HR 66-71 bpm. On Day -1 [redacted], BP was 102-114/63-68 with HR 77-80 bpm. On [redacted], predose (08:24) BP was 105-110/64-68 with HR 58-59 bpm. Twelve hours post-dosing (20:34), BP was **88/50** with HR 61 bpm. At end of study [redacted], BP was 106-109/71-72 with HR 72-80 bpm. Patient was discontinued from the study on 1/3/2007.

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
0069037	006	Atenolol	2	8	Other	Low vitals outside protocol parameters	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 127-135/75-80 with HR 71-78 bpm. On Day -1, BP was 117-127/72-78 with HR 76-82 bpm. At predose on [redacted] BP was 98-105/58-65 with HR **50**-52 bpm. At end of study [redacted] BP was 101-112/57-64 with HR 53-54 bpm. Patient was discontinued from the study on 12/29/2006.
0019047	001	Nebivolol	8	9	Other	Protocol requirements for SBP	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 113-117/74-76 with HR 67-75 bpm. On Day -1, BP was 109-130/69-75 with HR 80-108 bpm. Predose (07:45) on [redacted] BP was 99-104/64-67 with HR 65-67 bpm. At 2 hours post-dosing (10:04), BP was **87/58** with HR 66 bpm. At end of study, BP was 89-94/52-60 with HR 66-74 bpm. Patient was discontinued from the study on 9/22/2006.
0019086	001	Nebivolol	9	19	Other	Due to vitals on Day 16	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 120-124/75-86 with HR 78-82 bpm. On Day -1, BP was 119-133/72-84 and HR was 84-88 bpm. On [redacted] predose (07:51) BP was 107/58 with HR 59 bpm. Two hours post dosing (10:11), BP was **85/60** with HR 57 bpm. At end of study [redacted] BP was 119-130/70-75 with HR 74-75 bpm. Patient was discontinued from the study on 11/13/2006.
0019139	001	Nebivolol	9	10	Other	Protocol requirements for systolic and diastolic BP	**Met criteria for potentially clinically significant vital signs (SBP).** At Screening [redacted] BP was 116-127/72-76 with HR 52-82 bpm. On Day -1, BP was 114-135/66-69 with HR 61-73 bpm. Predose (07:55) on [redacted], BP was 119-141/71-75 with HR of 71-78 bpm. Four hours post-dosing (12:02), BP was **100**/76 with HR 59 bpm. At end of study [redacted] BP was 107-124/67-72 with HR 69-

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
							76 bpm. Patient was discontinued from the study on 11/30/2006.
0029029	002	Nebivolol	45	47	Other	Due to HR protocol safety requirements	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 117-127/71-79 with HR 60-70 bpm. On Day -1 [redacted] BP was 108-119/60-66 with HR 64-70 bpm. At predose on [redacted] (07:50), BP was 121/64 with HR 54 bpm. At four hours post-dose (11:50), BP was 105/61 with **HR 40** bpm (44 bpm on repeat). At end of study [redacted], BP was 139-144/87-90, with HR 70-73 bpm. Patient was discontinued from the study on 10/28/2006.
0029034	002	Nebivolol	8	9	Other	Due to HR protocol safety requirement	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 129-144/76-78 with HR 71-77 bpm. On Day -1 [redacted], BP was 130-137/69-74 with HR 62-67 bpm. On [redacted] at predose (07:56), BP was 128-133/69-73 with HR 59-62 bpm. Four hours post-dosing (11:55), BP was 128/69 with HR 51 bpm. At end of study [redacted] BP was 150/76 with HR 54 bpm. Patient was discontinued from the study on 10/5/2006.
0029052	002	Nebivolol	45	46	Other	Due to HR protocol safety requirements	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 128-131/85-90 with HR 61-66 bpm. On Day -1, BP was 111-115/71-80 with HR 65-68 bpm. Predose (08:15) on [redacted] BP was 116/73 with HR 54 bpm. At 4 hours post-dose (12:17), BP was 115/64 with HR **44** bpm. At end of study [redacted] BP was 114-129/68-75 and HR 58-65 bpm. The patient was discontinued from the study on 10/27/2006.

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
0029058	002	Nebivolol	8	9	Other	Per Medical Investigator due to protocol safety requirements DBP on Day 15	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted], BP was 124-134/74-81 with HR 64-73 bpm. On Day -1, BP was 102-115/56-64 with HR 59-74 bpm. AT predose (07:48) on [redacted] BP was 116-122/**49-59** with HR 63-76 bpm. Subsequent diastolic blood pressures dropped as low as **45** mm Hg. At end of study [redacted] BP was 113-136/53-67 and HR 49-54 bpm. Patient was discontinued from the study on 11/1/2006.
0029062	002	Nebivolol	36	36	Other	Per medical investigator due to HR protocol safety requirements on Day 43 Study Hour 4	**Met criteria for potentially clinically significant vital signs.** At Screening [redacted] BP was 124-131/74-82 and HR 58-65 bpm. On Day -1, BP was 117-124/66-77, with HR 67-78 bpm. Predose (07:46) on [redacted] BP was 124/76 with HR 51 bpm. Four hours post-dose (11:46), BP was 118/67 with HR **46** bpm. At end of study ([redacted]), BP was 113-124/57-66 with HR 57-59 bpm. Patient was discontinued from the study on 11/29/2006.

BP: blood pressure (in mm Hg); HR: heart rate (in beats per minute); SBP: systolic blood pressure; DBP: diastolic blood pressure
(Adapted from Sponsor, Clinical Study Report, Table 14.1.4, List of Subjects Who Prematurely Discontinued (Randomized Population), pages 112-116 of 5947 and Listing 16.2.7.1, Adverse Events, Safety Population, pages 1050- of 5947)

7.1.10.5 Demographics and Baseline Characteristics

Baseline demographics and characteristics are displayed in Table 26. There was an imbalance in the proportion of nonwhite versus white subjects in both the Safety and ITT populations. Both nebivolol- and atenolol-treated groups had fewer nonwhites compared with the placebo group. The safety population had one additional poor metabolizer in the atenolol and nebivolol treatment groups, respectively, compared with the ITT population.

Table 26. Demographic Characteristics—Safety and Intent-to-Treat Populations (NEB-PK-03)

Characteristic	Safety Population				ITT Population			
	Placebo (N=52)	Atenolol (N=50)	Nebivolol (N=55)	Total (N=157	Placebo (N=48)	Atenolol (N=29)	Nebivolol (N=42)	Total (N=119)
Mean age, years (SD)	30.3 (8.74)	29.3 (9.31)	28.3 (9.00)	29.3 (9.00)	30.4 (8.49)	27.8 (8.83)	28.4 (8.65)	29.1 (8.63)
Race, n (%)								
White	31 (59.6)	38 (76.0)	47 (85.5)	116 (73.9)	28 (58.3)	21 (72.4)	34 (81.0)	83 (69.7)
Nonwhite	21 (40.4)	12 (24.0)	8 (14.5)	41 (26.1)	20 (41.7)	8 (27.6)	8 (19.0)	36 (30.3)
Black	15 (28.8)	8 (16.0)	4 (7.3)	27 (17.2)	15 (31.3)	6 (20.7)	4 (9.5)	25 (21.0)
Asian	3 (5.8)	1 (2.0)	2 (3.6)	6 (3.8)	3 (6.3)	1 (3.4)	2 (4.8)	6 (5.0)
Other	3 (5.8)	3 (6.0)	2 (3.6)	8 (5.1)	2 (4.2)	1 (3.4)	2 (4.8)	5 (4.2)
Ethnicity, n (%)								
Hispanic	13 (25.0)	15 (30.0)	15 (27.3)	43 (27.4)	12 (25.0)	8 (27.6)	12 (28.6)	32 (26.9)
Non-Hispanic	39 (75.0)	35 (70.0)	40 (72.7)	114 (72.6)	36 (75.0)	21 (72.4)	30 (71.4)	87 (73.1)
CYP 2D6 status, n (%)								
Extensive Metabolizers	51 (98.1)	48 (96.0)	50 (90.9)	149 (94.9)	47 (97.9)	28 (96.6)	38 (90.5)	113 (95.0)
Poor Metabolizers	1 (1.9)	2 (4.0)	5 (9.1)	8 (5.1)	1 (2.1)	1 (3.4)	4 (9.5)	6 (5.0)

(Adapted from Sponsor, Clinical Study Report, Table 10.3-2, page 70 of 5947, Table 14.21 (pages 117-118 of 5947), and Table 14.22 (pages 119-120 of 5947).

7.1.10.6 Extent of Exposure

Treatment duration for the Safety and ITT populations is displayed in Table 27. For the Safety Population, the mean duration of treatment was 43.4 days, 38.2 days, and 47.3 days for subjects in the nebivolol, atenolol, and placebo treatment groups, respectively.

Table 27. Sponsor's Analysis: Treatment Duration for Safety and ITT Populations (NEB-PK-03)

Safety Population			
Duration of Treatment (Days)	Placebo (n=52)	Atenolol (n=50)	Nebivolol (n=55)
Mean	47.3	38.2	43.4
SD	7.96	17.74	13.62
Median	49.0	49.0	49.0
Min, Max	8, 49	1, 49	8, 49
n	52	50	55
ITT Population			
Duration of Treatment (Days)	Placebo (n=48)	Atenolol (n=29)	Nebivolol (n=42)
Mean	49.0	49.0	49.0
SD	0.00	0.19	0.00
Median	49.0	49.0	49.0
Min, Max	49, 49	48, 49	49, 49
n	48	29	42

Reproduced from Sponsor, Clinical Study Report, Table 14.3.1.1 and Table 14.3.1.3, pages 126 and 128 of 5947.

7.1.10.7 Compliance

In the safety population, mean compliance was 100%, 99.6%, and 100% in the placebo, atenolol, and nebivolol treatment groups, respectively.

In the ITT population, mean compliance was 100%, 99.7%, and 99.7% in the placebo (n=48), atenolol (n=29), and nebivolol (n=42) treatment groups, respectively.

7.1.10.8 Concomitant Medications

Concomitant medications were taken by 26.1% (41/157) of subjects in the Safety Population, including 23.6%, 26.0%, and 28.8% of subjects in the nebivolol, atenolol, and placebo treatment groups, respectively. The sodium chloride flush administered after the cosyntropin injection during the study was considered by one Investigator to be a concomitant medication for all subjects at that site (38/157 subjects or 24.2%). The analgesic, paracetamol, was the second most common medication and was taken by 2 (3.8%), 3 (6.0%), and 0 subjects in the placebo, atenolol, and nebivolol treatment groups, respectively.

7.1.10.9 Assays

- Cortisol, LH, Testosterone, Human Sex Hormone-Binding Globulin (SHBG): Electrochemiluminescence Immunoassay "ECLIA" ——, intended for use on t ——— Immunoassay analyzers
- ACTH: Enzyme-Linked ImmunoSorbent Assay (ELISA)
- Aldosterone: Enzyme immunoassay ———

7.1.10.10 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 EOS (Day 57).

As displayed in Table 28, although there were numerous withdrawals in the atenolol and nebivolol treatment groups, 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.

Table 28. 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 $AUC_{0\text{-}12\text{-}min}$ (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)

Between white and nonwhite populations, there were also no significant differences in the mean ACTH-stimulated $AUC_{0\text{-}120\ min}$ for serum cortisol levels at study end for nebivolol relative to placebo, as shown in Table 29.

Table 29. 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 by Race Group—Intent-to-Treat Population (NEB-PK-03)

	Placebo (N=48)		*Atenolol (N=29)*		*Nebivolol (N=42)*	
Serum Cortisol Levels, µg/dL x h	*White (n=28)*	*Nonwhite (n=20)*	*White (n=21)*	*Nonwhite (n=8)*	*White (n=34)*	*Nonwhite (n=8)*
Mean (SD)						
Day 8 (baseline)	56.54 (6.104)	52.93 (6.199)	57.54 (5.956)	54.55 (4.244)	55.61 (5.948)	56.09 (5.489)
Day 57	57.19 (7.026)	53.86 (6.900)	58.95 (6.626)	55.45 (5.191)	55.99 (5.593)	56.74 (6.213)
LSM[a] (SE)	56.522 (1.18)	54.183 (1.03)	57.971 (1.26)	55.058 (1.47)	56.416 (1.01)	54.589 (1.38)
LSMD[a,b] (90% CI)	—	—	1.45 (–0.60, 3.50)	0.88 (–1.82, 3.58)	–0.11 (–1.96, 1.75)	0.41 (–2.42, 3.23)
LSMD[a,c] (90% CI)	—	—	2.56 (–1.06, 6.19)	1.62 (–3.37, 6.60)	–0.19 (–3.46, 3.09)	0.75 (–4.46, 5.97)

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 14.4.1.1A.

(Reproduced from Sponsor, Clinical Study Report, Table 11.1.1.1-2, page 75 of 5947)

7.1.10.11 Secondary Pharmacodynamic End Points (Leutinizing Hormone, Total Testosterone)

The effects of nebivolol, atenolol, and placebo on mean luteinizing hormone and mean total testosterone are displayed in Table 30 and Table 31, respectively. The LSMD for mean luteinizing hormone and mean total testosterone, expressed as a percentage of placebo, was not statistically significant for the atenolol and nebivolol treatment groups. At Day 56, nebivolol increased and atenolol decreased mean total testosterone in a nonsignificant fashion, as seen in Table 31.

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Table 30. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Luteinizing Hormone Levels at Day 56--ITT 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 31. 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)

7.1.10.12 Additional Analyses (SHBG, Free Testosterone, Basal ACTH, Basal Cortisol, Basal Aldosterone, and $AUC_{0\text{-}120\ min}$ of Serum Aldosterone Levels after the IV administration of ACTH (250 µg at end of study):

7.1.10.12.1 SHBG

There were no significant changes in SHBG from baseline to end of study in any of the treatment groups, as shown in Table 32.

Table 32. SHBG Levels--ITT Population (NEB-PK-03)

SHBG Levels (nmol/l)	Placebo (N=48)	Atenolol (N=29)	Nebivolol (N=42)
Mean (SD)			
Day 7 (baseline)	24.76 (9.946)	23.72 (7.277)	26.59 (10.134)
Day 56	25.36 (8.899)	23.86 (7.634)	26.03 (10.023)
Adapted from Sponsor, Clinical Study Report, Table 14.4.3.1, page 137 of 5947			

7.1.10.12.2 Free Testosterone

The LSMD for mean free testosterone, expressed as a percentage of placebo, was not statistically significant for the atenolol and nebivolol treatment groups. At Day 56, nebivolol increased and atenolol decreased mean free testosterone in a nonsignificant fashion, as seen in Table 33.

Table 33. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Free Testosterone Levels at Day 56--ITT Population (NEB-PK-03)

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.
Cross-reference: Table 14.4.3.1.

(Reproduced from Sponsor, Clinical Study Report, Table 11.1.1.3.1-1, page 78 of 5947)

7.1.10.12.3 Basal Adrenocorticotropic Hormone (ACTH) Levels

Compared to placebo, nebivolol and atenolol had no significant effects on mean basal adrenocorticotropic hormone levels at Day 57, as shown in Table 34.

Table 34. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Basal Adrenocorticotropic Hormone Levels at Day 57--ITT Population (NEB-PK-03)

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.
Cross-reference: Table 14.4.3.2.

(Reproduced from Sponsor, Table 11.1.1.3.2-1, page 79 of 5947)

7.1.10.12.4 Basal Cortisol

Compared to placebo, nebivolol and atenolol had no significant effects on mean basal cortisol levels at Day 57, as shown in Table 35.

Table 35. Sponsor's Analysis: Effects of Nebivolol, Atenolol, and Placebo Administration on Mean Basal Cortisol levels at Day 57--ITT Population (NEB-PK-03)

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.
Cross-reference: Table 14.4.3.3.

(Reproduced from Sponsor, Clinical Study Report, Table 11.1.1.3.3-1, page 80 of 5947)

For the following parameters, there were no significant changes from baseline mean values in the three treatment groups, and compared to placebo, at end of study, there were no significant differences in either the nebivolol or atenolol treatment groups in the following parameters:

- Mean Basal aldosterone
- Mean ACTH-Stimulated $AUC_{0\text{-}120\ min}$ of Serum Aldosterone at End of Study

7.1.10.13 Other Analyses

Table 36 summarizes the results for other analyses.

Table 36. Other Analyses (NEB-PK-03)

#	Parameter	Result
1	Unstimulated Basal Cortisol Levels < 3 µg/dl on Day 8 or Day 57	No subjects in any of the treatment groups had unstimulated basal cortisol levels less than 3 µg/dl on Day 8 or Day 57.
2	Peak ACTH-Stimulated Cortisol Levels of < 19 µg/dl.	No subjects in any of the treatment groups had peak adrenocorticotropic hormone (ACTH)-stimulated cortisol levels of less than 19 µg/dl.
3	Peak ACTH-Stimulated Cortisol Level that was ≤ 7 µg/dl Above the Unstimulated Basal Cortisol Level.	One subject in the placebo treatment (1/48 or 2.08%) group had a peak ACTH-stimulated cortisol level that was ≤ 7 µg/dl above the unstimulated basal cortisol level.
4	Peak ACTH-Stimulated Aldosterone Level < 5 ng/dl Above Unstimulated Basal Aldosterone Level (Baseline [Day 8] and End of Study [Day 57])	On Day 8, 2 (4.2%), 1 (3.4%), and 3 (7.1%) of subjects in the placebo, atenolol, and nebivolol treatment groups, respectively, had peak ACTH-stimulated aldosterone level < 5 ng/dl above basal level. On Day 57, 4 (8.3%), 2 (6.9%), and 3 (7.1%) of subjects in the placebo, atenolol, and nebivolol treatment groups, respectively, had peak ACTH-stimulated aldosterone level < 5 ng/dl above basal level Poststudy, 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.
5	Post-ACTH Serum Cortisol (< 19 µg/dl) or Aldosterone (< 5 ng/dl Level Above Basal Unstimulated Aldosterone Level)	On Day 8 (baseline) and on Day 57, no subjects in any of the treatment groups had abnormal post-ACTH serum cortisol levels. Please see post ACTH serum aldosterone results described under #4.
Compiled by Karen A. Hicks, M.D. References: Tables 14.4.3.6, 14.4.3.7, 14.4.3.8, 14.4.3.9, 14.4.3.10.		

Two subjects (3.6%) in the nebivolol treatment group experienced chest discomfort, compared with no subjects in each of the placebo and atenolol treatment groups. However, 1 subject (1.9%) in the placebo treatment group and 1 subject (2.0%) in the atenolol treatment group experienced chest pain, compared to 0 patients in the nebivolol treatment group. The chest discomfort is further described in Table 39.

Table 39. Chest Pain and Testicular Pain (NEB-PK-03)

Study Center	Subject	Treatment	Age (years)/ Ethnicity	Adverse Event and Day of AE Start/Stop	Reviewer Comments
002	0029050	Nebivolol	36/Caucasian	Chest discomfort/heaviness in chest on 9/23/2006 (17:30-19:30) (Days 11/11) and 9/24/2006 (20:00-22:00) (Day 12/12) and chest discomfort/chest pressure on 10/29/2006 (09:50-20:00) (Day 47/47).	The subject completed the study on 11/1/2006. ECGs: • [redacted] (16:59:59): Sinus rhythm at 67 bpm with sinus arrhythmia. Normal tracing. • [redacted] (16:58:06): Normal sinus rhythm at 63 bpm. Normal tracing. • [redacted] (12:33:12): Sinus bradycardia at 48 bpm with sinus arrhythmia and occasional ectopic premature complexes. • [redacted] (18:34:22): Sinus rhythm at 72 bpm with nonspecific STT wave abnormality inferolaterally. Abnormal ECG. Changed from [redacted] • [redacted] (10:19:18): Sinus bradycardia at 59 bpm with occasional ectopic premature complexes. • [redacted] (15:09:29): Sinus rhythm with occasional ectopic premature complexes and nonspecific ST-T wave abnormality. Abnormal ECG. **No cardiac enzymes orECGs were checked during the chest discomfort on 9/23/2006 and 9/24/2006. Serial 12-lead ECGs and cardiac enzymes should have been obtained during symptoms on these dates. The ECG obtained during symptoms on [redacted] demonstrated no evidence of ischemia.** Note: Subject was initially randomized to 0065 and took this randomized double blind study drug from Days 8-42. On Day 43 (11/13/2006), a dosing error occurred, and the subject received and was dosed with randomization 0060 double blind study drug from Days 43-56.
004	0049140	Nebivolol	36/Caucasian	Testicular pain/right testicular pain on 1/22/2007 (Day 49/49) from 19:00 to 19:05.	The subject completed the study on 1/23/2007. At end of study, there were no testicular complaints or testicular physical exam findings.
002	0029026	Atenolol	45/Caucasian	Testicular pain from 10/7 – 10/12/2006 (Days 25-30) from 18:00 to 05:30.	The subject completed the study on 10/31/2006; however, this subject required a post study aldosterone test on 11/27/2006. At end of study, there were no testicular complaints or testicular physical exam findings.
005	0059012	Atenolol	25/Caucasian	Chest pain on 12/23/2006 (Day 10/10) from 10:35 to 10:40.	Subject did not complete the study. Subject was prematurely discontinued from the study on 1/8/2007 due to a protocol violation (subject did not self dose). ECG on [redacted] (9:58:18) revealed sinus rhythm and nonspecific ST-T wave changes inferolaterally. ECG on [redacted] (8:24:38) showed sinus bradycardia at 54 bpm but was otherwise normal. No ECG or cardiac enzymes were obtained at the time of chest pain.

7.1.10.14 Safety

3.1.11.1 Adverse Events

There were 157 subjects in the Safety Population including 55 subjects randomized to nebivolol, 50 subjects randomized to atenolol, and 52 subjects randomized to placebo. There were no deaths or serious adverse events.

A total of 57.7% (30/52) of subjects treated with placebo, 40.0% (20/50) treated with atenolol, and 38.2% (21/55) subjects treated with nebivolol experienced at least one treatment emergent adverse event (TEAE). Two subjects in the atenolol (2/50 or 4.0%) and two subjects in the nebivolol (2/55 or 3.6%) treatment groups experienced an adverse event leading to premature discontinuation. A Summary of Adverse Events for the Safety Population is displayed in Table 37.

Table 37. Sponsor's Analysis: Summary of Adverse Events (Safety Population) (NEB-PK-03)

	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.
Cross-reference: Table 14.5.1.1.

(Reproduced from Sponsor, Table 12.1.1-1, page 87 of 5947)

Adverse Events reported in ≥ 5% of Subjects in Any Treatment Group are displayed in Table 38.

Table 38. 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)

One subject in the atenolol group had a severe TEAE (headache). Five subjects experienced TEAEs of moderate intensity, including 2 subjects in the nebivolol group (depression and pharyngolaryngeal pain), 2 subjects in the atenolol group (bronchitis and pharyngolaryngeal pain), and 1 subject in the placebo group (toothache).

Two subjects experienced testicular pain, including one subject (2.0%) in the atenolol treatment group and 1 subject (1.8%) in the nebivolol treatment group, as further described in Table 39.

Study Center	Subject	Treatment	Age (years)/ Ethnicity	Adverse Event and Day of AE Start/Stop	Reviewer Comments
005	0059025	Nebivolol	44/Asian	Chest discomfort/right-sided chest discomfort from 1/19 – 1/20/2007 (Days 37/38) from 16:00 to 17:00 and the same symptoms on 12/16/2006 (Day 3/3) from 14:45 to 14:50.	ECGs • (11:26:23): Sinus bradycardia at 56 bpm, otherwise normal. Early repolarization. • (13:27:16): Sinus rhythm at 89 bpm. No significant change from **No ECGs or cardiac enzymes were obtained at the time of chest discomfort on 12/16/2006 or from 1/19 – 1/20/2007. Serial cardiac enzymes and ECGs should have been checked for the hour-long discomfort on 1/19/2007, and an ECG should have been obtained on 12/16/2006.**
Table compiled from Case Report Forms and Individual Review of ECG tracings.					

Two subjects each in the atenolol and nebivolol treatment groups discontinued the study because of an adverse event (AE), as displayed in Table 25.

Adverse events leading to discontinuation are shown in Table 40.

Table 40. Sponsor's Analysis: Adverse Events Resulting in Discontinuation of Treatment--Safety Population (NEB-PK-03)

	No. (%) of Subjects		
Adverse Event (Preferred Term)	***Placebo (N=52)***	***Atenolol (N=50)***	***Nebivolol (N=55)***
Subjects who discontinued because of AE[a]	0	2 (4.0)	2 (3.6)
Heart rate decreased	0	0	1 (1.8)
Hypotension	0	1 (2.0)	1 (1.8)
Bradycardia	0	1 (2.0)	0

a Subjects counted once for "one or more" adverse events.

Cross-reference: Table 14.5.2.3.

(Reproduced from Sponsor, Table 12.2.3-1, page 90 of 5947)

7.1.10.14.1 Laboratory Values

There were no clinically important changes in laboratory values, and no subject discontinued the study due to a potentially clinically significant (PCS) laboratory value. Less than 4% of subjects in any treatment group experienced a PCS laboratory parameter.

Per the sponsor, a potentially clinically significant neutrophil percentage was ≤ 25 (normal range: 39-78 %). A potentially clinically significant total bilirubin value was > 1.5 UNL (normal range: 1.71-20.52 umol/l). A potentially clinically significant uric acid value was > 1.1 UNL (normal range: 237.94-505.62 umol/l).

Subject 0039089, a 22 year old Black subject randomized to atenolol, had a low neutrophil percentage at screening (36%), Day -1 (31%), and Day 50 (23%), but a normal neutrophil percentage at the end of study : 43%)

Five subjects had an abnormal total bilirubin during the course of the study, including 2 subjects in the placebo treatment group, 2 subjects in the nebivolol treatment group, and 1 subject in the atenolol treatment group.

- Subject 0019043, a 19 year old Caucasian subject randomized to placebo, had a normal total bilirubin at screening 15.39 umol/l) and an abnormal total bilirubin on Day -1 (37.63 umol/l), Day 50 34.21 umol/l), and end of study (: 25.66 umol/l). At an unscheduled visit on the total bilirubin was normal at 18.81 umol/l.

- Subject 0029031, a 19 year old Caucasian subject randomized to placebo, had an abnormal total bilirubin at screening (49.60 umol/l), Day -1 30.79 umol/l), Day 50 : 29.08 umol/l), and end of study (51.31 umol/l).

- Subject 0069037, a 27 year old Caucasian subject randomized to atenolol, had an abnormal total bilirubin at screening (25.66 umol/l), Day -1 (34.21 umol/l), and end of study 39.34 umol/l).

- Subject 0029058, an 18 year old Caucasian subject randomized to nebivolol, had an abnormal total bilirubin at end of study 32.50 umol/l), when the value was normal at screening 11.97 umol/l).

- Subject 0059019, a 22 year old Caucasian subject randomized to nebivolol, had an abnormal total bilirubin at screening 34.21 umol/l), Day -1 (: 25.66 umol/l), Day 50 (30.79 umol/l), and end of study (34.21 umol/l).

Two placebo subjects had PCS values for uric acid on Day 50 of 571.06 umol/l (404.50 umol/l at screening) and 559.16 umol/l (452.09 umol/l at screening), respectively.

Table 41. Number (%) of Subjects with Potentially Clinically Significant Laboratory Parameters (Safety Population) (NEB-PK-03)

Laboratory Parameter (PCS Criterion)[a]	Placebo (N=52) n/m (%)	Atenolol (N=50) n/m (%)	Nebivolol (N=55) n/m (%)
Hematology			
Neutrophils low	0	1/50 (2.0)	0
Chemistry			
Total bilirubin high	2/52 (3.8)	1/50 (2.0)	2/55 (3.6)
Uric acid high	2/52 (3.8)	0	0

[a]No subjects had non-PCS baseline and PCS postbaseline values for hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, protein, albumin, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, or urine specific gravity or pH.
PCS=potentially clinically significant; n=number of subjects with an available non-PCS baseline value and at least one PCS postbaseline value; m=number of subjects with an available non-PCS baseline value and at least one postbaseline value.
Cross-reference: Table 14.5.4.2
(Adapted from Sponsor, Table 12.3.1.2-1, page 92 of 5947 and Table 14.5.4.3, pages 177-179 of 5947)

7.1.10.14.2 Vital Signs

There were no clinically important symptomatic changes in vital signs.

The mean changes in vital signs from baseline to end of study are displayed in Table 42.

Table 42. Sponsor's Analysis: Change from Baseline in Vital Signs Parameters (Safety Population) (NEB-PK-03)

Parameter[a]	*Placebo (N=52)*[a]	*Atenolol (N=50)*[a]	*Nebivolol (N=55)*[a]
Systolic blood pressure,[b] mm Hg			
Baseline[c]	122.79 (9.58)	118.83 (10.33)	118.56 (8.74)
Change from baseline[d]	0.47 (10.45)	–2.85 (10.68)	–3.59 (11.37)
Diastolic blood pressure,[b] mm Hg			
Baseline[c]	73.45 (7.42)	71.23 (7.46)	71.78 (6.30)
Change from baseline[d]	0.04 (7.12)	–2.56 (7.68)	–4.42 (7.73)
Pulse rate,[b] bpm			
Baseline[c]	75.15 (9.38)	74.83 (7.98)	75.15 (9.30)
Change from baseline[d]	7.10 (10.97)	–1.38 (14.52)	–4.62 (10.10)

a All subjects had available baseline and postbaseline values.
b Mean of three readings at each visit.
c Mean (SD) of baseline (last assessment prior to first dose of double-blind study drug).
d Mean (SD) of change from baseline to End of Study (last nonmissing postbaseline assessment in the study).
Cross-reference: Tables 14.5.5.4 through 14.5.5.6.

(Reproduced from Sponsor, Table 12.4.1-1, page 93 of 5947)

The number of subjects with postbaseline PCS values is displayed in Table 43. Four subjects in the nebivolol treatment group had postbaseline PCS vital sign values: 1 subject with PCS decreased DBP and pulse, 1 subject with PCS decreased pulse rate, and 2 subjects with PCS weight gain. One subject in the atenolol treatment group had a PCS decreased pulse. No subjects with postbaseline PCS values had concomitant treatment emergent adverse events (TEAEs). Subject 0049059 in the nebivolol treatment group with a PCS value for pulse rate was withdrawn due to a protocol violation in which he received study drug despite an exclusionary pulse rate on Day 15.

Table 43. Sponsor's Analysis: Number (%) of Subjects with Potentially Clinically Significant Vital Sign Values (Safety Population) (NEB-PK-03)

Parameter[a]		*Placebo (N=52) n/m (%)*	*Atenolol (N=50) n/m (%)*	*Nebivolol (N=55) n/m (%)*
Diastolic blood pressure[b]	Decrease[c]	0	0	1/55 (1.8)
Pulse	Decrease[d]	0	1/50 (2.0)	2/55 (3.6)
Weight	Increase[e]	0	0	2/55 (3.6)

a No subject had a potentially clinically significant postbaseline value for systolic blood pressure (increased or decreased), increased diastolic blood pressure, increased pulse rate, or weight loss.
b Mean of three readings at each visit.
c Less than or equal to 50 mm Hg and decrease from baseline greater than or equal to 15 mm Hg
d Less than or equal to 50 bpm and decrease from baseline of 15 bpm or more.
e Increase from baseline greater than or equal to 7%.
n = number of subjects with at least one potentially clinically significant postbaseline value; m = number of subjects with baseline and at least one postbaseline value.
Cross-reference: Table 14.5.5.1

(Reproduced from Sponsor, Table 12.4.1-2, page 94 of 5947)

Four subjects in the nebivolol treatment group experienced TEAEs potentially associated with a PCS vital sign value, including one subject each with postural dizziness, decreased pulse rate, hypotension, and hypertension. In

the atenolol treatment group, 1 subject experienced the TEAE of hypotension with no associated PCS value. Additionally, one placebo-treated subject had a TEAE of increased appetite but no associated PCS value for weight.

7.1.10.14.3 Electrocardiograms

There were no clinically important changes in ECG parameters.

7.1.10.14.4 Physical Examination

In all treatment groups, there were no clinically important changes in the physical examination. No subjects developed breast or testicular masses during the course of the study. The male breast examination questionnaire for all subjects remained negative.

7.1.10.15 Summary

NEB-PK-03 was performed to evaluate the effect of nebivolol 10 mg on adrenal function, LH levels, and total testosterone levels in healthy male subjects including extensive metabolizers (EMs) and poor metabolizers (PMs) of CYP 2D6.

In this study, the ITT population was actually a Per Protocol population due to the significant number of drop-outs in the atenolol and nebivolol treatment groups. A total of 157 subjects were randomized to double-blind treatment, including 55 subjects to nebivolol, 50 subjects to atenolol, and 52 subjects to placebo. However, only 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%) had a postbaseline series of cortisol levels after ACTH administration, took the double-blind study drug as assigned, and completed the study.

In NEB-PK-03, at the doses and duration studied, nebivolol and atenolol had no significant effect on $AUC_{0\text{-}120\ min}$ of serum cortisol levels following IV ACTH (250 μg) administration at end of study (Day 57).

Similarly, nebivolol and atenolol did not significantly affect LH, total testosterone, free testosterone, basal ACTH, basal cortisol, basal aldosterone, and $AUC_{0\text{-}120\ min}$ of serum aldosterone levels after the IV administration of ACTH (250 μg) at end of study.

Therefore, after 49 days of nebivolol treatment, including 7 days at the 5 mg dosage and 42 days at the 10 mg/day dosage, nebivolol did not demonstrate any significant changes in adrenal or gonadal function.

Some limitations to study interpretation include the large standard deviation and wide confidence intervals seen in the atenolol and nebivolol treatment groups for the mean total testosterone levels at baseline and on Day 56, possibly suggesting inaccuracy of the assay utilized. Per DRUP, wide confidence intervals in serum testosterone levels are common.

At Day 56, there was an increase in mean total and mean free testosterone in the nebivolol treatment group. Therefore, one must consider whether the increase in testosterone level could become statistically and clinically significant if the study was of greater duration. Per DRUP, the approximately 8% increase in total testosterone levels at the end of study does not approach a level of concern. Other agents, such as dutasteride, have been approved with greater increases (up to 18%).

7.2 Study NEB-323, "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) (Final Report Date: February 15, 2006)

7.2.1 Protocol, Amendment, and Post Hoc Changes

The study description was based on the original protocol dated June 17, 2003 and Protocol Amendment 1 dated August 19, 2003.

Amendment 1 removed the following from the original protocol:
- The term "extension" from the study description and protocol title
- References regarding study visits and procedures from the previous study
- Collection of supine and standing blood pressures
- Performance of urinalysis
- Reference to Cruickshank et al., 1994, from page 38

Amendment 1 added the following to the original protocol:
- Reference to "The Seventh Report of the Joint National committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)" as the treatment guideline for this study
- Patients were initiated on 5 mg of nebivolol at Visit 1 and titrated to control over a 2-week period
- The study was to be terminated/stopped upon approval of the nebivolol New Drug Application (NDA) by the FDA
- A statement regarding the gap in nebivolol treatment between the last visit of the previous study and the first visit of this study
- A statement regarding the continuation of antihypertensive treatment during the gap as determined by the investigator
- Verapamil was added to the prohibited medications list
- Pregnancy testing was added to each 3-month visit

The final statistical plan superseded the protocol-defined statistical plan and was finalized and implemented prior to data analysis.

Changes to the protocol-defined statistical plan included the following:
- Although the protocol referred to the study baseline at Visit 1 as Day 0, for analysis purposes, study baseline was designated as Day 1
- Although the protocol stated the study was to close upon approval by the FDA of the nebivolol NDA for hypertension, the last patient completed the study in September 2004. Since the sample size in the trial was less than 20% of that anticipated, and because the trial was administratively ended earlier than planned, no formal statistical comparisons were made.
- Section 7.2 of the protocol stated that "Treatment groups will be compared with respect to demographics (age, race, gender), diabetes, and baseline measurements (vital signs, physical examination, etc.) using analysis of variance (ANOVA) for continuous variables or Fisher Exact for discrete variables." Since there were no treatment groups in NEB-323, no treatment group comparisons were performed, and summary statistics were presented.
- The primary method of handling missing data was the observed cases (OC), no replacement of missing data
- The last observation carried forward (LOCF) was the secondary method of handling data and was only performed on the primary efficacy parameter
- Goal blood pressure was defined in the protocol as < 140/90 mm Hg for patients with uncomplicated hypertension or < 130/80 mm Hg for patients with diabetes or chronic kidney disease. Since patients with chronic kidney disease could not be reliably identified in this study, only a patient's diabetes status was used to determine whether the lower hypertension goal was relevant to that patient

There were two deviations from the final statistical analysis plan:

- The final number of patients who participated in the trial was 85, not 82. Additionally, although there were supposed to have been up to 10 clinic visits in the study, patients had up to 6 clinic visits only.
- Although the target days for Visits could have been different than the original target days, for presentation purposes, the original target day schedule was used.

7.2.2 Study Design

This was a multicenter, open-label study evaluating the long-term safety and efficacy of nebivolol administered orally once daily in patients with mild to moderate hypertension, defined as an average sitting DBP $\geq$ 95 mm Hg and $\leq$ 109 mm Hg when untreated. All patients received nebivolol 5 mg, 10 mg, or 20 mg.

7.2.3 Objectives

The objectives of this study were to

- assess the long-term safety profile of nebivolol for the treatment of elevated blood pressure in patients with mild to moderate hypertension
- assess the long-term efficacy of nebivolol in patients with mild to moderate hypertension

7.2.4 Inclusion and Exclusion Criteria

Inclusion Criteria (Must be present)

1. Signed informed consent
2. Age $\geq$18 years
3. Successful completion of a previous nebivolol study within the past 12 weeks (NEB202, NEB203, NEB302, NEB306, NEB321, NEB306)
4. High probability for compliance and completion of the study

Exclusion Criteria (Cannot be present)

1. **Sitting diastolic blood pressure (DBP) defined as an average value > 109 mm Hg**
2. Secondary hypertension
3. Malignant hypertension (retinal hemorrhage, exudates, or papillary edema)
4. **Sitting systolic hypertension defined as an average sitting SBP > 199 mm Hg)**
5. **Sitting heart rate defined as an average value < 50 bpm**
6. Recent history or presence of asthma, bronchospasm, or chronic obstructive airway disease
7. Chronic atrial fibrillation or recurrent tachyarrhythmia
8. Sick sinus syndrome, including second or third degree atrioventricular (AV) block
9. History of sensitivity or significant adverse reaction to beta-blockers
10. Myocardial infarction or cerebrovascular accident within 6 months. If the Screening (Visit 1) electrocardiogram (ECG) had diagnostic pathological Q waves and the timing of the event associated with the Q waves was unknown, the patient was excluded
11. Heart failure requiring treatment. A left ventricular ejection fraction (LVEF) value was not required to participate in this trial. However, if an LVEF had been measured within 12 months prior to Visit 1, the LVEF must have been $\geq$ 0.40
12. Hemodynamically significant valvular heart disease
13. Presence of severe peripheral vascular disease
14. Pregnant or nursing women, or women of childbearing potential not using appropriate contraception as determined by the principal investigator. For the purposes of the study, a woman of childbearing potential was defined as any female who was biologically capable of becoming pregnant. For this study, abstinence was not considered appropriate contraception.
15. Presence of any condition that may have, in the judgment of the investigator, jeopardized the participant's adherence to the protocol or ability to complete the trial (e.g., alcohol or drug abuse, disabling or terminal illness, mental disorders)

16. Concomitant therapy with medications that may have affected blood pressure
    a. Oral and/or ophthalmic beta-adrenergic blocking agents (e.g., atenolol, metoprolol, propranolol, timolol)
    b. Theophylline or beta agonists
    c. Long-acting oral nitrates (e.g., Isordil)
    d. Treatment within 180 days (6 months) of the initiation of Visit 1 with a protease inhibitor as the effects of this class of drugs on the pharmacokinetics of nebivolol were poorly defined at the time of study initiation
17. Morbid obesity, if it prevented the use of a large blood pressure cuff on the upper arm to accurately measure blood pressure
18. Use of investigational treatment within the past 30 days of the patient's signing informed consent. Nebivolol was excluded from this criterion if it was received in a recent nebivolol study.

7.2.5 Study Plan

Patients who successfully completed a prior nebivolol study were eligible for enrollment in Study NEB-323.

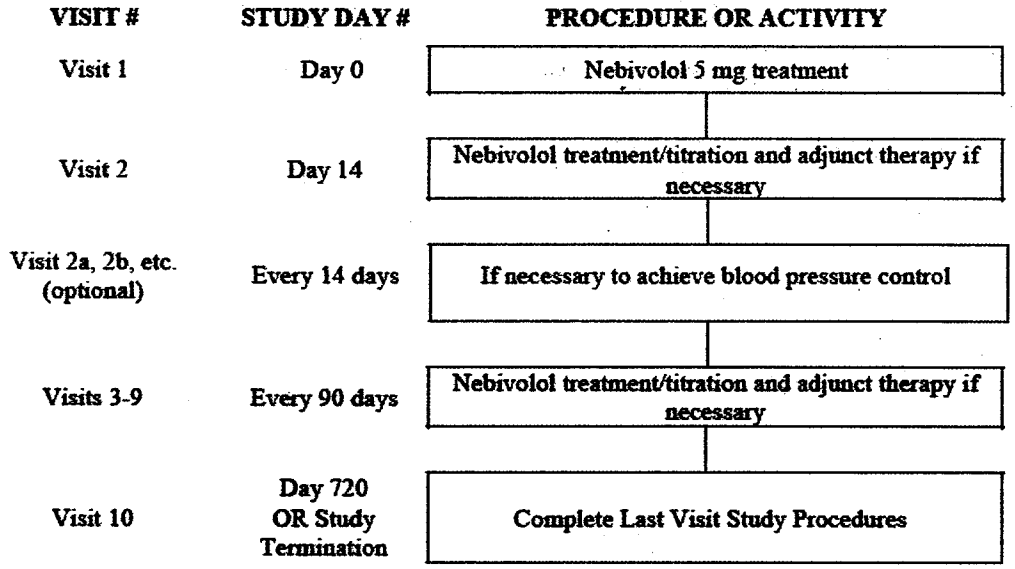
In most cases, there was a gap in nebivolol treatment of up to 12 weeks between completion of the prior study and entry into Study NEB-323. During this period, patients could receive any antihypertensive therapy thought to be appropriate by the investigator. If the investigator thought the patient's therapy could be discontinued upon entry into NEB-323, then the patient was initiated on nebivolol 5 mg once daily as initial monotherapy. However, if a patient was currently receiving therapy with a beta-blocker, the beta-blocker was discontinued, and nebivolol was initiated. If a patient was receiving antihypertensive therapy other than a beta-blocker that could not be discontinued, nebivolol 5 mg once daily was initiated as adjunctive therapy.

There were to be a total of up to 10 clinic visits in Study NEB-323. Visit 1 (Day 0) was the baseline study visit, and Visit 2 (Day 14) was used to titrate the dose of nebivolol and/or adjunctive medications. Titration of antihypertensive medications was guided by goal blood pressure in JNC-7, defined as < 140/90 mm Hg for patients with uncomplicated hypertension or < 130/80 mm Hg for patients with diabetes or chronic kidney disease.

During the trial, patients could have their nebivolol doses titrated, even if they were receiving adjunctive therapy. The investigator could also add adjunctive therapy, as necessary to achieve goal blood pressure.

The study design is displayed in Figure 1. Nebivolol doses of 5 mg, 10 mg, and 20 mg were used since they were common to all of the previous feeder studies for NEB-323.

Figure 1. Study Design (NEB-323)



(Reproduced from Sponsor, NEB-323 Clinical Study Report, Figure 9.1-01, page 18)

The schedule of procedures/events is summarized in Table 44.

Table 44. List of Study Procedures (NEB-323)

Visit # / Day #	Visit 1 Day 0	Visit 2 Day 14	Visit 2a, 2b, 2c Titration Visit(s)[2] (Optional)	Visits 3-9 Day 105-630	Study Termination or Day 720
Procedure/Activity					
Signed informed consent	X				
Inclusion/exclusion criteria	X				
Medical history/demographics	X				
Record previous medications	X				
Record concomitant medications	X	X	X	X	X
Check for use of prohibited medications	X	X	X	X	X
Check for use of restricted medications	X	X	X	X	X
Trough sitting blood pressures and heart rates	X	X	X	X	X
Body weight and height[1]	X			X	X
Physical examination	X				X
Laboratory evaluation	X			X	X
β-HCG urine pregnancy test	X			X	X
12-lead electrocardiogram	X			X	X
Interview patient / check for compliance	X	X	X	X	X
Dispense study medication	X	X	X	X	
Collect unused study medication		X	X	X	X
Adverse Event assessment		X	X	X	X

[1]Height was measured only at Visit 1 (Day 0).
[2]Optional visit(s) depended on satisfactory achievement of JNC-7 goal blood pressures.

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 9.5-01, page 24)

7.2.6 Dosage, Duration, and Adjustment of Therapy

Patients received up to 720 days of oral nebivolol once daily, with a starting daily dose of 5 mg. The dose of nebivolol could be titrated up to 10 mg or 20 mg, and adjunctive therapy could be utilized to achieve blood pressure goals. All medications were administered in an open-label fashion. Patients were instructed to take nebivolol at the same time each morning between 7 AM and 10 AM, with or without breakfast. On clinic days, study drug administration was delayed until trough hemodynamic assessments were made.

Table 45. Study Medication Administered (NEB-323)

Total Daily Dose[a]	Tablet Strength [Lot number]
Nebivolol 5 mg	5 mg nebivolol [R1K2856, R1L1378]
Nebivolol 10 mg	10 mg nebivolol [R1K2857, R1L1379]
Nebivolol 20 mg	20 mg nebivolol [R1K3674, R1L4366]

[a] Study medication administered once daily in the morning.

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 9.4-01, page 21)

7.2.7 Concomitant Therapy

Adjunctive antihypertensive therapy was allowed. All prescription and over-the-counter concomitant medications, including nutraceuticals and dietary supplements, were recorded.

7.2.8 Prohibited and Restricted Medications

Prohibited Medications*

- Any antihypertensive medication not given as part of the study
- Oral and ophthalmic beta-adrenergic blocking agents (e.g., atenolol, metoprolol, propranolol, timolol)
- Theophylline or beta-agonists
- Long-acting oral nitrates (e.g., Isordil®)
- Treatment with a protease inhibitor within 180 days of the initiation of screening

*Although calcium-channel blocking agents were allowed as adjunctive therapy, the sponsor recommended verapamil be avoided due to its effects on cardiac contractility and conduction.

Restricted Medications

- Use of short-acting nitrates (e.g., sublingual nitroglycerin) was prohibited within 4 hours before clinic visits
- Once a patient had been enrolled (Visit 1), use of antihistamines within 24 hours of a subsequent clinic visit was prohibited

7.2.9 Endpoints

Primary Efficacy Variable: The primary efficacy variable was the percent of patients who achieved goal blood pressure defined as < 140/90 mm Hg for patients with uncomplicated hypertension or < 130/80 mm Hg for patients with diabetes or chronic kidney disease.

Secondary Efficacy Variables:

1. The change of the average sitting diastolic blood pressure (DBP) taken at trough drug plasma level (24 ± 2 hours post-previous morning's dose) at the end of treatment compared to baseline
2. The change of the average sitting systolic blood pressure (SBP) taken at trough drug plasma level (24 ± 2 hours post-previous morning's dose) at the end of treatment compared to baseline.
3. The change of the average sitting heart rate taken at trough drug plasma level (24 ± 2 hours post previous morning's dose) at end of treatment compared to baseline
4. Effect of nebivolol over time. The percent of patients who achieved goal blood pressure and change from baseline in blood pressure parameters were presented by visit.

Primary Safety Variable: The primary safety variable for the study was the incidence of adverse events (AEs) and percent of patients with at least 1 AE from baseline to end of treatment, as well as all ongoing AEs from previous nebivolol studies

Secondary Safety Variables:

1. The incidence of clinically significant ECG changes at end of treatment
2. The incidence of clinically significant laboratory changes at end of treatment
3. The incidence of clinically significant physical examination changes at end of treatment

7.2.10 Statistical Methods

Although the sponsor anticipated a sample size of approximately 500 patients would receive long-term exposure to nebivolol in NEB-323, only 85 patients chose to enroll in this study. Therefore, no formal statistical comparisons were made in this report and descriptive statistics were presented instead.

The primary population for efficacy was the intent-to-treat (ITT) population, which included all patients who took at least 1 dose of study medication. The ITT population was also used for safety analyses.

The primary efficacy variable, the percent of patients who achieved goal blood pressure, defined as < 140/90 mm Hg for patients with uncomplicated hypertension of < 130/80 mm Hg for patients with diabetes or chronic kidney disease, was the only parameter analyzed using the last-observation-carried forward (LOCF) method.

7.2.11 Results

7.2.11.1 Sites, Investigators, and Study Dates

A total of 26 investigators conducted Study NEB-323 at 26 sites from October 1, 2003 through September 22, 2004. Only 18 investigators enrolled patients in Study NEB-323.

7.2.11.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with ICH Good Clinical Practices (GCP) Guidelines (E6) and the general principles found in the Declaration of Helsinki. Since the sponsor had no efficacy claims, there were no protocol deviations.

7.2.11.3 Disposition of Subjects

A total of 85 patients were enrolled in Study NEB-323. Seventy-four (87.1%) of these 85 patients were terminated from the study by the sponsor, four patients (4.7%) experienced treatment failure, one patient (1.2%) was lost to follow-up, three patients (3.5%) withdrew consent, and three patients (3.5%) discontinued study medication due to other reasons. Patient #3021000980 was discontinued because Inclusion Criteria #3 regarding the 12-week duration from the previous clinical trial was not met. Patients #3021003987 and #3021004084 were discontinued by the investigator due to difficulty in scheduling visits.

7.2.11.4 Demographics and Baseline Characteristics

Baseline demographics and characteristics are displayed in Table 46.

Table 46. Sponsor's Analysis: Baseline Demographics (ITT Population) (NEB-323)

Parameter	Nebivolol (n=85)
Age (years)	
N	85
Mean (SD)	55.2 (11.0)
Median	55.0
Min-Max	25.0-78.0
Age Group (65)	
< 65	65 (76.5%)
≥ 65	20 (23.5%)
Age Group (75)	
< 75	83 (97.6%)
≥ 75	2 (2.4%)
Sex	
Male	46 (54.1%)

Parameter	Nebivolol (n=85)
Ethnicity	
Caucasian	64 (75.3%)
Black	19 (22.4%)
Hispanic	2 (2.4%)
Diabetes	6 (7.1%)
Poor Metabolizer	6 (7.1%)
Body Mass Index (kg/m^2)	
N	85
Mean (SD)	29.9 (4.34)
Median	29.8
Min-Max	17.8-40.8
Height (cm)	
N	85
Mean (SD)	171.9 (10.7)
Median	170.0
Min-Max	155.0-198.0
Weight (kg)	
N	85
Mean (SD)	88.7 (16.8)
Median	87.7
Min-Max	53.2-123.2
Reproduced from Sponsor, NEB-323 Clinical Study Report, Tables 1.1 and 1.2, pages 3-4 of 864)	

7.2.11.5 Prior, Adjunct, and Concomitant Medications

A total of 67 patients (67/85 or 78.8%) received at least 1 medication within 30 days prior to Visit 1. The most common prior medications (≥ 5% of patients) included acetylsalicylic acid in 18 patients (21.2%), atorvastatin in 16 patients (18.8%), multivitamins in 15 patients (17.6%), fish oil and paracetamol in 7 patients each (8.2%), and calcium and ibuprofen in 5 patients each (5.9%).

A total of 71 patients (71/85 or 83.5%) used adjunct therapy during NEB-323. The most common (≥ 5% of patients) adjunctive antihypertensive treatments included hydrochlorothiazide in 28 patients (32.9%), metoprolol succinate in 14 patients (16.5%), amlodipine in 8 patients (9.4%), carvedilol and chlorthalidone in 7 patients (8.2%) each, dyazide and olmesartan in 6 patients (7.1%) each, and atenolol, Blopress Plus (candesartan cilexetil/hydrochlorothiazide), lisinopril, ramipril, and valsartan) in 5 patients (5.9%) each. Other adjunctive antihypertensive therapy included metoprolol in 2 patients (2.4%) and bucindolol hydrochloride in 3 patients (3.5%). Four patients (4.7%) used vardenafil hydrochloride (levitra). With the exception of Patient 2741000295 who started carvedilol on Day 313, metoprolol and carvedilol were discontinued on or prior to Day 0.

A total of 74 patients (74/85 or 87.1%) received concomitant medications. The most common concomitant medications included acetylsalicylic acid in 20 patients (23.5%), atorvastatin in 16 patients (18.8%), multivitamins in 16 patients (18.8%), vicodin in 10 patients (11.8%), ibuprofen in 9 patients (10.6%), paracetamol in 9 patients (10.6%), fish oil in 9 patients (10.6%), calcium in 5 patients (5.9%), and rosuvastatin calcium in 5 patients (5.9%).

The incidence of adjunct therapy is presented in Table 47. Overall, 43.5% of patients used nebivolol alone, compared with 56.5% of patients who used nebivolol + adjunct therapy.

Table 47. Sponsor's Analysis: Incidence of adjunct Therapy (ITT Population) (NEB-323)

Treatment Period	Patients	Nebivolol Alone n (%)	Nebivolol + Adjunct n (%)
Days 0 to 14	85	54 (63.5)	31 (36.5)
Days 15 to 90	83	40 (48.2)	43 (51.8)
Days 91 to 180	82	39 (47.6)	43 (52.4)
Days 181 to 270	78	38 (48.7)	40 (51.3)
Days 271 to 360	61	34 (55.7)	27 (44.3)
Overall	85	37 (43.5)	48 (56.5)

Data Source: Table 2.6

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 11.4-05, page 41)

The incidence of adjunct therapy in person-days is presented in Table 48. Overall, nebivolol alone was used for 35.1 patient-years, and nebivolol plus adjunct therapy was used for 29.6 patient-years.

Table 48. Sponsor's Analysis: Use of Adjunct Therapy: Person-Days (ITT Population) (NEB-323)

Treatment Period	Person-Days	Nebivolol Alone n (%)	Nebivolol + Adjunct n (%)
Days 0 to 14	1260	935 (74.2)	325 (25.8)
Days 15 to 90	6286	3653 (58.1)	2633 (41.9)
Days 91 to 180	7223	3580 (49.6)	3643 (50.4)
Days 181 to 270	6209	3218 (51.8)	2991 (48.2)
Days 271 to 360	2621	1410 (53.8)	1211 (46.2)
Overall	23599	12796 (54.2)	10803 (45.8)

Data Source: Table 2.7

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 11.4-06, page 41)

7.2.11.6 Primary Efficacy Endpoint

The primary efficacy variable was the percent of patients who achieved goal blood pressure at the end of treatment. At Day 0, 30.6% of patients in both the LOCF and OC populations had already achieved blood pressure goal. At the last visit, fifty patients (58.8%) in the ITT LOCF and ITT OC populations achieved goal blood pressure (< 140/90 mm Hg for patients with uncomplicated hypertension or < 130/80 mm Hg for patients with diabetes), as shown in Table 49.

Table 49. Sponsor's Analysis: Percent of Patients Who Achieved Goal Blood Pressure (ITT Population) (NEB-323)

Scheduled Visit	ITT LOCF		ITT OC	
	N	n (%)	N	n (%)
Day 0	85	26 (30.6)	85	26 (30.6)
Day 14	85	37 (43.5)	84	37 (44.0)
Day 90	85	62 (72.9)	80	58 (72.5)
Day 180	85	57 (67.1)	81	56 (69.1)
Day 270	85	55 (64.7)	65	46 (70.8)
Day 360	85	50 (58.8)	31	21 (67.7)
Last Visit	85	50 (58.8)	85	50 (58.8)

Data Source: Tables 2.1 and 2.2

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 11.4-01, page 37)

7.2.11.7 Secondary Efficacy Analyses

7.2.11.7.1 Change of the Average Sitting Diastolic Blood Pressure Taken at Trough Drug Plasma Level (24 ± 2 Hours Post-Previous Morning's Dose) at the End of Treatment Compared to Baseline

At the last visit, the mean change from Day 8 in sitting diastolic blood pressure was -8.6 mm Hg, as shown in Table 50. The maximum mean change in sitting DBP from Day 0 was seen at Day 270 (-11.0 mm Hg). The values in Table 50 are not placebo-subtracted.

Table 50. Sponsor's Analysis: Change from Day 0 in Sitting Diastolic Blood Pressure (mm Hg) (ITT Population) (NEB-323)

Scheduled Visit		Value	Change from Day 0
Day 0	N	85	--
	Mean (SD)	92.0 (7.19)	--
	Median	92.0	--
	Min-Max	75.0 – 108.0	--
Day 14	N	84	84
	Mean (SD)	87.1 (8.24)	-4.9 (7.62)
	Median	89.0	-5.0
	Min-Max	70.0 – 106.0	-26.0 – 17.0
Day 90	N	80	80
	Mean (SD)	82.9 (6.84)	-9.3 (7.94)
	Median	83.0	-9.5
	Min-Max	66.0 – 107.0	-26.0 – 28.0
Day 180	N	81	81
	Mean (SD)	81.5 (7.94)	-10.5 (8.52)
	Median	81.0	-10.0
	Min-Max	68.0 – 109.0	-34.0 – 8.0
Day 270	N	65	65
	Mean (SD)	81.4 (7.85)	-11.0 (9.17)
	Median	81.0	-11.0
	Min-Max	64.0 – 97.0	-36.0 – 7.0
Day 360	N	31	31
	Mean (SD)	81.4 (8.41)	-8.9 (10.4)
	Median	79.0	-10.0
	Min-Max	67.0 – 102.0	-23.0 – 23.0
Last Visit	N	85	85
	Mean (SD)	83.5 (7.65)	-8.6 (8.86)
	Median	83.0	-8.0
	Min-Max	67.0 – 102.0	-28.0 – 23.0

Data Source: Table 2.3

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 11.4-02, page 38 of 79)

7.2.11.7.2 Change of the Average Sitting SBP Taken at Trough Drug Plasma Level (24 ± 2 Hours Post-Previous Morning's Dose) at the End of Treatment Compared to Baseline

The mean change from Day 0 in sitting SBP was -5.4 mm Hg at the last visit and was -9.2 mm Hg at Day 270, as seen in Table 51.

Table 51. Sponsor's Analysis: Change from Day 0 in Sitting Systolic Blood Pressure (mm Hg) (ITT Population) (NEB-323)

Scheduled Visit		Value	Change from Day 0
Day 0	N	85	--
	Mean (SD)	140.1 (13.1)	--
	Median	139.0	--
	Min-Max	113.0 – 175.0	--
Day 14	N	84	84
	Mean (SD)	137.7 (14.2)	-2.4 (13.6)
	Median	134.5	-3.0
	Min-Max	109.0 – 174.0	-33.0 – 40.0
Day 90	N	80	80
	Mean (SD)	132.2 (12.6)	-8.0 (15.5)
	Median	132.5	-8.0
	Min-Max	105.0 – 171.0	-48.0 – 58.0
Day 180	N	81	81
	Mean (SD)	131.6 (12.1)	-8.0 (14.9)
	Median	131.0	-8.0
	Min-Max	107.0 – 169.0	-51.0 – 28.0
Day 270	N	65	65
	Mean (SD)	130.6 (12.0)	-9.2 (14.9)
	Median	130.0	-9.0
	Min-Max	103.0 – 161.0	-56.0 – 37.0
Day 360	N	31	31
	Mean (SD)	134.3 (12.5)	-3.3 (14.0)
	Median	133.0	-4.0
	Min-Max	114.0 – 168.0	-29.0 – 26.0
Last Visit	N	85	85
	Mean (SD)	134.6 (12.6)	-5.4 (14.8)
	Median	133.0	-6.0
	Min-Max	104.0 – 168.0	-45.0 – 47.0

Data Source: Table 2.4

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 11.4-03, page 39 of 79)

7.2.11.7.3 Change of the Average Sitting Heart Rate Taken at Trough Drug Plasma Level (24 ± 2 Hours Post Previous Morning's Dose) at End of Treatment Compared to Baseline

As expected with a beta blocker, heart rate decreased and the change from Day 0 in sitting heart rate was -5.7 bpm at the last visit. The change from Day 0 in sitting heart rate is presented in Table 52.

Table 52. Sponsor's Analysis: Change from Day 0 in Sitting Heart Rate (bpm) (ITT Population) (NEB-323)

Scheduled Visit		Value	Change from Day 0
Day 0	N	85	--
	Mean (SD)	70.7 (9.29)	--
	Median	69.0	--
	Min-Max	51.0 – 101.0	--
Day 14	N	84	84
	Mean (SD)	67.5 (7.68)	-3.0 (7.91)
	Median	65.5	-2.0
	Min-Max	53.0 – 88.0	-22.0 – 16.0
Day 90	N	80	80
	Mean (SD)	65.3 (7.57)	-5.3 (9.16)
	Median	64.5	-3.5
	Min-Max	51.0 – 84.0	-32.0 – 15.0
Day 180	N	81	81
	Mean (SD)	64.4 (6.89)	-6.3 (8.83)
	Median	63.0	-4.0
	Min-Max	48.0 – 83.0	-26.0 – 11.0
Day 270	N	65	65
	Mean (SD)	64.0 (8.27)	-6.8 (9.02)
	Median	64.0	-5.0
	Min-Max	38.0 – 85.0	-32.0 – 18.0
Day 360	N	31	31
	Mean (SD)	65.6 (7.24)	-4.5 (8.29)
	Median	65.0	-3.0
	Min-Max	50.0 – 81.0	-27.0 – 7.0
Last Visit	N	85	85
	Mean (SD)	65.0 (7.66)	-5.7 (8.53)
	Median	64.0	-5.0
	Min-Max	49.0 – 83.0	-27.0 – 18.0

Data Source: Table 2.5

(Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 11.4-04, page 40)

7.2.11.7.4 Effect of Nebivolol Over Time (The Percent of Patients who Achieved Goal Blood Pressure and Change from Baseline in Blood Pressure Parameters by Visit)

Please see Table 49 for details. At Day 0, 30.6% of patients in both the ITT LOCF and ITT OC populations achieved goal blood pressure. At Day 14, 43.5% of patients in the ITT LOCF population and 44.0% of patients in the ITT OC population had achieved goal blood pressure. At the last visit, 58.8% of patients in both study populations had achieved blood pressure goal.

7.2.11.8 Overall Efficacy Conclusions

Due to the small sample size, the sponsor did not make any efficacy claims with NEB-323. Additionally, there is no placebo group for comparison in this study. However, the decreases in SBP and DBP seen in this study support the efficacy of nebivolol proven in the pivotal trial results submitted in the first cycle review.

7.2.11.9 Safety Evaluation

7.2.11.9.1 Extent of Exposure

The mean duration of exposure was 277.6 days, as shown in Table 53. Approximately 74% of subjects received more than 270 days of nebivolol treatment.

Table 53. Sponsor's Analysis: Duration of Nebivolol Exposure (Days) in NEB-323 (ITT)

Duration (Days)	Nebivolol
N	85
Mean (SD)	277.6 (72.7)
Median	294.0
Min-Max	1.0-348.0
1-90	3 (3.5%)
91-180	4 (4.7%)
181-270	15 (17.6%)
271-360	63 (74.1%)
Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 1.8, page 40 of 864.	

Total nebivolol exposure from the feeder study as well as NEB-323 is displayed in Table 54. Mean exposure was 537.4 days. Approximately 87% of patients received over 270 days of nebivolol treatment.

Table 54. Duration of Total Nebivolol Exposure (Days) (ITT)

Duration (Days)	Nebivolol
N	85
Mean (SD)	537.4 (139)
Median	569.0
Min-Max	175.0-730.0
1-90	1 (1.2%)
91-180	2 (2.4%)
181-270	8 (9.4%)
271-360	74 (87.1%)
Reproduced from Sponsor, NEB-323 Clinical Study Report, Table 1.8, page 40 of 864.	

7.2.11.9.2 Adverse Events

A total of 57 subjects (57/85 or 67.1%) experienced 186 adverse events.

There were no deaths or discontinuations due to an adverse event. There was one serious adverse event of left breast cancer in Subject 2652000370, a 67 year-old white female who previously completed both NEB-305 and NEB-306. No patients became pregnant during the study.

Three other neoplasms were reported in this study including one basal cell carcinoma, 1 dysplastic naevus syndrome, and 1 skin papilloma which are not likely related to nebivolol therapy.

In terms of reproductive system disorders, there was one report (1.2%) of intermenstrual bleeding and one report (1.2%) of prostatitis.

7.2.11.9.3 Primary Safety Variable

The primary safety variable was the incidence of adverse events and percent of patients with at least 1 AE from baseline of NEB-323 to end of treatment, as well as all ongoing AEs from previous nebivolol studies.

A total of 57/85 (67.1%) patients experienced adverse events. Table 55 summarizes the most frequent adverse events ($\geq$ 2.0% of patients).

Table 55. Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2.0% of Patients (ITT Population)

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)

7.2.11.9.4 Secondary Safety Variables

The secondary safety variables included

- Incidence of clinically significant ECG changes at end of treatment
- Incidence of clinically significant laboratory changes at end of treatment
- Incidence of clinically significant physical examination changes at end of treatment

According to Table 3.2.1, there was an 8.2 ms (26.6) change in QTcF from Study Day 0 to Last Visit. At Day 0, QTcFs ranged from 223.0 to 478.0. On Day 180, QTcF ranges of 362 to 511 ms were reported. On Days 360 and at the last visit, QTcF ranges were reported to be 377.0 – 524 ms and 200 to 524 ms, respectively.

Patient #3193001089 was reported to have a QTcF of 524 ms at Day 360 . His baseline QTcF was 434 msec. However, the data set stated that at Visit 10 (Day 720) on ——— , he reportedly had a QTcB of 544 ms.

From the ECG data set, Patient #3021004084 had a QTcB of 530 ms at Visit 0 on ——— (HR 80 bpm). Additionally, at Visit 7 (———), Patient #2405002965 had a QTcB of 526 ms.

However, when I reviewed the tracings, I did not find the QTcBs or QTcFs to be over 500 msec. Instead, I measured the QTcB and QTcF intervals as follows:

- Patient #3021004084: On ——→ , QTcB was 471 msec and QTcF was 446 msec.
- Patient #2405002965: On —— QTcB was 480 ms and QTcF was 480 ms.
- Patient #319001089: On —— (technically poor tracing with NSSTTW changes and u waves), QTcB was 430 msec and QTcF was 418 msec.

I do not think any of these corrected QT values are clinically significant.

Summary laboratory statistics revealed mean decreases in cholesterol and LDL but increases in triglycerides from Study Day 0 to Last Visit. The decreases in cholesterol and LDL could have been due to concomitant therapy with cholesterol lowering agents; however, the increase in triglycerides may have been related to dietary indiscretion or nonfasting results.

Table 56 describes criteria for identifying laboratory values as "clinically significantly abnormal."

Table 56. Criteria for "Clinically Significantly Abnormal" Laboratory Values (NEB-323)

CHEMISTRY	Criterion Value
Potassium	< 2.8 or > 6.5 meq/L
BUN	≥30 mg/dl
Creatinine	≥2.0 mg/dl
LDH	≥3x ULN
Uric Acid Men Women	 ≥10.5 mg/dl ≥8.5 mg/dl
Alkaline Phosphatase	≥3x ULN
AST (SGOT)	≥3x ULN
ALT (SGPT)	≥3x ULN

ULN: Upper limit of normal

HEMATOLOGY	Criterion Value
Hematocrit Men Women	 ≤37% ≤32%
Hemoglobin Men Women	 ≤11.5 g/dl ≤9.5 g/dl
WBCs	≤2,800/mm^3 or ≥16,000/mm^3
Eosinophils	≥10%
Neutrophils	≤15%
Platelet Count	≤75,000/mm^3 or ≥700,000/mm^3

URINALYSIS	Criterion Value
Protein	Increase of ≥2 units
Glucose	Increase of ≥2 units
Casts	presence

(Reproduced from Final Protocol, dated June 17, 2003, Version 2.2, page 40)

There were a few noteworthy laboratory values of clinical significance:

Liver Function Levels of Clinical Significance

- Patient #2652000370 was a 68 year old Caucasian female with a history of heartburn, gastroesophageal reflux disease, obesity, hyperlipidemia, and myxomatous cysts left fingers. She had an ALT of clinical significance on Day 260. At Day 0, the patient's ALT was 25 U/L (normal range, 0-48 U/L). ALT on Days 180, 270, and 360 was 135, 61, and 146 U/L, respectively. The AST remained within normal limits. The subject was also taking esomeprazole and fish oil. The patient discontinued when the sponsor terminated the study.

- Patient #2741000877 was a 50 year old Caucasian man who had an elevated ALT (SGPT) on Days 0, 90, 180, and 270 of 92 U/L, 70 U/L/, 55 U/L, and 66 U/L, respectively, during Study NEB-323. This patient had an elevated ALT (61 U/L; normal range: 0-48 U/L) upon entering NEB-302. Concomitant medications included Allegra, Clarinex, Celestone, and Acular for the treatment of colds, allergies, and hemorrhoids. The sponsor summarized this patient's ALT results and medications in Table 57.

Table 57. Patient #2741000877, Site 274 (NEB-323)

Study/Nebivolol Duration	Study Visit	Date	Nebivolol Dose	Adjunct Therapy	ALT (0-48 U/L)
NEB-302 (84 days)	Screen	[redacted]			61
	Baseline	10/29/2002	10 mg		77
	Study End	1/23/2003	10 mg		97
NEB-306 (182 days)	Study Start	1/23/2003	5 mg	12.5 mg HCTZ	97
	Study End	7/24/2003	5 mg	12.5 mg HCTZ	76
NEB-323 (314 days)	Day 0	[redacted]	5 mg		92
			10 mg		
			10 mg	25 mg HCTZ	
	Day 90		10 mg	25 mg HCTZ	70
	Day 180		10 mg	25 mg HCTZ	55
	Day 270		10 mg	25 mg HCTZ	66

Renal Function Levels of Clinical Significance

- Patient #1991000951 was a 66 year old Hispanic female with a history of bladder incontinence, osteoarthritis of her knees, slight atrophy of the nasal mucosa, probable old septal infarction, foot pain, fibrocystic breast disease—right cyst, varicose veins, bilateral medial pterygia, and allergy to penicillin and sulfur. She had a BUN of clinical significance on Day 270. On Days 1, 90, 180, 270, and 360 (last visit), BUN/Creatinine were 21/0.9, 22/1.1, 32/1.4, 26/1.3, and 34/1.6, respectively. Her concomitant medications included acetylsalicylic acid, multivitamins, naproxen, and rofecoxib. The patient discontinued when the sponsor terminated the study. I suspect the worsening creatinine is more a reflection of her concomitant medications (acetylsalicylic, naproxen, and rofecoxib) than of a relationship with nebivolol.

Uric Acid Levels of Clinical Significance

- Patient #1991000951 was a 66 year old Hispanic female, previously described above. She had a uric acid of clinical significance at Day 270. At Day 0, her uric acid level was 6.8 mg/dl. At Day 90, 180, and 270, uric acid increased to 7.7 mg/dl, 8.1 mg/dl, and 8.7 mg/dl.

Hematology Laboratory Parameters of Clinical Significance

- Patient #2741000295 was a 71 year old Caucasian man with ongoing chronic left esophoria, otitis externa, dizziness, constipation, and headaches. He had an eosinophil count of clinical significance at Day 270. At Day 0 and Day 90, his eosinophil count was normal at 4.1% and 5.4%, respectively (normal range, 0-7%). At Day 180 and 270 (last visit), the eosinophil count was 7.9% and 10.3%, respectively. Concomitant medications included mometasone furoate, Vicks cough syrup, Theraflu, tramadol hydrochloride, cyclobenzaprine hydrochloride, and acetaminophen/hydrocodone. The patient discontinued when the sponsor terminated the study.

- Patient #3315001481 was a 75 year old Caucasian man with a history of hyperlipidemia, colitis, osteoarthritis, erectile dysfunction, and degenerative disc disease. The patient had hematocrit and hemoglobin values of clinical significance at Day 180 (last visit) of 33.9% and 11 g/dl, respectively. At Day 0, the patient's hematocrit was 41.8% (normal range, 36-49%) and hemoglobin was 14.1 g/dl (normal range, 11.8-16.8 g/dl).

In my opinion, nebivolol was not related to any of the laboratory abnormalities listed above. Although there were other patients with laboratory values of clinical significance, in many cases the values were abnormal at baseline or I did not believe the abnormalities were related to treatment with nebivolol.

Except for Patient #2652000370, who developed left breast cancer, there were no clinically important changes in physical examination from Day 0 to Last Visit. However, testicular and breast examinations were not specifically performed.

7.2.11.10 Summary

This was an open-label study that enrolled 85 patients only, despite the initial anticipated sample size of approximately 500 patients. There was no placebo group. The study was terminated early by the sponsor. Due to poor enrollment, the sponsor did not make any efficacy claims.

There were no significant safety issues. One 57 year old woman (1/39 or 2.6%) developed the serious adverse event of breast cancer after 596 days of exposure to nebivolol (ISS number: 2652000370); however, this rate was not thought to exceed that in the general population, as the risk of developing breast cancer increases with age and one in eight women develop breast cancer during the course of their lives.

7.3 Study NEBI-0398, "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" (Signature Page Dates of 4/28/2006 and 5/1/2006) (PRACS Institute, Ltd. Clinical Summary Report Amendment No. 1, May 20, 2005) (Study Dates: Subjects 1-17: June 20-July 2, 2004; Subjects 18-26: August 1-13, 2004; Subjects 27-34: September 19-October 1, 2004)

7.3.1 Summary

A total of 34 healthy non-tobacco using adult male volunteers ≥ 18 years of age were enrolled and completed this study. With the exception of Subject 27, who was classified as an "intermediate metabolizer," the remainder of the subjects were extensive CYP2D6 metabolizers. Qualifying subjects were to have a heart rate ≥ 50 bpm in the supine position as determined by ECG measurements as well as no signs or symptoms of orthostatic hypotension, defined as greater than 20/10 mm Hg difference between supine and standing SBP/DBP readings at screening or prior to Day 1 dosing. Subjects were dosed as follows:

Table 58. Dosing Groups (NEBI-0398)

Group	Dosing Dates
Group A (Subjects 01 through 17)	June 20, 2004 and June 22-30, 2004
Group B (Subjects 18 through 26)	August 1, 2004 and August 3-11, 2004
Group C (Subjects 27 through 34)	September 19, 2004 and September 21-29, 2004

On Day -1, volunteers entered the clinic and had baseline blood pressures and heart rates recorded at predetermined time points. On Day 1, subjects received a single dose of 100 mg (1 x 100 mg tablet) of sildenafil citrate. Serial PK samples and vital signs were obtained up to 48 hours following dosing. From Days 3 to 9, a 10 mg daily dose (1 x 10 mg tablet) of nebivolol was administered. PK samples to assess the attainment of steady-state were obtained prior to dosing and 2 hours post-dosing on Days 7 and 8. On Day 9, serial PK samples and vital signs were obtained up to 24 hours following dosing. On Day 10, a single 100 mg dose of sildenafil citrate (1 x 100 mg tablet) along with a 10 mg dose of nebivolol (1 x 10 mg tablet) was administered simultaneously and serial PK samples and vital signs were obtained. On Day 11, a single 10 mg dose of nebivolol was administered to evaluate the PK and PD of nebivolol following the co-administration with Viagra.® Each subject received the following treatments:

Table 59. Treatment Regimen (NEBI-0398)

Treatment	Regimen
Treatment A	100 mg (1x100 mg) Viagra® once daily on Day 1
Treatment B	10 mg (1x10 mg) Nebivolol administered on Days 3 through 9, and Day 11
Treatment C	100 mg (1x100 mg) Viagra® co-administered with 10 mg (1x10 mg) Nebivolol once daily on Day 10.

The PK sampling schedule is displayed in Table 60.

Table 60. PK Sampling Schedule (NEBI-0398)

Day	PK Sampling Schedule
Day 1	0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours
Day 3	0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 11, and 15 hours
Day 10	0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 26, 36, 48, and 72 hours

Electrocardiograms (12-lead ECGs) were conducted at Screening and Study Exit as well as prior to dosing and 2, 4, 12, and 24 hours after dosing on Days 1, 3, 9, and 10.

The sponsor added individual plasma concentrations of d-nebivolol and l-nebivolol together for each subject to provide an estimate of the d,l-nebivolol plasma concentration.

Day 9 plasma levels were thought to represent nebivolol steady-state administration alone, and Day 10 plasma levels were thought to represent nebivolol steady state administration in conjunction with sildenafil citrate. Day 1 plasma levels represented single-dose sildenafil citrate administered alone, and Day 10 plasma levels represented single-dose sildenafil citrate in combination with steady-state nebivolol.

Pharmacokinetic results are presented in Tables 61 through 67.

Table 61. Mean (%CV) *d*-Nebivolol Pharmacokinetic Parameters in Thirty-Three Subjects Following a Single, Daily, Oral 10 mg (1x10 mg) Dose of Nebivolol Hydrochloride Tablets to Steady-State Conditions in the Presence or Absence of a Single, Oral 100 mg (1x100 mg) Dose of Sildenafil Citrate (NEBI-0398)

PROTOCOL NUMBER NEBI-0398				
Parameter	**Absence of Sildenafil Citrate (Day 9)**	**Presence of Sildenafil Citrate (Day 10)**	**Least Squares Mean Ratio (%)***	**90% Confidence Interval (%)***
AUCtau (ngxhr/mL)	4.271 (68.3)	4.671 (53.2)	114.6[#]	108.8 – 120.7[#]
CPEAK (ng/mL)	0.730 (49.2)	0.751 (45.8)	103.3[#]	93.9 – 113.6[#]
KEL (hr^{-1})	0.0843 (44.0)	0.0826 (27.3)	97.9	85.7 – 110.1
HALFLIFE (hr)	9.709 (39.8)	9.031 (27.6)	93.2	81.4 – 105.0
TPEAK (hr)	1.409 (54.3)	1.894 (37.8)	134.5	113.8 – 155.2
Cl/F (L/hr)	1544 (48.3)	1314 (44.5)	85.3	80.2 – 90.4
Vd/F (L)	19909 (52.2)	16162 (37.8)	81.8	68.4 – 95.3
CTROUGH[§] (ng/mL)	0.039 (118.3)	0.045 (126.9)	109.3[#]	101.0 – 118.2[#]
CSS (ng/mL)	0.178 (68.3)	0.195 (53.2)	114.6[#]	108.8 – 120.7[#]
FLUCT1 (%)	447.2 (32.9)	401.8 (34.4)	89.8	81.3 – 98.3
FLUCT2 (%)	1244 (24.4)	1279 (33.5)	101.8	88.2 – 115.4

* Comparing steady state *d*-nebivolol PK parameters in the presence (Day 10) vs. the absence (Day 9) of sildenafil citrate.
§ The CTROUGH listed here refers to the pre-dose concentration obtained approximately 10 minutes prior to dosing on Days 9 and 10.
# The natural log transformed data for this parameter was utilized in the calculation of these values.

Source: Section 14.1 – Attachment 1A and Section 14.6 – Attachment 2A.

(Reproduced from Sponsor, NEBI-0398 Clinical Study Report, page 11 of 129)

Table 62. Mean (%CV) *l*-Nebivolol Pharmacokinetic Parameters in Thirty-Three Subjects Following a Single, Daily, Oral 10 mg (1x10 mg) Dose of Nebivolol Hydrochloride Tablets to Steady-State Conditions in the Presence or Absence of a Single, Oral 100 mg (1x100 mg) Dose of Sildenafil Citrate (NEBI-0398)

PROTOCOL NUMBER NEBI-0398				
Parameter	**Absence of Sildenafil Citrate (Day 9)**	**Presence of Sildenafil Citrate (Day 10)**	**Least Squares Mean Ratio (%)***	**90% Confidence Interval (%)***
AUCtau (ngxhr/mL)	9.675 (35.8)	11.110 (29.0)	116.5[#]	112.7 – 120.5[#]
CPEAK (ng/mL)	1.525 (35.3)	1.595 (34.2)	104.8[#]	96.6 – 113.6[#]
KEL (hr^{-1})	0.0523 (19.1)	0.0531 (16.3)	101.5	95.0 – 107.9
HALFLIFE (hr)	13.80 (23.0)	13.37 (15.3)	96.9	89.7 – 104.1
TPEAK (hr)	1.409 (57.8)	1.652 (39.0)	117.3	97.3 – 137.3
Cl/F (L/hr)	575.8 (36.3)	488.1 (31.9)	85.0	81.2 – 88.7
Vd/F (L)	11581 (44.3)	9536 (40.7)	82.5	75.0 – 90.0
CTROUGH[§] (ng/mL)	0.140 (35.3)	0.163 (41.1)	114.4[#]	110.3 – 118.7[#]
CSS (ng/mL)	0.403 (35.8)	0.463 (29.0)	116.5[#]	112.7 – 120.5[#]
FLUCT1 (%)	354.4 (22.8)	315.7 (22.7)	88.9	81.6 – 96.3
FLUCT2 (%)	1045 (30.4)	971.2 (28.6)	92.7	83.4 – 102.0

* Comparing steady state *l*-nebivolol PK parameters in the presence (Day 10) vs. the absence (Day 9) of sildenafil citrate.
§ The CTROUGH listed here refers to the pre-dose concentration obtained approximately 10 minutes prior to dosing on Days 9 and 10.
# The natural log transformed data for this parameter was utilized in the calculation of these values.

Source: Section 14.2 – Attachment 1B and Section 14.7 – Attachment 2B.

(Reproduced from Sponsor, NEBI-0398 Clinical Study Report, page 12 of 129)

Table 63. Mean (%CV) d, *l*-Nebivolol Pharmacokinetic Parameters in Thirty-Three Subjects Following a Single, Daily, Oral 10 mg (1x10 mg) Dose of Nebivolol Hydrochloride Tablets to Steady-State Conditions in the Presence or Absence of a Single, Oral 100 mg (1x100 mg) Dose of Sildenafil Citrate (NEBI-0398)

PROTOCOL NUMBER NEBI-0398				
Parameter	Absence of Sildenafil Citrate (Day 9)	Presence of Sildenafil Citrate (Day 10)	Least Squares Mean Ratio (%)*	90% Confidence Interval (%)*
AUCtau (ngxhr/mL)	13.95 (44.9)	15.78 (35.2)	115.8[#]	111.4 – 120.3[#]
CPEAK (ng/mL)	2.250 (39.3)	2.337 (36.9)	104.4[#]	95.9 – 113.6[#]
KEL (hr^{-1})	0.0628 (23.4)	0.0658 (20.5)	104.8	98.4 – 111.3
HALFLIFE (hr)	11.73 (28.2)	10.97 (20.7)	93.6	85.4 – 101.7
TPEAK (hr)	1.424 (56.3)	1.788 (41.4)	125.3	105.4 – 145.2
Cl/F (L/hr)	829.7 (39.3)	705.7 (35.1)	85.3	81.3 – 89.2
Vd/F (L)	13683 (40.1)	10816 (29.2)	79.3	71.0 – 87.7
CTROUGH[‡] (ng/mL)	0.179 (50.9)	0.208 (58.1)	113.9[#]	107.8 – 120.5[#]
CSS (ng/mL)	0.581 (44.9)	0.658 (35.2)	115.8[#]	111.4 – 120.3[#]
FLUCT1 (%)	376.0 (25.1)	336.4 (25.1)	89.4	81.8 – 96.9
FLUCT2 (%)	1332 (38.0)	1246 (36.9)	93.3	81.6 – 105.1

* Comparing steady state *d,l*-nebivolol PK parameters in the presence (Day 10) vs. the absence (Day 9) of sildenafil citrate.
‡ The CTROUGH listed here refers to the pre-dose concentration obtained approximately 10 minutes prior to dosing on Days 9 and 10.
# The natural log transformed data for this parameter was utilized in the calculation of these values.

Source: Section 14.3 – Attachment 1C and Section 14.8 – Attachment 2C.

(Reproduced from Sponsor, NEBI-0398 Clinical Study Report, page 13 of 129)

Table 64. Mean (%CV) Sildenafil Pharmacokinetic Parameters in Thirty-Four Subjects Following a Single, Oral 100 mg (1x100 mg) Dose of Sildenafil Citrate in the Presence or Absence of a Steady-State Concentration of 10 mg Oral Nebivolol Hydrochloride (1x10 mg) Tablets

PROTOCOL NUMBER NEBI-0398				
Parameter	Absence of Steady-State Nebivolol (Day 1)	Presence of Steady-State Nebivolol (Day 10)	Least Squares Mean Ratio (%)*	90% Confidence Interval (%)*
AUCL (ngxhr/mL)	1279 (36.5)	1010 (37.0)	79.2[#]	74.2 – 84.4[#]
AUCI (ngxhr/mL)	1312 (35.9)	1044 (36.6)	79.7[#]	74.9 – 84.9[#]
CPEAK (ng/mL)	382.8 (40.5)	289.9 (37.0)	77.0[#]	70.6 – 83.9[#]
KEL (hr^{-1})	0.2524 (26.5)	0.2393 (29.7)	94.7	87.8 – 101.5
HALFLIFE (hr)	2.982 (33.8)	3.169 (32.4)	106.1	97.3 – 114.9
TPEAK (hr)	1.471 (39.2)	1.532 (35.6)	104.3	89.4 – 119.1
Cl/F (L/hr)	90.44 (49.7)	112.6 (46.2)	126.0	116.9 – 135.1
Vd/F (L)	365.4 (39.2)	471.2 (31.2)	129.4	118.7 – 140.0

* Comparing sildenafil PK parameters in the presence (Day 10) vs. the absence (Day 1) of steady-state levels of nebivolol hydrochloride.
# The natural log transformed data for this parameter was utilized in the calculation of these values.

Source: Section 14.4 – Attachment 1D and Section 14.9 – Attachment 2D

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Table 65. Mean (%CV) N-Desmethylsildenafil Pharmacokinetic Parameters in Thirty-Four Subjects* Following a Single, Oral 100 mg (1x100 mg) Dose of Sildenafil Citrate in the Presence or Absence of a Steady-State Concentration of 10 mg Oral Nebivolol Hydrochloride (1x10 mg) Tablets

PROTOCOL NUMBER NEBI-0398				
Parameter	Absence of Steady-State Nebivolol (Day 1)	Presence of Steady-State Nebivolol (Day 10)	Least Squares Mean Ratio (%)*	90% Confidence Interval (%)*
AUCL (ngxhr/mL)	495.9 (40.4)	417.8 (39.5)	84.4[#]	80.7 – 88.2[#]
AUCI (ngxhr/mL)	523.7 (39.7)	439.3 (38.4)	84.1[#]	80.5 – 87.9[#]
CPEAK (ng/mL)	147.6 (39.8)	122.6 (38.0)	83.5[#]	76.0 – 91.7[#]
KEL (hr^{-1})	0.1415 (46.9)	0.1423 (40.6)	100.6	86.3 – 115.0
HALFLIFE (hr)	5.883 (40.5)	5.776 (44.0)	98.2	82.8 – 113.7
TPEAK (hr)	1.426 (40.6)	1.429 (36.4)	100.2	86.6 – 113.7
Cl/F' (L/hr) [§]	219.3 (37.3)	260.9 (39.0)	119.5	113.9 – 125.1
Vd/ F' (L) [¶]	1677 (33.3)	2003 (42.3)	119.3	101.7 – 136.9

* Comparing N-desmethylsildenafil PK parameters in the presence (Day 10) vs. the absence (Day 1) of steady-state levels of nebivolol hydrochloride.
[#] The natural log transformed data for this parameter was utilized in the calculation of these values.
[§] Cl/F' refers to the apparent clearance and was calculated as Cl/F' = Dose/AUCI, where the Dose was equal to the administered sildenafil dose and F' refers to the fraction of the bioavailable dose of sildenafil systemically converted to N-desmethylsildenafil.
[¶] Vd/F'refers to the apparent volume of distribution and was calculated as Vd/F' = (Cl/F')/KEL, where F' refers to the fraction of the bioavailable dose of sildenafil systemically converted to N-desmethlysildenafil.

Source: Section 14.5 – Attachment 1E and Section 14.10 – Attachment 2E.

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The pharmacodynamic results are presented in Table 66 and Table 67. There was a statistically significant ($p < 0.01$) depression in systolic and diastolic blood pressure when sildenafil citrate was coadministered with steady-state levels of nebivolol. 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. For steady state nebivolol on Day 9, the time to peak decrease in SBP was 8.41 hours and for peak decrease in DBP was 12.38 hours. Additionally, steady-state nebivolol resulted in decreases in average and peak heart rate of -11.64 and -19.03 bpm, respectively. For steady state nebivolol on Day 9, the time to peak HRT change was 7.27 hours.

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. For single dose sildenafil citrate on Day 1, the time to peak decrease in SBP was 6.68 hours and the time to peak decrease in DBP was 6.97 hours. Single-dose sildenafil also increased average heart rate by 3 bpm and decreased peak heart rate by 7 bpm. For single-dose sildenafil, the time to peak heart rate change was 7.32 hours.

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. Coadministration of sildenafil with steady-state nebivolol still resulted in decreases in average and peak heart rate of -9.31 and -18.68 bpm, respectively, although these decreases were less than those seen with steady-state nebivolol alone. For combination dosing of nebivolol at steady state and sildenafil citrate on Day 10, the time to peak HRT change was 6.32 hours.

Table 66. 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 (1x10 mg) Tablets, or Both

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, NEBI-0398 Clinical Study Report, page 16 of 129)

Table 67. Mean (%CV) Depression of Nebivolol Pharmacodynamic Parameters (after pre-dose profile adjustment) in Thirty-Four Subjects following a Single, Oral 10 mg (1x10 mg) Tablet of Nebivolol Hydrochloride or Steady-State Concentration of 10 mg Oral Nebivolol Hydrochloride (1x10 mg daily for 7 days) Tablets

PROTOCOL NUMBER NEBI-0398				
Parameter	Single-Dose Nebivolol (Day 3)	Steady-State Nebivolol (Day 9)	Least Squares Mean Ratio (%)	90% Confidence Interval (%)
HRTavg* (beats/minute)	-6.85 (60.46)	-11.64 (44.09)	170.1	151 – 189
HRTpeak* (beats/minute)	-14.17 (37.83)	-19.03 (30.03)	134.3	124 – 145
THRTpeak (hr)	-10.50 (80.14)	-7.27 (95.69)	69.2	48 – 91
AUCHRT* (bpm*hr)	-164.3 (60.46)	-279.5 (44.09)	170.1	151 – 189
DBPavg* (mmHg)	-6.14 (57.78)	-8.97 (45.06)	146.1	133 – 159
DBPpeak* (mmHg)	-12.68 (35.16)	-15.86 (31.84)	125.1	116 – 134
TDBPpeak (hr)	-10.50 (76.95)	-12.38 (76.69)	117.9	94 – 142
AUCDBP* (mmHg*hr)	-147.4 (57.78)	-215.3 (45.06)	146.1	133 – 159
SBPavg* (mmHg)	-8.79 (49.16)	-12.92 (36.67)	146.9	135 – 159
SBPpeak* (mmHg)	-17.38 (32.92)	-22.70 (35.10)	130.6	122 – 139
TSBPpeak (hr)	-9.47 (85.83)	-8.41 (85.68)	88.8	67 – 110
AUCSBP* (mmHg*hr)	-211.0 (49.16)	-310.0 (36.67)	146.9	135 – 159

* A negative sign (-) in front of a value represents a decrease 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, NEBI-0398 Clinical Study Report, page 1 of 129)

Baseline demographic information is displayed in Table 68. All volunteers were men. There were 28 Caucasians (82.4%), 2 Blacks (5.9%), 3 Hispanics (8.8%), and 1 Asian (2.9%).

Table 68. Baseline Demographics (NEBI-0398)

	Age (yr)	Weight (lb)	Height (in)
N	34	34	34
Mean (SD)	29.1 (11.50)	172.1 (23.34)	69.7 (2.86)
Median	24.0	176.0	70.0
Range	18.0 to 59.0	131.0 to 218.0	63.0 to 77.0
Reproduced from Sponsor, Clinical Safety Report (NEBI-0398), Table 1.1, page 1 of 23) Data Listings 1 and 10			

7.3.2 Adverse Events

Twelve out of the thirty-four subjects who were entered into and completed this study experienced 17 adverse events. There were no deaths or serious adverse events. The adverse events are summarized in Table 69. Overall, there were no clinically significant changes in laboratory values or ECGs during the course of this study.

Table 69. Adverse Events (NEBI-0398)

Adverse Event	Nebivolol Single-dose (1x100 mg) (n=34) n, (%)	Viagra (1x100 mg) (n=34) n, (%)	Nebivolol steady-state (1x10 mg) (n=34) n, (%)	Nebivolol steady state (1x10 mg) + Viagra (1x100 mg) (n=34) n, (%)	Reviewer Comments
Any AE	2 (5.9%)	6 (17.6%)	5 (14.7%)	4 (11.8%)	
Back pain	1 (2.9%)	1 (2.9%)	1 (2.9%)		
Sore Upper Back			1 (2.9%)		
Light-headed		1 (2.9%)		1 (2.9%)	Subject 8 in Viagra (1x100 mg): From 12:10 to 12:14 on ———, this subject experienced lightheadedness. Resting blood pressure was 101/67 and pulse was 61 bpm at 12:11. Average Baseline BP was approximately 108/70 with a heart rate of 62. ECGs at 07:11:19, 09:22:21, 11:22:19, and 19:32 were unremarkable. Subject 30 in combination group: From 09:10 to 09:12 on ——— this subject experienced lightheadedness. At 09:07, resting blood pressure was 96/61 with a heart rate of 68 bpm. Average baseline blood pressure was 102/64, with a heart rate of 68 bpm. ECGs at 7:22, 9:51, 11:42, and 19:57 were unremarkable.
Shortness of Breath		1 (2.9%)			
Headache			2 (5.9%)	1 (2.9%)	
Disoriented			1 (2.9%)		
Fatigue				1 (2.9%)	
Feeling Hot				1 (2.9%)	Subject 19 in combination group: From 16:00 on 8/10/2004 to 10:00 on 8/11/2004, the subject felt hot and complained of a headache. There were no significant changes in resting vital signs during that time. The subject had some nonspecific ST-T wave changes on ECG during these symptoms.
Oral Pain	1 (2.9%)				
Tickle in Throat		1 (2.9%)			
Increased urination		1 (2.9%)			
Pain on urination		1 (2.9%)			
Analysis by Karen A. Hicks, M.D.					

7.3.3 Conclusions

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. 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 extremely hazardous and possibly deadly.
6. 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.
7. There were no clinically significant changes in laboratory results or ECG parameters during this study.

7.4 Study NEBI-0438, Pharmacokinetic Report, "Single-Dose Fasting In Vivo Bioequivalence Study of Nebivolol Tablets (5 mg; Mylan) to Nebivolol Tablets (5 mg; Menarini) in Healthy Volunteers" (Date of Study: Clinical Period 1: December 3, 2005-December 7, 2005; Clinical Period 2: December 17, 2005-December 21, 2005) (Analytical Phase: January 13, 2006-February 17, 2006 (*d*-nebivolol and *l*-nebivolol); February 16, 2006-March 2, 2006 (conjugated plus non-conjugated nebivolol) (Signature Dates: April 27, 2006 and May 1, 2006)

7.4.1 Objective

The objective of this study was to investigate the bioequivalence of Mylan's nebivolol 5 mg tablets to Menarini's Nebivolol 5 mg tablets following a single, oral 10 mg (2 x 5 mg) dose administered under fasting conditions. The single-dose pharmacokinetics were assessed by statistical comparisons of various pharmacokinetic parameters derived from the plasma concentration-time curves of *d*-nebivolol, *l*-nebivolol, *d,l*-nebivolol, and nebivolol glucuronides.

7.4.2 Study Plan

A total of 48 healthy nonsmoking male and female healthy volunteers between the ages of 18 and 55 were enrolled in and completed the study. Subjects were assigned to the following treatments:

Treatment A = Mylan Nebivolol Tablets, 5 mg
10 mg (2 x 5 mg), Fasting Administration
Lot # R1N2235; Mylan Repackaging Lot # R1N3880, Exp. N/A
Assay Potency: [redacted]

Treatment B = Menarini Nebivolol Tablets 5 mg
10 mg (2 x 5 mg), Fasting Administration
Lot #53123; Mylan Repackaging Lot #R1N3710, Exp. 08/08
Manufacturing Date: 08/05
Assay Potency: [redacted]

Following a 10-hour fast, each subject received either a single, oral 10 mg (2x5 mg) dose according to the following randomization scheme.

Sequence	Subjects
AB	3, 4, 6, 7, 8, 12, 15, 16, 18, 20, 21, 23, 26, 27, 29, 32, 34, 36, 38, 39, 41, 44, 45, 46
BA	1, 2, 5, 9, 10, 11, 13, 14, 17, 19, 22, 24, 25, 28, 30, 31, 33, 35, 37, 40, 42, 43, 47, 48

Period 1 was dosed on December 4, 2005, and Period 2 was dosed on December 18, 2005. There were 14 days between periods. Subjects were released 24 hours after dosing. Blood samples for PK monitoring were collected at the following times after dosing: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10, 12, 16, 24, 48, and 72 hours.

Samples were assayed for *d*-and *l*-nebivolol in the Bioanalytical Department of Mylan Pharmaceuticals Inc. from January 13, 2006 to February 17, 2006 using high performance liquid chromatography with tandem mass spectrometric detection and a limit of quantification of 0.2 ng/ml for Standard Curve Range II (for poor metabolizers) and 0.04 ng/ml for Standard Curve III (extensive metabolizers).. Samples were assayed for conjugated plus non-conjugated nebivolol in the same Department from February 16, 2006 to March 2, 2006 using a similar method with a limit of quantification of 0.3 ng/ml.

Safety assessments included vital signs, 12-lead ECGs, laboratory evaluation (serum chemistry, hematology, and urinalysis), and adverse event reporting. Seated resting blood pressure and pulse rate as well as temperature and respiration rate were measured within 60 minutes prior to dose administration. Blood pressure and pulse rate were repeated at 2, 4, 8, 12, 24, and 48 hours after drug administration.

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software and an alpha level of 0.05.

7.4.3 Results

A total of 48 healthy male and female volunteers were enrolled in and completed the study. Baseline demographics are displayed in Table 70. All subjects were Caucasian, with the exception of 1 native American male and 2 Black males.

Table 70. Baseline Demographics (NEBI-0438)

	All Subjects (N=48)	Males (N=28)	Females (N=20)
Age	26.5 (±10.7)	25.6 (±9.4)	27.8 (±12.4)
Weight (lbs)	163.5 (±26.6)	178.0 (±20.8)	143.2 (±19.6)
Height (in.)	67.7 (±4.1)	70.0 (±3.5)	64.5 (±2.4)
BMI	25.0 (±2.9)	25.6 (±2.5)	24.3 (±3.4)

(Reproduced from PRACS Clinical Study Report (March 31, 2005), Table 11.1, page 26 of 510)

Subject disposition is described in Table 71.

Table 71. Summary of Subject Disposition (NEBI-0438)

	Sequence		Total
	AB	BA	
Subjects Randomized	24	24	48
Subjects Successfully Completed	24	24	48
Subjects Who Withdrew Consent	0	0	0
Subjects Dropped by Investigator	0	0	0

A: Nebivolol Tablets 5 mg (Lot No.: R1N3880)
B: Nebivolol Tablets 5 mg (Lot No.: R1N3710)

(Reproduced from PRACS Clinical Study Report (March 31, 2005), Table 10.2, page 25 of 510)

During the conduct of this study, there were 71 protocol deviations in 32 subjects. Seventy of the protocol deviations involved deviations in blood sampling times and one deviation involved the administration of an over-the-counter medication (monistat) for treatment of the adverse event of vulvovaginal mycotic infection.

Pharmacokinetic results are summarized in Tables 72 through 75.

Table 72. Sponsor's Analysis: Mean (%CV) *d*-Nebivolol Pharmacokinetic Parameters in Forty-Eight Healthy Adult Subjects Following a Single Oral 10 mg (2 x 5 mg) Dose of Nebivolol Tablets Under Fasting Conditions (NEBI-0438)

PROTOCOL NUMBER NEBI-0438				
Parameter	**Treatment A Nebivolol Tablets (Mylan)**	**Treatment B Nebivolol Tablets (Menarini)**	**LSMEANS* Ratio (B/A)**	**90% Confidence Interval****
AUCL (ng x hr/mL)	12.43 (242.4)	12.55 (246.5)	1.02	97% - 107%
AUCI (ng x hr/mL)	13.92 (240.0)	13.96 (244.2)	1.02	97% - 107%
CPEAK (ng/mL)	1.347 (89.75)	1.330 (98.01)	1.05	98% - 113%
KEL (hr^{-1})	0.0837 (35.91)	0.0785 (32.48)		
HALF (hr)	9.432 (39.66)	9.787 (35.10)		
TPEAK (hr)	1.563 (70.90)	1.546 (72.79)		

*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$
**Used Natural Log Transformed Parameter

Source: Section 14.1 Attachment 1A and Section 14.5 Attachment 2A

(Reproduced from Sponsor, Clinical Study Report, Table 4.1, page 9 of 89)

Table 73. Sponsor's Analysis: Mean (%CV) *l*-Nebivolol Pharmacokinetic Parameters in Forty-Eight Healthy Adult Subjects Following a Single Oral 10 mg (2 x 5 mg) Dose of Nebivolol Tablets Under Fasting Conditions (NEBI-0438)

PROTOCOL NUMBER NEBI-0438				
Parameter	**Treatment A Nebivolol Tablets (Mylan)**	**Treatment B Nebivolol Tablets (Menarini)**	**LSMEANS* Ratio (B/A)**	**90% Confidence Interval****
AUCL (ng x hr/mL)	23.76 (243.2)	24.24 (240.1)	0.97	93% - 101%
AUCI (ng x hr/mL)	31.51 (281.2)	32.15 (275.1)	0.97	93% - 101%
CPEAK (ng/mL)	2.377 (57.76)	2.367 (60.79)	1.01	94% - 109%
KEL (hr^{-1})	0.0463 (25.81)	0.0434 (19.28)		
HALF (hr)	16.47 (41.83)	17.06 (37.59)		
TPEAK (hr)	1.396 (79.31)	1.345 (82.73)		

*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$
**Used Natural Log Transformed Parameter

Source: Section 14.2 Attachment 1B and Section 14.6 Attachment 2B

(Reproduced from Sponsor, Clinical Study Report, Table 4.2, page 10 of 89)

Table 74. Sponsor's Analysis: Mean (%CV) *d, l*-Nebivolol Pharmacokinetic Parameters in Forty-Eight Healthy Adult Subjects Following a Single Oral 10 mg (2 x 5 mg) Dose of Nebivolol Tablets Under Fasting Conditions

PROTOCOL NUMBER NEBI-0438				
Parameter	**Treatment A Nebivolol Tablets (Mylan)**	**Treatment B Nebivolol Tablets (Menarini)**	**LSMEANS* Ratio (B/A)**	**90% Confidence Interval****
AUCL (ng x hr/mL)	36.65 (239.1)	37.16 (239.1)	0.99	94% - 103%
AUCI (ng x hr/mL)	43.81 (266.5)	44.62 (263.5)	0.97	93% - 101%
CPEAK (ng/mL)	3.684 (68.63)	3.665 (73.45)	1.02	95% - 110%
KEL (hr^{-1})	0.0624 (27.04)	0.0559 (22.83)		
HALF (hr)	12.26 (43.16)	13.41 (38.56)		
TPEAK (hr)	1.443 (72.67)	1.372 (82.57)		

*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$
**Used Natural Log Transformed Parameter

Source: Section 14.3 Attachment 1C and Section 14.7 Attachment 2C

(Reproduced from Sponsor, Clinical Study Report, Table 4.3, page 11 of 89)

Table 75. Sponsor's Analysis: Mean (% CV) Nebivolol Glucuronides Pharmacokinetic Parameters in Forty-Eight Healthy Adult Subjects Following a Single Oral 10 mg (2 x 5 mg) Dose of Nebivolol Tablets Under Fasting Conditions

PROTOCOL NUMBER NEBI-0438				
Parameter	**Treatment A Nebivolol Tablets (Mylan)**	**Treatment B Nebivolol Tablets (Menarini)**	**LSMEANS* Ratio (B/A)**	**90% Confidence Interval****
AUCL (ng x hr/mL)	378.9 (90.51)	390.3 (96.84)	0.99	95% - 104%
AUCI (ng x hr/mL)	393.2 (93.02)	405.2 (100.8)	1.00	95% - 104%
CPEAK (ng/mL)	59.11 (42.90)	59.36 (43.24)	1.01	96% - 106%
KEL (hr^{-1})	0.1160 (38.60)	0.1135 (34.65)		
HALF (hr)	7.077 (53.36)	7.213 (55.37)		
TPEAK (hr)	2.115 (32.81)	2.055 (32.96)		

*Ratio (A/B) = $e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$
**Used Natural Log Transformed Parameter

Source: Section 14.4 Attachment 1D and Section 14.8 Attachment 2D

(Reproduced from Sponsor, Clinical Study Report, Table 4.4, page 12 of 89)

7.4.4 Safety

7.4.4.1 Adverse Events

There were no deaths, serious adverse events, or discontinuations due to adverse events. Thirteen subjects (13/48 or 27.1%) experienced a total of 15 adverse events which are summarized in Table 76.

Table 76. Listing of Adverse Events by Body System (NEBI-0438)

Subject No.	Adverse Event*	Onset Date	Onset Time	Resolution Date	Resolution Time	Serious	Intensity	Relationship	Outcome	Counter Measure	Study Period	Treatment
01	Headache	13 Dec 05	1600	14 Dec 05	0700	N	Mild	Not related	Resolved	None	I	B
01	Vomiting	13 Dec 05	2100	13 Dec 05	2101	N	Mild	Not related	Resolved	None	I	B
06	Abdominal pain upper	05 Dec 05	1900	05 Dec 05	2300	N	Mild	Remotely	Resolved	None	I	A
08	Headache	18 Dec 05	1445	18 Dec 05	1730	N	Mild	Probably	Resolved	None	II	B
11	Dizziness	04 Dec 05	0934	04 Dec 05	0945	N	Mild	Not related	Resolved	Other	I	B
17	Vulvovaginal mycotic infection	12 Dec 05	0700	20 Dec 05	1000	N	Moderate	Not related	Resolved	Therapy required	I	B
18	Dizziness	18 Dec 05	1100	18 Dec 05	1230	N	Mild	Probably	Resolved	None	II	B
26	Dizziness	18 Dec 05	1150	19 Dec 05	0900	N	Mild	Probably	Resolved	None	II	B
39	Headache	18 Dec 05	1213	18 Dec 05	1900	N	Mild	Probably	Resolved	None	II	B
40	Headache	18 Dec 05	1100	18 Dec 05	1400	N	Mild	Probably	Resolved	None	II	A
42	Headache	18 Dec 05	0715	19 Dec 05	0645	N	Mild	Probably	Resolved	None	I	B
43	Cough	10 Dec 05	1800	19 Dec 05	1000	N	Mild	Not related	Resolved	None	I	B
43	Headache	18 Dec 05	1915	19 Dec 05	0630	N	Mild	Probably	Resolved	None	II	A
44	Headache	18 Dec 05	1545	19 Dec 05	0700	N	Mild	Probably	Resolved	None	II	B
48	Dizziness	18 Dec 05	0912	18 Dec 05	0917	N	Mild	Not related	Resolved	Other	II	A

*MedDRA Version 8.1
Treatment: A: Nebivolol Tablets 5 mg (Lot No.: R1N3880)
B: Nebivolol Tablets 5 mg (Lot No.: R1N3710)

(Reproduced from PRACS Clinical Study Report (March 31, 2005), Table 12.4, page 30 of 510)

7.4.4.2 Vital Signs

A single 10 mg dose of nebivolol HCl resulted in an 11 to 12 mm Hg decrease in SBP that was maximal between 8 and 12 hours post dosing and an 11 to 13 mm Hg decrease in DBP that was maximal 12 hours after dosing. The changes were similar between treatment groups.

A single 10 mg dose of nebivolol HCl also resulted in a 12 to 13 bpm decrease in pulse rate which was maximal 4 hours following dosing. The changes in heart rate were similar between treatment groups.

7.4.4.3 Laboratory Evaluation

Although a number of healthy volunteers had abnormal laboratory results, none of them were thought to be clinically important or drug-related.

7.4.4.4 Electrocardiograms

Subject 2 in Treatment Group A experienced a QTc of 457 msec 8 hours post-dosing. Subject 2's baseline QTc was 427 msec. In Treatment Group B, Subjects 2, 18, and 44 experienced QTcs of 441, 447, and 445, respectively. Baseline QTc for Subjects 2, 18, and 44 were 429 ms, 421 ms, and 408 ms, respectively. None of these changes in QTc were thought to be clinically important, and no subject experienced torsade de pointes.

7.4.5 Summary

For the natural log transformed parameters LNAUCL, LNAUCI, and LNCPEAK for *d*-nebivolol, *l*-nebivolol, *d,l*-nebivolol, and nebivolol glucuronides, the 90% confidence intervals fall within 80-125% for the test to reference ratio; therefore, 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.

There were no important safety issues.

7.5 Additional Studies

The sponsor submitted 4 studies evaluating nitric oxide and peroxynitrite release from human endothelial cells following incubation with nebivolol, d,l-nebivolol and various metabolites. The studies are summarized in the following table.

Study	Title	Summary
MPNEB-0508 (November 2005)	Comparative Acute Effects of Nebivolol, *d,l*-Nebivolol and Four Glucuronide Metabolites on Endothelial-Dependent Nitric Oxide Release from Normotensive Black American and White Donors	Following acute treatment with 1.0 μM of nebivolol, *d*-nebivolol, *l*-nebivolol or one of four stereoselective glucuronide metabolites, investigators compared nitric oxide (NO) release in human umbilical vein endothelial cells from Black American and White donors. Acute nitric oxide release was highest in White and Black donors who had received *l*-nebivolol, followed by the racemate, glucuronide metabolites, and *d*-nebivolol. White donors consistently had higher measurements of nitric oxide than Black donors. The duration of this response was not evaluated.
MPNEB-0509 (November 2005)	Comparative Acute Effects of Nebivolol, *d*- and *l*-nebivolol, and Six Stereospecific Hydroxy Metabolites on Endothelial-Dependent Nitric Oxide Release from Normotensive Black American and White Donors	Following acute treatment with 1.0 μM of nebivolol, *d*-nebivolol, *l*-nebivolol or one of six stereoselective hydroxy metabolites, investigators compared nitric oxide (NO) release in human umbilical vein endothelial cells from Black American and White donors. Acute NO release was highest with 4'(R)-Hydroxy-7-fluoro-6-hydroxy-*l*-nebivolol followed by 4'(R)-Hydroxy-5-fluoro-6-hydroxy-*l*-nebivolol, 4 (S)-Hydroxy-7'fluoro-6'-hydroxy-*l*-nebivolol, and *l*-nebivolol. *d*-Nebivolol released the lowest amount of nitric oxide. HUVEC from White donors consistently released more nitric oxide than HUVEC from Black donors. The duration of this response was not evaluated.
MPNEB-0511 (December 2005)	Effects of Nebivolol on Nitric Oxide Release in Human Endothelium from Mexican Americans and Whites: Comparison to Atenolol	Endothelial NO release was studied following acute stimulation with various nebivolol concentrations (0, 1.0 μM, and 5.0 μM) or with atenolol (1.0 μM or 5.0 μM) from White and Mexican American HUVEC donors with or without preincubation for 24 hours with nebivolol or atenolol at 1.0 μM or 5.0 μM.. In both White and Mexican American donors, nitric oxide release was dose-dependent; however, nitric oxide release was greater in White donors. After preincubation with nebivolol, nitric oxide release was substantially increased in both White and Mexican American donors. However, following acute stimulation with atenolol after pre-incubation with atenolol, nitric oxide release in both White and Mexican American donors was minimally increased. The duration of this response was not evaluated.
MPNEB-0513 (January 10, 2006)	Comparative Chronic Effects of Nebivolol, *d,l* nebivolol and Six Stereospecific Hydroxy Metabolites on Endothelial-Dependent Nitric oxide Release from Normotensive Black American and White Donors	Investigators evaluated the chronic (pretreatment) effects (1.0 μM x 6 hours) of nebivolol racemate, its separate enantiomers, and six stereoselective hydroxyl metabolites of nebivolol on endothelial dependent NO release in human umbilical vein endothelial cells isolated from normotensive White and Black American donors with matched risk factor profiles. The release of NO was stimulated using a calcium ionophore, a receptor independent stimulus of maximal NO biosynthesis. NO release following preincubation with the 6 hydroxy metabolites was superior to *d*-nebivolol in both races.

7.6 Line-by-Line Labeling Review

Completed and circulating to review team via email.

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

/s/

Karen Hicks
10/19/2007 09:06:00 PM
MEDICAL OFFICER

3/7/06

NDA 21,742

CLINICAL CONSULTATION

FROM: Hylton V. Joffe, 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: Endocrinologic Effects of Nebivolol (NDA 21,742)

DATE CONSULT RECEIVED: February 23, 2006

DATE CONSULT COMPLETED: March 6, 2006

MATERIAL RECEIVED FOR REVIEW

The consultation package included the two-volume briefing document and the electronic submission. An independent search of the human English literature in PubMed using terms such as "nebivolol", "nebivolol AND cortisol", "nebivolol AND aldosterone", "nebivolol AND ACTH" was also performed.

ADMINISTRATIVE BACKGROUND

The Cardio-Renal Division seeks advice regarding potential adverse endocrinologic effects of nebivolol, a new β1 receptor antagonist that has been developed for the management of hypertension.

REQUESTED ACTION OF DMEP

Cardio-Renal has asked the following questions:

1. For the clinical studies (NEB-CAN-09, NEB-BEL-52, and NEB-BEL-55, as well as referenced studies by Pesant and Rakhmatullaeva):
    a. Do the above studies rule out a possible endocrine effect of nebivolol? If not, why not?
    b. As some of these studies were performed 10 years ago, do you agree with the methods used in these studies to obtain hormone measurements? Could more accurate results of hormone measurements be made with the technology we have today?

c. In these studies, was the duration of nebivolol therapy adequate for detecting any possible endocrine changes? If not, what would be the recommended duration of therapy prior to hormonal testing?
d. Do we agree with the Sponsor's interpretation of the study results regarding the hormone effects?
e. If none of the above studies are sufficient to rule out a possible endocrine effect of nebivolol in humans, what are our recommendations for further testing or clinical trials in humans to better determine this?
f. In the Rakhmatullaeva study, nebivolol decreased luteinizing hormone (LH) and follicle stimulating hormone (FSH) and increased testosterone. Rakhmatullaeva attributes this finding to the antihypertensive effect of nebivolol. Do we agree or do these changes reflect nebivolol's endocrine effect in humans?

2. In the 13 week study in mice and rats (Appendix 7), there appears to be a significant dose-related decrease in the percentage of normal sperm and sperm count in the mouse. There was also a significant dose-dependent increase in adrenal and prostate weight and a significant decrease in the weight of the seminal vesicles that did not completely normalize during recovery. Dose-dependent Leydig cell hyperplasia was noted. LH increased significantly and estradiol decreased by Week 13 in the nebivolol 40 mg/kg/day mouse model. Several estradiol measurements were not obtained because they were apparently below the limit of quantification of the assay. Is the assay adequate for appropriately interpreting the changes in estradiol seen in this study? Do these study results rule out a possible endocrine effect of nebivolol?

3. Do we agree that nebivolol exerts no unique or clinically relevant adverse effects on adrenal function at therapeutic dosing regimens?

4. Do we agree that the pre-clinical reproductive tract observations are not clinically relevant?

5. Do we agree that the reproductive/developmental toxicity profile of nebivolol is consistent with the beta-antagonist class?

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 β1-receptor antagonist that has been developed for the treatment of r ——————— : 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 30-April-2004 to gain approval for marketing nebivolol in the United States. On 31-May-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. These concerns were also expressed in the 11-July-2005 consultation letter from the Division of Reproductive and Urologic Drug Products.

On 10-February-2006, the Sponsor submitted a response to these concerns in a briefing document in preparation for the granted Type B End of Review Meeting scheduled for 17-March-2006. The responses pertinent to this consult are summarized below:

Leydig Cell Tumors

In a 2-year carcinogenicity study, nebivolol 40 mg/kg/day induced Leydig cell tumors in male mice. The Sponsor claims this is not relevant to humans because:

1. A complete battery of gene-toxicity testing with nebivolol was negative
2. In a 13-week rodent study, increased LH levels were associated with nebivolol-induced Leydig cell hyperplasia. The Sponsor claims that no LH increases have been observed with nebivolol in controlled clinical studies.
3. Mice tumors occur at doses 424-fold higher than the 10 mg daily maximum recommended human dose.
4. No increase in endocrinologic or Leydig cell tumors have been observed in nebivolol's pooled adverse event database and pharmacovigilance database.

Adrenal Gland Dysfunction

The Sponsor claims that nebivolol exerts no unique, clinically relevant effects on adrenal function at the doses intended for clinical use (up to 10 mg once daily) because:

1. Nebivolol-induced increases in adrenal weight and adrenal cortical hypertrophy occur in rats but not mice or dogs. Other beta-blockers also cause increased adrenal weight and hypertrophy (e.g. atenolol, carvedilol) and adrenal hyperplasia (e.g. atenolol) in rats.
2. Nebivolol blunts the corticosterone response to adrenocorticotropic hormone (ACTH) in rats but had no effects on the hypothalamus-pituitary-adrenal (HPA) axis in humans (tested using insulin-induced hypoglycemia and ACTH-stimulated glucocorticoid and mineralocorticoid production).
3. Nebivolol did not affect basal, non-stimulated cortisol levels in three clinical studies (NEB-CAN-09, NEB-BEL-55, and the Pesant study). Another study (BEN-BEL-52) showed a statistically significant decrease in basal, non-stimulated cortisol levels and urinary cortisol levels in subjects given nebivolol for 7 days, but the Sponsor questions the relevance of this study because the maximal cortisol response to acute ACTH stimulation was unchanged and the 4-

week NEB-CAN-09 and 12-week Pesant studies did not show an effect on basal, non-stimulated cortisol levels.

4. Nebivolol did not have consistent effects on basal aldosterone levels across clinical studies. In NEB-BEL-55, mean basal, non-stimulated aldosterone levels were significantly lower in the nebivolol than the placebo groups after 7 days of treatment (no changes in 24-hour urinary aldosterone levels). However, in the NEB-BEL-52 and NEB-CAN-09 studies, non-stimulated aldosterone levels were unaffected by nebivolol. Finally, in the Pesant study, mean aldosterone levels increased in the nebivolol group and decreased in the atenolol group.
5. Nebivolol does not have consistent effects on renin concentrations. There was no decrease in basal, non-stimulated renin levels in NEB-BEL-52 or in plasma renin activity (PRA) in the Pesant study. The Sponsor attributed the statistically significant decrease in basal, non-stimulated plasma renin levels in NEB-CAN-09 to the known class effect of beta-blockers on the renin-angiotensin-aldosterone system.
6. The Sponsor did not identify any trends suggestive of symptoms of adrenal dysfunction in the phase 3 studies and the pharmacovigilance database.

Reproductive Tract Abnormalities

The Sponsor initially attributed the non-clinical reproductive tract effects of nebivolol to stress or chronic sympathetic stimulation. After this hypothesis was rejected by the FDA, the Sponsor consulted a panel of scientific advisors. This panel concluded that the reproductive tract changes in rats were consistent with reduced feed intake and reduced body weight (the nebivolol-induced changes in the reproductive tract only occurred when ≥20% body weight loss occurred).

The Sponsor claims there were no associations between nebivolol and disruption of the hypothalamic-pituitary-gonadal axis in clinical studies because:

1. Nebivolol did not affect basal, non-stimulated LH, FSH, estradiol, progesterone, or testosterone in men and women in the 4-week NEB-CAN-09 study.
2. Nebivolol did not affect basal, non-stimulated LH, prolactin, or testosterone levels in men and women in the 7-day NEB-BEL-52 study.
3. Nebivolol did not affect basal, non-stimulated FSH, LH, estradiol, prolactin, or testosterone levels in men in the 7-day NEB-BEL-55 study.
4. In NEB-BEL-52, there was a normal response of ACTH, cortisol, prolactin, and growth hormone to insulin-induced hypoglycemia, confirming overall integrity of the HPA.
5. In Rakhmatullaeva's study (12-weeks of 5 or 10 mg daily nebivolol), baseline LH and FSH were significantly higher and mean baseline testosterone levels were significantly lower in a group of hypertensive men compared with normotensive controls. At the end of treatment, mean values for these hormones in patients with hypertension approached the baseline values of the control group.

6. The Sponsor found no evidence from the clinical database to suggest an increase in incidence of adverse events in the reproductive system and breast disorders system organ class.

Developmental and Reproductive Toxicity

The Sponsor claims that nebivolol has no unique effects on the development and reproductive systems and that the observed findings in non-clinical models are consistent with those reported for the class of beta-blockers.

CLINICAL STUDIES

This review will focus on the 5 clinical studies upon which the Sponsor is drawing conclusions regarding potential endocrinologic effects of nebivolol in humans.

NEB-CAN-09 Evaluation of the Efficacy and Safety of Racemic and d-Nebivolol (Hormonal Measurements as Safety Labs after 4 Weeks of Treatment)

Sponsor: Janssen Research Foundation
Investigator: Yves Lacourciere (Quebec, Canada)
Study Period: March-October 1993

Objectives: To compare the antihypertensive efficacy, safety, and tolerability of racemic nebivolol (nebivolol) to that of the d-isomer (d-nebivolol) in patients with mild to moderate essential hypertension. The goal of this study was to assess whether the presence or absence of the l-isomer of nebivolol results in therapeutic or safety differences between the compounds.

Study Design: Single center, double-blind, randomized, cross-over study in 30 subjects comparing nebivolol 5 mg/day and d-nebivolol 2.5 mg/day. Following a 2-4 week single-blind placebo run-in period, subjects were randomly assigned to one of the two treatment sequences, each of which lasted 4 weeks and were separated by a 2-4 week single-blind placebo washout period. Study Visits occurred every 2 weeks (total visits = 9)

Reviewer's comments: The 5 mg/day dose of nebivolol used in this study is one-half the maximum recommended dose (10 mg/day) in humans for which the Sponsor is seeking approval.

Primary Endpoint: Sitting diastolic clinic blood pressure 23-25 hours after last dose

Secondary Endpoints Included:

Blood pressure responder = decrease of ≥10 mmHg in diastolic blood pressure between baseline (end of run-in phase) and last visit of each treatment period OR patients whose diastolic blood pressure normalized (<90 mmHg) at the end of each treatment period.

1. Response rate based on clinic blood pressure measurements
2. Response rate based on ambulatory blood pressure measurements
3. Normalization rate based on clinic blood pressure measurements
4. Normalization rate based on ambulatory blood pressure measurements
5. Sitting systolic clinic blood pressure 23-25 hours after last dose
6. Mean 24-hour ambulatory blood pressure

Protocol Amendments: The study was amended to include hormonal evaluation (see below) to assess the endocrinologic effects of nebivolol and d-nebivolol in humans.

Inclusion Criteria Included:

1. Men or women 18-70 years old
2. Mild to moderate hypertension (mean of 3 diastolic blood pressures ≥95 and ≤114 mmHg after 2 weeks of the placebo run-in period or at the end of the 4-week placebo run-in period) off anti-hypertensive drugs for at least 4 weeks
3. Confirmed mild to moderate hypertension using ambulatory blood pressure monitoring (mean daytime diastolic blood pressure ≥90 mmHg).

Exclusion Criteria Included:

1. Secondary or malignant hypertension
2. Asthma or chronic obstructive pulmonary disease
3. Resting bradycardia <60 bpm, cardiac arrhythmias
4. Patients with diabetes who were using insulin
5. Myocardial infarction or stroke within 6 months prior to enrollment
6. Renal artery disease, heart failure, or hemodynamic valvular disease
7. Women of child-bearing potential not using contraceptives or women who were pregnant or nursing
8. Significant renal disease (e.g. creatinine >2.2 mg/dL) or liver disease (AST and/or ALT >2.5x upper limit of normal)
9. Concomitant medications affecting blood pressure, e.g. tricyclic antidepressants, non-steroidal anti-inflammatory drugs, glucocorticoids
10. ≥50% of ideal body weight

Assessments Included:

1. Sitting and standing blood pressures 23-25 hours post-dose.

2. Ambulatory blood pressure monitoring at the end of the run-in and at the end of the two treatment periods.

3. Laboratory safety tests – in addition to standard testing, the following hormonal assays were obtained at the end of the run-in phase and at the end of each treatment period:
    a. ACTH
    b. Aldosterone
    c. Cortisol
    d. Testosterone
    e. LH
    f. FSH
    g. Plasma renin concentration
    h. Progesterone
    i. Estradiol

Reviewer's comments: The study protocol does not describe the methodological details regarding determination of these hormone levels. Issues that may impact interpretation of the test results include:

1. **It is not clear if the ACTH sample was appropriately collected on ice (if ACTH is not collected on ice, proteolysis may reduce test-tube concentrations).**
2. **Levels of cortisol, ACTH, and testosterone are highest in the morning hours. It is not clear whether these hormone levels were drawn consistently in the mornings for all subjects.**
3. **Unstimulated cortisol and ACTH levels were obtained in this study. These usually provide limited data regarding the integrity of the HPA axis. For example, ACTH is released in bursts and levels can vary from minute to minute.**
4. **It is not clear which testosterone assay was used in this study and whether the assay is reliable for measuring the low testosterone levels typically found in women.**
5. **It is not clear how the renin and aldosterone levels were obtained. These levels are dependent on body position and dietary sodium intake. In addition, unstimulated renin and aldosterone levels provide limited data with regard to the integrity of the renin-angiotensin-aldosterone system.**
6. **There was no assessment of free estradiol and free testosterone levels, either directly or via measurement of sex hormone-binding globulin (SHBG).**
7. **Estradiol and progesterone levels vary widely in premenopausal women depending on the timing of the draw with the menstrual cycle – this study did not take this into account.**

Statistics: Sample size calculations were based on mean 24 hour ambulatory blood pressure readings to detect a treatment difference of ≥5 mmHg between nebivolol and d-nebivolol.

Results

Disposition: A total of 32 patients entered the trial. Of these, 2 failed the run-in screen. Therefore, 30 patients were randomized to the treatment periods. All 30 completed the study.

Patient Demographics (n=30)	
Age, yr	47.8±8.7
Body Mass Index, kg/m^2	27.2±2.6
Men, n (%)	20 (67)
Cigarette smoker, n (%)	3 (10)
No alcohol consumption, n (%)	16 (53)
No caffeine intake, n (%)	14 (47)
Previously treated for hypertension, n (%)	26 (87)
Currently receiving anti-hypertensive therapy, n (%)	3 (10)

Plus-minus values = mean ± SD

Primary and Secondary Outcomes: Selected outcomes are displayed in the Table below. Both treatments lowered clinic systolic and diastolic blood pressures by a similar amount. There were also no between treatment differences when the data were analyzed by responder rate or by ambulatory blood pressure measurements.

Clinic Blood Pressures – Effectiveness				
	Baseline		Termination	
	Nebivolol	d-Nebivolol	Nebivolol	d-Nebivolol
Sitting				
Diastolic	99.2±7.4	98.8±6.0	91.4±7.6*	90.1±8.5*
Systolic	146.2±14.6	147.5±14.6	136.6±15.8*	134.3±14.3*
Standing				
Diastolic	98.8±7.0	99.3±6.5	92.2±8.7*	90.9±8.2*
Systolic	144.0±16.8	145.4±14.2	135.7±17.9*	134.2±15.0*

*$p<0.05$ compared to baseline

Safety

Adverse Events: There were a total of 22 adverse events reported by 14 subjects. All reported adverse events are summarized in the Table below.

Adverse Events				
	Baseline		Termination	
	Placebo run-in	Placebo washout	Nebivolol (n=30)	d-Nebivolol (n=30)
Headache	1	3	0	2
Fatigue	1	1	2	1
Dyspnea	1	0	0	2
Palpitations	0	2	1	0
Urinary frequency	0	0	2	0
Dizziness	0	0	0	1
Leg edema	1	0	0	0
Nausea	0	0	0	1
TOTALS	**4**	**6**	**5**	**7**

Hormone Results:

Summary results are presented in the Tables that follow. After these Tables, I present the results for individual subjects.

Testosterone (nmol/L) by Sex and Treatment							
		Raw Score			Difference from Baseline		
Sex	**Treatment**	Mean	N	Std	Mean	N	Std
Male	Nebivolol	17.67	20	4.45	-0.26	20	3.35
	d-Nebivolol	15.95	20	4.81	-1.98	20	2.49
	Baseline	17.93	20	5.46			
Female	Nebivolol	0.66	10	0.25	0.00	10	0.34
	d-Nebivolol	0.68	10	0.40	0.02	10	0.18
	Baseline	0.66	10	0.46			

Reference Range: Men: 9.4-37 nmol/L
Women: 0.87-3.12 nmol/L

No statistical tests were applied to the testosterone data.

Reviewer's comments: As expected, testosterone levels were very low in the women. There is essentially no change in testosterone levels in men and women when nebivolol 5 mg daily is given for 4 weeks. However, some testosterone assays are unreliable in the female range. It is not clear whether the assay used in the study was adequate to detect the low testosterone levels in women.

Progesterone (nmol/L) by Sex and Treatment							
		Raw Score			Difference from Baseline		
Sex	Treatment	Mean	N	Std	Mean	N	Std
Male	Nebivolol	1.1	20	0.72	-0.4	20	1.89
	d-Nebivolol	0.9	20	1.27	-0.6	20	2.05
	Baseline	1.5	20	1.65			
Female	Nebivolol	0.8	10	0.69	-5.0	10	7.04
	d-Nebivolol	4.4	10	9.96	-1.4	10	7.46
	Baseline	5.8	10	7.30			

Reference Range: Men: 0.4-1.0 nmol/L
Women: 0.06-114 nmol/L

Progesterone: In men, nebivolol and d-nebivolol caused reductions (no statistical tests applied) in progesterone levels compared to baseline (1.5±1.7 to 1.1±0.7 nmol/L for nebivolol and 1.5±1.7 to 0.9±1.3 nmol/L for d-nebivolol). In women, nebivolol and d-nebivolol caused reductions (no statistical tests applied) in progesterone levels compared to baseline (5.8±7.3 to 0.8±0.7 nmol/L for nebivolol and 5.8±7.3 to 4.4±10.0 nmol/L for d-nebivolol).

Reviewer's comments: Statistical tests should have been applied to all the hormone results, including progesterone and testosterone. The study report does not provide reasons as to why this was not done. There are very large standard deviations in the progesterone results (often larger than the mean results) in both the men and women. In women, the progesterone results are uninterpretable because the measurements were not obtained with regard to the menstrual cycle (in healthy women, progesterone values can range from 0.06-114 nmol/L depending on the timing of the measurement).

Other Hormonal Measurements					
Hormone	Baseline	Termination		Change	
	(n=30)	Nebivolol (n=30)	d-Nebivolol (n=30)	Nebivolol (n=30)	d-Nebivolol (n=30)
ACTH (pmol/L)	7.6±4.4	7.6±2.8	7.8±3.2	-0.00±3.9	0.2±3.1
Aldosterone (pmol/L)	276.6±103.7	274.7±108.5	278.3±125.2	-1.9±77.1	1.7±124.3
Cortisol (nmol/L)	378.4±144.0	426.6±103.3	399.7±132.3	48.3±136.9	21.3±149.5
LH (IU/L)	9.7±13.0	7.9±9.2	7.3±9.0	-1.8±9.1	-2.3±10.6
FSH (IU/L)	10.7±13.5	8.0±8.1	9.9±13.4	-2.6±8.0	-0.8±8.5
Estradiol (pmol/L)	214.5±276.1	226.7±196.3	190.0±150.5	12.2±267.6	-24.6±219.0
Renin (ng/L)	8.2±9.7	5.0±3.8*	4.6±3.9*	-3.1±7.4	-3.5±7.7

*$p<0.05$ compared to baseline

No between treatment differences were observed.

Renin: Nebivolol and d-nebivolol caused significant reductions ($p<0.05$) in plasma renin concentrations compared to baseline (8.2±9.7 to 5.0±3.8 ng/L for nebivolol and 8.2±9.7 to 4.6±3.9 ng/L for d-nebivolol).

Other: There were no statistically significant changes from baseline with nebivolol or d-nebivolol for ACTH, aldosterone, cortisol, LH, FSH and estradiol.

Reviewer's comments: There are very large standard deviations (often larger than the mean results) for some of these hormones, especially aldosterone, cortisol, LH, FSH, and estradiol. This is probably related to the non-normality of hormone data and the methodology of collection -- e.g. dietary sodium intake around the time of the aldosterone and renin collection, time of day when cortisol was drawn, time of menstrual cycle when estradiol was drawn, etc. This large degree of variability in the data makes it difficult to detect statistical differences even if true differences exist. The renin results may be real or may be confounded by dietary sodium intake and body position. Reduced renin levels have been reported with other beta-blockers, as described in the briefing package.

Hormonal changes from baseline for each subject and each assay are displayed in the Tables below.

LABTEST=Testosterone LABUNIT=NMOL/L SEX=Male

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
201	46	23.5	18.6	-4.9	22	-1.5
202	50	14.9	15.8	0.9	15.4	0.5
203	34	14.8	12.1	-2.7	12.4	-2.4
204	55	21	23	2	20.4	-0.6
205	49	13.5	11.7	-1.8	12.5	-1
206	35	13	16.8	3.8	20.6	7.6
208	37	17.2	14.9	-2.3	19.5	2.3
209	57	12.2	11	-1.2	14.1	1.9
211	52	12.8	10.7	-2.1	13.4	0.6
212	52	21	15.5	-5.5	17.3	-3.7
213	45	15.2	11.1	-4.1	14.1	-1.1
214	40	21.4	22.1	0.7	19.9	-1.5
216	45	17.1	14.9	-2.2	18.1	1
217	35	12.9	12.4	-0.5	13.7	0.8
219	61	20.2	16.5	-3.7	15	-5.2
220	60	35.6	29.5	-6.1	30	-5.6
223	56	22.7	19.9	-2.8	19.1	-3.6
224	46	17.6	16.5	-1.1	24.4	6.8
227	48	16.7	14.2	-2.5	15.8	-0.9
228	32	15.3	11.8	-3.5	15.7	0.4

Reviewer's comments: All baseline and post-nebivolol testosterone levels in men were within the normal range, although a decrease as great as 5.6 nmol/L occurred in one of the subjects.

LABTEST=Testosterone LABUNIT=NMOL/L SEX=Female

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
207	44	0.6	0.5	-0.1	0.5	-0.1
210	60	1.4	1.1	-0.3	0.9	-0.5
215	46	0.8	1	0.2	1	0.2
218	51	0.2	0.4	0.2	0.6	0.4
221	51	0.6	0.8	0.2	0.6	0
222	66	0.3	0.3	0	0.2	-0.1
225	38	1.5	1.5	0	0.9	-0.6
226	53	0.3	0.4	0.1	0.4	0.1
229	42	0.3	0.4	0.1	0.7	0.4
230	49	0.6	0.4	-0.2	0.8	0.2

Reviewer's comments: For unclear reasons, more than one-half of the women had baseline and post-nebivolol testosterone levels below the lower limit of the reference range for women (<0.87 nmol/L).

LABTEST=Progesterone LABUNIT=NMOL/L SEX=Male

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
201	46	0.2	5.8	5.6	1.2	1
202	50	0.4	0.9	0.5	3.9	3.5
203	34	0.2	0.2	0	0.7	0.5
204	55	0.4	0.1	-0.3	0.91	0.51
205	49	1	0.1	-0.9	1.04	0.04
206	35	1	0.6	-0.4	1.2	0.2
208	37	0.2	0.7	0.5	1.2	1
209	57	0.2	0.1	-0.1	1	0.8
211	52	0.2	0.29	0.09	1.4	1.2
212	52	3.9	0.2	-3.7	0.8	-3.1
213	45	4.5	1.1	-3.4	0.9	-3.6
214	40	0.2	0.5	0.3	1.15	0.95
216	45	2.9	0.9	-2	0.9	-2
217	35	2.7	2.1	-0.6	0.9	-1.8
219	61	3.9	1.4	-2.5	0.9	-3
220	60	5.1	0.9	-4.2	1.5	-3.6
223	56	0.8	1.2	0.4	0.2	-0.6
224	46	0.95	0.2	-0.75	1.2	0.25
227	48	0.6	0.1	-0.5	1.2	0.6
228	32	1.6	0.6	-1	0.5	-1.1

Red = above the reference range; Blue= below the reference range

LABTEST=Progesterone LABUNIT=NMOL/L SEX=Female

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
207	44	19.5	32.4	12.9	0.58	-18.92
210	60	0.2	0.32	0.12	0.1	-0.1
215	46	13.5	0.8	-12.7	1.3	-12.2
218	51	1.9	0.2	-1.7	0.7	-1.2
221	51	0.78	0.2	-0.58	1.8	1.02
222	66	3.5	1.3	-2.2	0.2	-3.3
225	38	15.2	2.3	-12.9	2	-13.2
226	53	1.5	1.2	-0.3	0.1	-1.4
229	42	1.1	5.3	4.2	0.6	-0.5
230	49	0.6	0.1	-0.5	0.4	-0.2

ACTH (pmol/L) - all values remained within the reference range

Patient	Age	Baseline	d-Nebivolol	d-Nebivolol - change from baseline	Nebivolol	Nebivolol - change from baseline
201	46	6.8	8	1.2	3.9	-2.9
203	34	4.8	4.8	0	5.1	0.3
206	35	13.3	6.3	-7	8.8	-4.5
208	37	4.5	6.5	2	5.3	0.8
210	60	4.1	5.4	1.3	4.9	0.8
211	52	4.1	5.5	1.4	8.9	4.8
213	45	6.9	5.7	-1.2	6.7	-0.2
215	46	6.5	4.8	-1.7	6.9	0.4
217	35	8.1	5.4	-2.7	9.5	1.4
219	61	6	4.3	-1.7	9.7	3.7
222	66	3.8	3.9	0.1	10.6	6.8
223	56	3.1	2.9	-0.2	6.7	3.6
227	48	11.1	10.4	-0.7	14.2	3.1
228	32	7.6	10.3	2.7	11.6	4
230	49	8.2	9.5	1.3	5.5	-2.7
202	50	10.4	7.8	-2.6	8.4	-2
204	55	16.5	10.5	-6	5.9	-10.6
205	49	10.1	15	4.9	12.2	2.1
207	44	2.5	6.4	3.9	4.1	1.6
209	57	20.9	14.5	-6.4	13.3	-7.6
212	52	7.3	9.4	2.1	7.3	0
214	40	6	8.7	2.7	6.3	0.3
216	45	4.5	6.3	1.8	4.1	-0.4
218	51	4.9	8.4	3.5	5.3	0.4
220	60	11.5	12.8	1.3	8.5	-3
221	51	7.3	12.2	4.9	6.3	-1
224	46	15.3	11.3	-4	7.7	-7.6
225	38	3.7	5.5	1.8	7.8	4.1
226	53	2.9	4.1	1.2	3.7	0.8
229	42	4.9	6.1	1.2	8.1	3.2

Aldosterone (pmol/L)

Patient	Age	Baseline	Outside Reference Range?	d-Nebivolol	Outside Reference Range?	d-Nebivolol - change from baseline	Nebivolol	Outside Reference Range?	Nebivolol - change from baseline
201	46	440		470	High	30	392		-48
203	34	373		297		-76	294		-79
206	35	559	High	284		-275	635	High	76
208	37	255		374		119	206		-49
210	60	189		228		39	219		30
211	52	308		380		72	391		83
213	45	197		289		92	178		-19
215	46	268		130		-138	175		-93
217	35	274		275		1	324		50
219	61	174		117		-57	183		9
222	66	317		268		-49	295		-22
223	56	275		172		-103	277		2
227	48	357		322		-35	367		10
228	32	234		344		110	264		30
230	49	215		189		-26	256		41
202	50	150		257		107	256		106
204	55	228		250		22	201		-27
205	49	335		239		-96	356		21
207	44	394		325		-69	144		-250
209	57	295		142		-153	253		-42
212	52	202		89		-113	191		-11
214	40	270		531	High	261	402		132
216	45	304		341		37	302		-2
218	51	89		142		53	179		90
220	60	243		185		-58	154		-89
221	51	366		237		-129	330		-36
224	46	395		398		3	323		-72
225	38	354		593	High	239	382		28
226	53	123		397		274	240		117
229	42	115		84		-31	72	Low	-43

<u>Reviewer's comments</u>: The aldosterone values are difficult to interpret without knowing each subject's dietary sodium intake and whether there was consistent body positioning prior to and at the time of the collection. Even then, isolated random aldosterone levels are of limited utility unless there are large changes.

Cortisol (nmol/L)

Patient	Age	Baseline	Outside Reference Range?	d-Nebivolol	Outside Reference Range?	d-Nebivolol - change from baseline	Nebivolol	Outside Reference Range?	Nebivolol - change from baseline
201	46	287		416		129	340		53
203	34	487		284		-203	428		-59
206	35	819	High	405		-414	591		-228
208	37	191	Low	394		203	338		147
210	60	583		768	High	185	362		-221
211	52	364		265		-99	581		217
213	45	306		222		-84	225		-81
215	46	164	Low	309		145	319		155
217	35	179	Low	287		108	362		183
219	61	429		370		-59	498		69
222	66	428		645		217	484		56
223	56	396		414		18	379		-17
227	48	444		388		-56	487		43
228	32	338		476		138	490		152
230	49	254		311		57	651		397
202	50	368		277		-91	337		-31
204	55	437		426		-11	394		-43
205	49	395		312		-83	565		170
207	44	192	Low	448		256	353		161
209	57	338		107	Low	-231	301		-37
212	52	452		507		55	566		114
214	40	396		478		82	366		-30
216	45	372		501		129	356		-16
218	51	246		253		7	463		217
220	60	299		414		115	320		21
221	51	648		574		-74	542		-106
224	46	577		473		-104	456		-121
225	38	333		494		161	384		51
226	53	320		443		123	493		173
229	42	309		329		20	368		59

Reviewer's comments: The random cortisol levels (1) are difficult to interpret without knowing what time of day the bloods were drawn, and (2) offer limited data with regard to the integrity of the HPA axis.

LABTEST=Luteinizing Hormone LABUNIT=IU/L SEX=Male

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
201	46	3	3	0	2	-1
202	50	2	3	1	2	0
203	34	4	3	-1	4	0
204	55	3	5	2	4	1
205	49	8	7	-1	8	0
206	35	6	4	-2	3	-3
208	37	4	3	-1	4	0
209	57	3	3	0	3	0
211	52	1	2	1	2	1
212	52	4	4	0	5	1
213	45	3	2	-1	3	0
214	40	3	2	-1	3	0
216	45	2	2	0	3	1
217	35	2	4	2	3	1
219	61	4	5	1	4	0
220	60	5	5	0	6	1
223	56	2	3	1	2	0
224	46	4	2	-2	3	-1
227	48	2	2	0	2	0
228	32	4	3	-1	2	-2

LABTEST=Luteinizing Hormone LABUNIT=IU/L SEX=Female

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
207	44	6	6	0	5	-1
210	60	16	15	-1	16	0
215	46	4	4	0	3	-1
218	51	26	26	0	22	-4
221	51	37	37	0	32	-5
222	66	24	29	5	25	1
225	38	6	4	-2	2	-4
226	53	24	20	-4	33	9
229	42	59	2	-57	11	-48
230	49	19	10	-9	20	1

Red = Above the reference range

Reviewer's comments: Presumably, many of the women with LH levels above the reference range were post-menopausal as evidenced by their age.

LABTEST=FSH LABUNIT=IU/L SEX=Male

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
201	46	4	3	-1	3	-1
202	50	3	4	1	4	1
203	34	5	4	-1	4	-1
204	55	4	5	1	3	-1
205	49	22	24	2	25	3
206	35	5	4	-1	6	1
208	37	6	5	-1	8	2
209	57	2	4	2	2	0
211	52	3	3	0	3	0
212	52	7	10	3	7	0
213	45	5	4	-1	5	0
214	40	1	2	1	1	0
216	45	1	1	0	1	0
217	35	5	3	-2	4	-1
219	61	4	4	0	4	0
220	60	3	2	-1	2	-1
223	56	2	2	0	3	1
224	46	3	3	0	3	0
227	48	7	7	0	7	0
228	32	4	4	0	2	-2

LABTEST=FSH LABUNIT=IU/L SEX=Female

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
207	44	2	5	3	3	1
210	60	10	9	-1	13	3
215	46	3	3	0	2	-1
218	51	34	36	2	27	-7
221	51	51	55	4	24	-27
222	66	28	18	-10	21	-7
225	38	3	2	-1	3	0
226	53	28	44	16	21	-7
229	42	45	4	-41	11	-34
230	49	20	23	3	19	-1

Red = Above the reference range

<u>Reviewer's comments</u>: Presumably, many of the women with FSH levels above the reference range were post-menopausal as evidenced by their age.

LABTEST=Estradiol LABUNIT=PMOL/L SEX=Male

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
201	46	154.1	71.9	-82.2	158.8	4.7
202	50	64	116.7	52.7	116.6	52.6
203	34	46.8	46.8	0	95.5	48.7
204	55	193.2	174.9	-18.3	114.8	-78.4
205	49	138.7	115.9	-22.8	173.1	34.4
206	35	84.3	41.1	-43.2	49.9	-34.4
208	37	111.9	92.5	-19.4	138.4	26.5
209	57	37.2	49.6	12.4	18.3	-18.9
211	52	172.8	148.9	-23.9	177.1	4.3
212	52	81.6	109.3	27.7	116.6	35
213	45	116.3	151.4	35.1	122.4	6.1
214	40	117.2	136.8	19.6	171.9	54.7
216	45	71.3	132.8	61.5	133.4	62.1
217	35	92	109.3	17.3	139.2	47.2
219	61	17.2	84.2	67	65.2	48
220	60	207.5	126.6	-80.9	233.8	26.3
223	56	111.2	154.9	43.7	94	-17.2
224	46	235	337.5	102.5	268.3	33.3
227	48	109.9	132.3	22.4	89.6	-20.3
228	32	126.8	121.5	-5.3	105.3	-21.5

LABTEST=Estradiol LABUNIT=PMOL/L SEX=Female

PATIENT	AGE	BASELINE	d-Nebivolol	d-Nebivolol - Change from baseline	Nebivolol	Nebivolol - Change from baseline
207	44	1225.1	279.2	-945.9	671.5	-553.6
210	60	466.8	539.5	72.7	278.3	-188.5
215	46	425.8	377	-48.8	409.8	-16
218	51	24.9	69.6	44.7	940.7	915.8
221	51	66.9	52.6	-14.3	293.9	227
222	66	261.5	346.2	84.7	495.5	234
225	38	1053.3	451.9	-601.4	204	-849.3
226	53	376.4	587.9	211.5	422.4	46
229	42	46.1	149.7	103.6	232.6	186.5
230	49	200.5	391	190.5	270.7	70.2

<u>Reviewer's comments</u>: The estradiol levels in women are uninterpretable because they were not drawn with regard to timing of the menstrual cycle. The estradiol levels in men were lower than those in women; the men's estradiol levels should have been analyzed separately.

Sponsor's Conclusions: ACTH, cortisol, aldosterone, and basal non-stimulated sex hormone concentrations (estradiol, testosterone, progesterone) and gonadotropins (LH, FSH) levels were unaffected by 4 weeks of treatment with nebivolol 5 mg daily. The Sponsor attributes the high intersubject variability in LH, FSH, progesterone, and estradiol levels in women to the inclusion of both cycling and post-menopausal women and the fact the hormone measurements were not performed at a specific time within

the menstrual cycle. There was a significant decrease from baseline to endpoint in mean basal levels of plasma renin.

Reviewer's comments: **Although the treatment duration was reasonable, there are several methodological issues delineated in my comments above that limit the conclusions that can be drawn from this study. In brief, (1) hormonal assays were not described, (2) there was no regard to timing when levels were drawn (e.g. estradiol and progesterone levels not drawn at appropriate times during the menstrual cycle), (3) unprovoked hormonal measurements offer limited assessment of the integrity of several hormonal systems (e.g. cortisol, aldosterone), (4) only 5 mg of nebivolol was evaluated in this study – perhaps higher doses have more profound effects, and (5) compliance was reportedly assessed in this study but results were not provided to make an assessment as to whether subjects had adequate exposure to nebivolol.**

I conclude from the current study that 4 weeks of nebivolol 5 mg daily may have no effect on testosterone levels (assuming the correct assay was used and levels were drawn around the same time of day) and on single timepoint ACTH levels (very crude assessment of the HPA axis and assumes the ACTH was collected on ice and drawn at the same time of day). Based on the methodology, we cannot reliably exclude an effect of nebivolol on most of the hormones measured in this study. The Sponsor may be able to provide details about the methods used for these hormonal assays that may alleviate some of my concerns with regard to interpretation of the results.

NEB-BEL-55 Effects of Nebivolol on the Endocrine System in Male Volunteers (ACTH Stimulation Test)

Sponsor: Janssen Research Foundation
Investigator: J. De Cree (Merksem, Belgium)
Study Period: March-May 1995

Objectives: To explore the effects of nebivolol 5 mg daily for 7 days on the pituitary-adrenal-testicular system.

Study Design: Single center, randomized, double-blind, placebo-controlled, cross-over study in 8 healthy men. Subjects were randomly assigned to one of the two treatment sequences (nebivolol vs. placebo), each of which lasted 8 days and were separated by a washout period of at least 8 days.

Reviewer's comments: **The 5 mg/day dose of nebivolol used in this study is one-half the maximum recommended dose (10 mg/day) in humans for which the Sponsor is seeking approval. Seven days is too short an exposure to obtain meaningful ACTH stimulation results (see comments below). The sample size of 8 subjects is small.**

Primary Endpoint: Results of the ACTH stimulation test

Secondary Endpoints: Basal hormone levels, 24-hour urine collection results

Inclusion Criteria Included:

1. Healthy Caucasian men 18-60 years old
2. Smokes <10 cigarettes, 2 cigars, 2 pipes per day
3. Weight within 20% of ideal body weight

Reviewer's comments: No women were included in this study. There is no explicit mention about hypertension as an exclusion/exclusion criterion but in the demographic table (see below) there were some subjects with elevated blood pressures.

Exclusion Criteria Included:

1. Alcohol or drug abuse
2. Concomitant medications

Assessments Included:

1. On the last day of each double-blind phase, venous samples were collected 2-hours after drug intake for:
    a. Cortisol
    b. Aldosterone
    c. 17-hydroxy-progesterone
    d. Progesterone
    e. ACTH
    f. Estradiol
    g. Testosterone
    h. Sex hormone binding globulin (SHBG)
    i. Prolactin
    j. LH
    k. FSH
    l. Androstenedione
    m. Dihydroepiandrosterone (DHEA)

Reviewer's comments: No Day 1 testing was performed. Data obtained at the end of the placebo treatment periods were used for baseline measures. In the group that received nebivolol first, the data obtained at the end of the placebo period will represent baseline data only if there is no carry-over effect of nebivolol. Testing for carry-over effect was explicitly performed in this study.

Several issues raised in the prior trial apply to this trial, too. For example, the time of day of the hormone blood collection is not explicitly stated. Aldosterone levels are affected by body position and dietary sodium intake.

2. ACTH 0.25 mg injected intravenously after collection of basal hormones, then venous samples were collected 30 minutes, 1 hour and 2 hours later for:
    a. Cortisol
    b. Aldosterone
    c. 17-hydroxyprogesterone
    d. Progesterone

Reviewer's comments: The 0.25 mg ACTH dose is commonly used to assess the integrity of the HPA axis. However, this test has several limitations (Salvatori, 2005). First, this dose causes ACTH levels to increase ~1,000 times higher than what is observed in maximally stressed individuals, thereby potentially causing a falsely normal cortisol response by an adrenal gland that is in fact partially impaired. Second, this test will be falsely negative in patients with newly-acquired (i.e. <1 month) secondary adrenal insufficiency (e.g. ACTH deficiency) because adrenal atrophy only occurs in the setting of chronic ACTH deficiency. Some experts recommend a low-dose ACTH stimulation test (1 µg) to identify milder forms of adrenal insufficiency. This test has technical issues because ACTH tends to stick to the tubings, so that patients may get even less or no ACTH exposure.

3. 24-hour urine collection from day 7 to day 8 of each double-blind phase for:
    a. Total cortisol
    b. Aldosterone
    c. Creatinine

Assays:

1. Commercially available RIA kits - cortisol [redacted], progesterone, testosterone, and aldosterone [redacted] estradiol [redacted], ACTH [redacted]
2. FSH, LH, prolactin, SHBG (time-resolved fluoroimmunoassay, [redacted])
3. Androstenedione, DHEA, 17 alpha-hydroxy-progesterone ([redacted])

Reviewer's comments: RIA is still used for measuring cortisol, progesterone, testosterone, aldosterone, and ACTH. Time-resolved fluoroimmunoassay is also still used for measuring FSH, LH, prolactin, and SHBG.

Statistical Analyses: No formal sample size calculations were performed. Non-parametric analyses (Koch) were used for the hormonal results to test for carry-over, period, and treatment effects.

Results: A total of 8 subjects entered the trial. There were no dropouts or protocol violations.

Patient Demographics (n=8)			
	Placebo → nebivolol	**Nebivolol → placebo**	**All subjects**
Men, n	4	4	8
Age, yr median (min-max)	35 (24-57)	45 (36-55)	43.5 (24-57)
Weight, kg median (min-max)	74 (60-75)	79.5 (65-90)	74.5 (60-90)
Systolic blood pressure, mmHg median (min-max)	118 (104-128)	149.5 (140-151)	134 (104-151)
Diastolic blood pressure, mmHg medium (min-max)	74.5 (68-81)	91 (89-92)	85 (68-92)

Basal Hormones:

1. Aldosterone levels were lower after nebivolol – borderline statistical significance (485 vs. 566 pmol/L; p=0.057)
2. There was a significant carry-over effect for estradiol (p=0.0571, 10% level).
3. FSH was non-significantly lower in the second period.
4. There were no other differences between placebo and nebivolol

Reviewer's comments: The random aldosterone levels are difficult to interpret without knowing dietary sodium intake, and even if sodium intake was known, a random level would still offer little, if any, useful information. The lack of difference in estradiol levels cannot be definitely concluded because there was a carry-over effect of nebivolol on estradiol levels measured at the end of the placebo treatment period for the subjects who received nebivolol first.

Hormones After ACTH Stimulation:

1. No differences in post-ACTH levels between placebo and nebivolol
2. There was a significant carry-over effect for aldosterone (p=0.057 for weighted average; p=0.029 for %AUC).

Reviewer's comments: Please see my comments above regarding limitations of the ACTH stimulation test. The dose used and the short duration of therapy does not exclude the possibility of partial adrenal insufficiency.

24-Hour Urinary Collection: Comparable aldosterone and cortisol levels under both treatments.

ACTH Stimulation – SI Units						
Lab Test	**Placebo**			**Nebivolol 5 mg**		
	n	**Mean (95% CI)**	**Median**	**n**	**Mean (95% CI)**	**Median**
17-OH-Progesterone (nmol/L)						
Baseline	8	4.6 (3.1, 6.1)	4.1	8	5.0 (2.7, 7.2)	3.9
30 min post ACTH	8	9.0 (6.7, 11.2)	8.7	8	10.0 (7.8, 12.1)	9.8
1 hr post ACTH	8	8.3 (6.7, 9.9)	7.8	8	8.6 (6.7, 10.5)	7.8
2 hr post ACTH	8	9.9 (8.6, 11.2)	9.9	8	9.8 (8.1, 11.5)	10.5
Aldosterone (pmol/L)						
Baseline	8	562 (497, 628)	**566**	8	481 (399, 563)	**485 (p=0.057)**
30 min post ACTH	8	942 (740, 1144)	997	8	875 (724, 1027)	857
1 hr post ACTH	8	854 (648, 1059)	958	8	816 (691, 940)	774
2 hr post ACTH	8	695 (518, 871)	717	8	712 (590, 834)	735
Cortisol (nmol/L)						
Baseline	8	248 (203, 292)	255	8	272 (211, 333)	263
30 min post ACTH	8	664 (593, 735)	687	8	669 (599, 739)	695
1 hr post ACTH	8	742 (673, 812)	745	8	758 (669, 846)	752
2 hr post ACTH	8	908 (787, 1030)	935	8	916 (801, 1030)	940
Progesterone (nmol/L)						
Baseline	8	1.3 (0.95, 1.55)	1.2	8	1.4 (1.02, 1.77)	1.4
30 min post ACTH	8	3.0 (2.51, 3.51)	3.3	8	3.4 (2.78, 4.07)	3.3
1 hr post ACTH	8	3.5 (2.93, 4.05)	3.5	8	3.5 (2.85, 4.10)	3.5
2 hr post ACTH	8	4.1 (3.16, 5.04)	4.0	8	4.3 (3.89, 4.79)	4.6

ACTH Stimulation – U.S. Units						
Lab Test	**Placebo**			**Nebivolol 5 mg**		
	n	**Mean (95% CI)**	**Median**	**n**	**Mean (95% CI)**	**Median**
17-OH-Progesterone (µg/L)						
Baseline	8	1.5 (1.0, 2.0)	1.4	8	1.7 (0.9, 2.4)	1.3
30 min post ACTH	8	3.0 (2.2, 3.7)	2.9	8	3.3 (2.6, 4.0)	3.2
1 hr post ACTH	8	2.7 (2.2, 3.3)	2.6	8	2.8 (2.2, 3.5)	2.6
2 hr post ACTH	8	3.3 (2.8, 3.7)	3.3	8	3.2 (2.7, 3.8)	3.5
Aldosterone (ng/dL)						
Baseline	8	20 (18, 23)	**20**	8	17 (14, 20)	**17 (p=0.057)**
30 min post ACTH	8	34 (27, 41)	36	8	32 (26, 37)	31
1 hr post ACTH	8	31 (23, 38)	35	8	29 (25, 34)	28
2 hr post ACTH	8	25 (19, 31)	26	8	26 (21, 30)	26
Cortisol (µg/dL)						
Baseline	8	9 (7, 11)	9	8	10 (8, 12)	10
30 min post ACTH	8	24 (21, 27)	25	8	24 (22, 27)	25
1 hr post ACTH	8	27 (24, 29)	27	8	27 (24, 31)	27
2 hr post ACTH	8	33 (29, 37)	34	8	33 (29, 37)	34
Progesterone (ng/mL)						
Baseline	8	0.4 (0.3, 0.5)	0.4	8	0.4 (0.3, 0.6)	0.4
30 min post ACTH	8	0.9 (0.8, 1.1)	1.0	8	1.1 (0.9, 1.3)	1.0
1 hr post ACTH	8	1.1 (0.9, 1.3)	1.1	8	1.1 (0.9, 1.3)	1.1
2 hr post ACTH	8	1.3 (1.0, 1.6)	1.3	8	1.4 (1.2, 1.5)	1.4

Basal Levels of Hormones – SI Units						
Lab Test	Placebo			Nebivolol 5 mg		
	n	Mean (95% CI)	Median	n	Mean (95% CI)	Median
ACTH (pg/mL)	6	14.0 (7.7, 20.3)	13.5	8	10.6 (5.4, 15.9)	8.7
Androstenedione (nmol/L)	8	5.5 (3.90, 7.15)	5.0	8	5.4 (3.59, 7.11)	4.6
Dihydroepiandrosterone (nmol/L)	8	12.7 (10.75, 14.55)	13.0	8	12.1 (10.56, 13.64)	12.0
FSH (U/L)	8	3.4 (2.29, 4.48)	3.1	8	3.0 (2.36, 3.62)	2.9
LH (U/L)	8	2.5 (0.81, 4.12)	1.7	8	2.0 (1.20, 2.78)	1.9
Estradiol (pmol/L)	8	52 (31, 73)	52	8	53 (37, 73)	62
Prolactin (ng/mL)	8	3.0 (1.65, 4.30)	2.2	8	3.9 (2.07, 5.73)	3.5
SHBG (nmol/L)	8	25.6 (17.3, 34)	24.0	8	27.9 (16.9, 38.9)	26.5
Testosterone (nmol/L)	8	16.6 (11.2, 21.9)	15.0	8	15.8 (9.78, 21.85)	14.0

Basal Levels of Hormones – U.S. units						
Lab Test	Placebo			Nebivolol 5 mg		
	n	Mean (95% CI)	Median	n	Mean (95% CI)	Median
Androstenedione (µg/L)	8	1.6 (1.12, 2.05)	1.4	8	1.5 (1.0, 2.0)	1.3
Dihydroepiandrosterone (nmol/L)	8	3.7 (3.10, 4.19)	3.7	8	3.5 (3.04, 3.93)	3.5
Estradiol (pg/mL)	8	14 (8, 20)	14	8	14 (10, 20)	17
Testosterone (ng/mL)	8	4.8 (3.2, 6.3)	4.3	8	4.6 (2.8, 6.3)	4.0

24-Hour Urine – SI Units						
Lab Test	Placebo			Nebivolol 5 mg		
	n	Mean (95% CI)	Median	n	Mean (95% CI)	Median
Aldosterone (nmol/mg cr)	8	0.010 (0.007, 0.013)	0.011	8	0.010 (0.009, 0.012)	0.011
Cortisol (nmol/mg cr)	8	0.28 (0.21, 0.35)	0.26	8	0.26 (0.20, 0.33)	0.24

Reviewer's comments: Since only 8 subjects were studied, it would have been useful to see hormonal results for each individual participant to assess whether any subject had abnormal basal or provoked hormonal values.

Adverse Effects: One subject developed a headache at the end of the placebo intake, another developed influenza-type symptoms at the end of the nebivolol intake (symptoms still present at the end of the trial).

Reviewer's comments: The pain from the headache may have raised the ACTH and cortisol levels in the subject on placebo. The viral-type syndrome may have raised the ACTH and cortisol levels in the subject taking nebivolol. Without individual data, it is impossible to tell whether these changes potentially occurred or affected the results.

Sponsor's Conclusions: There were no significant differences between nebivolol and placebo in the basal, non-stimulated serum concentrations of testosterone, estradiol, FSH, LH, prolactin, and cortisol, and 24-hour urinary cortisol corrected for urinary

creatinine following 7 days of treatment with nebivolol 5 mg/day. Serum aldosterone levels were significantly lower in the nebivolol versus placebo group, although the mean non-stimulated 24-hour urinary excretion of aldosterone corrected for urinary creatinine excretion was comparable between groups. Mean blood cortisol and aldosterone levels after ACTH stimulation were normal and did not differ between treatments.

Reviewer's comments: The short 7-day dosing period and high-dose ACTH stimulation method are inadequate for assessing potential effects of nebivolol on the HPA axis. The random basal aldosterone findings are uninterpretable. My conclusions based on the data available are that no obvious effects of nebivolol were seen in these 8 men given 5 mg of nebivolol daily. However, the dose used, duration of therapy, and method of testing the integrity of the HPA axis were suboptimal. I cannot rule out a long-term effect of nebivolol on the endocrinologic system.

NEB-BEL-52 Effects of Nebivolol on Hormonal Responses to Insulin Induced Hypoglycemia

Sponsor: Janssen Research Foundation
Investigator: L. Vanhaelst, MD, Ph.D. (Brussels, Belgium)
Study Period: November 1992

Objectives: To explore the effects of nebivolol 5 mg daily for 7 days on the hormonal responses to insulin-induced hypoglycemia.

Study Design: Single center, open-label study in 12 healthy volunteers. Insulin provocation was performed at 10 am at baseline (day 0; 24 hours before the first dose of nebivolol) and at 10 am (2 hours after the last dose of nebivolol 5 mg) on day 7.

Reviewer's comments: Insulin-induced hypoglycemia is the gold standard for assessing the integrity of the entire HPA axis. To draw accurate conclusions, this test requires that glucose be lowered below 40 mg/dL. Nonetheless, this study has similar weaknesses to NEB-BEL-52: (1) The 5 mg/day dose of nebivolol used in this study is one-half the maximum recommended dose (10 mg/day) in humans for which the Sponsor is seeking approval, and (2) nebivolol exposure was only for 7 days.

Inclusion Criteria Included:
1. Healthy Caucasian men and premenopausal women 18-45 years old
2. Within 10% of ideal body weight
3. <10 cigarettes/day or <2 cigars/day or <2 pipes/day

Exclusion Criteria Included:
1. Alcohol or drug abuse
2. Supine resting blood pressure <100/65 mmHg

3. Resting heart rate <55 beats/min
4. Pregnant, nursing, or not using adequate, non-hormonal contraception
5. Use of ovulation inhibitors within one hormonal cycle of the trial
6. Concomitant medications except paracetamol (acetaminophen)
7. Reversed sleep-wake cycle

Assessments Included:

1. Blood hormones before and after each insulin provocation test
   - 30, -15, 0, 10, 20, 40, 60, 90, and 120 minutes
   Intravenous insulin 0.15 U/kg immediately after the 0 timepoint blood draw
   Glucose, ACTH, cortisol, growth hormone, prolactin measured at all timepoints
2. Aldosterone, testosterone, LH, active renin immediately prior to insulin only
3. 24-hour urine (for cortisol, aldosterone, creatinine) started on the days prior to the first and last doses of nebivolol
4. Standard labs (e.g. hematology, chemistry, urinalysis) prior to the insulin tests

Assays and Methods:

1. Radioimmunoassays – ACTH, cortisol, growth hormone, prolactin, 24-hour urine
2. Immediate centrifugation – aldosterone, active renin
3. ACTH placed on ice prior to centrifugation
4. Samples stored at -20°C until analyses (on completion of trial)

Statistical Analyses:

No formal sample size calculations were performed. All subjects were analyzed regardless of their compliance with the protocol (unless there were no treatment data). All hypothesis tests were two-sided, and $p \leq 0.05$ was considered significant.

The Wilcoxon matched-pairs signed ranks test was used to compare steady state hormone levels and 24-hour urinary hormones on Day 0 vs. Day 7

The Friedman test was used to compare ACTH, glucose, cortisol, growth hormone, prolactin at -30, -15, and 0 minute timepoints. If no statistical differences were found, the baseline values were defined as the average of the -15 min and 0 min timepoints. If a significant change was found, the 0 minute value was used as the reference.

Area under the curve (AUC) and C_{max} were calculated for each variable for the 2-hour observation period after insulin administration. The Day 0 and Day 7 values were compared with the Wilcoxon signed-ranks test.

Protocol Deviations: There were 3 protocol deviations:

1. Two subjects were overweight – both with body mass index 26.0 kg/m^2
2. One subject had a left nephrectomy and polycystic kidney disease of the right kidney

Reviewer's comments: The slightly overweight subjects should not affect results of the study. The subject with a left nephrectomy was probably not a good

candidate for this study, particularly if the left adrenal gland was also removed at the time of nephrectomy.

Results: There were no withdrawals or treatment interruptions. One subject had a history of left nephrectomy (polycystic kidney disease), another had a history of pre-eclampsia, and third had a history of ureterolithiasis.

Patient Demographics (n=12)	
Age, yr, Median (min-max)	24 (20-45)
Weight, kg Median (min-max)	69.5 (51-87)
Body Mass Index, kg/m^2 Median (min-max)	21.9 (20-26)
Men/Women	6/6
Non-smoker/cigarettes <10/day, n	10/2
Supine blood pressure, mmHg, median (min-max) Systolic Diastolic	 121 (110-130) 74 (70-80)
Standing blood pressure, mmHg, median (min-max) Systolic Diastolic	 120 (102-130) 76 (72-82)

At the end of the 7-day treatment period, there were decreases in mean steady state levels of ACTH, aldosterone, cortisol, and prolactin. The only significant change was seen for plasma cortisol (11.4 to 7.8 µg/dL; p=0.003).

Changes in Steady State Hormone Levels Immediately Prior to Insulin Administration					
Hormone	**Mean (SEM)**			**95% Confidence Interval for the Mean Change from Baseline**	**Change from Baseline p-value**
	Baseline (Day 0)	**Endpoint (Day 7)**	**Change (Day 0 to Day 7)**		
ACTH (ng/L)	19.7 (3.6)	14.9 (2.3)	-4.8 (3.1)	-11.5, 1.9	0.23
Active renin (ng/L)	12.6 (1.6)	12.4 (2.5)	-0.3 (2.6)	-6.0, 5.4	0.39
Aldosterone (ng/L)	88.3 (15.5)	78.6 (12.9)	-9.7 (18.7)	-50.9, 31.6	0.85
Cortisol (µg/dL)	11.4 (1.7)	7.8 (1.2)	-3.6 (1.2)	-6.3, -0.8	**0.003**
Glucose (mg/dL)	74.9 (1.6)	74.4 (1.9)	-0.5 (1.8)	-4.5, 3.5	0.97
Growth hormone (mU/L)	4.2 (1.8)	5.4 (1.9)	1.2 (1.5)	-2.2, 4.5	0.32
LH (U/L)	5.4 (0.9)	4.8 (1.0)	-0.6 (1.4)	-3.6, 2.4	0.76
Prolactin (mU/L)	264.6 (14.4)	226.4 (15.7)	-38.2 (19.0)	-80.0, 3.7	0.11
Testosterone (µg/L)	2.1 (0.6)	2.4 (0.7)	0.2 (0.2)	-0.1, 0.6	1.00

Reviewer's comments: Testosterone levels should have been analyzed separately in men and women because women have much lower testosterone levels than do men.

Glucose: The glucose nadir occurred 20-30 minutes post-insulin dose. The glucose response to insulin was similar before and after the 7 day treatment with nebivolol.

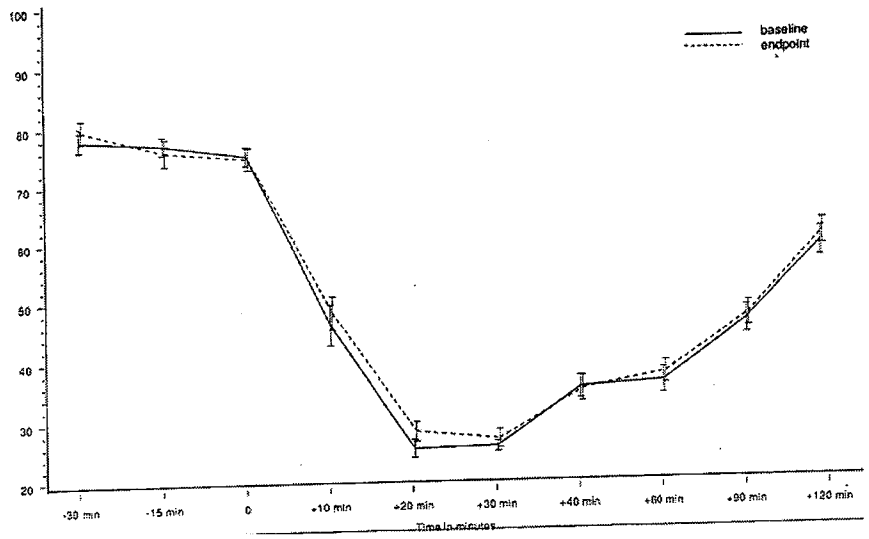
The minimal glucose level achieved during the insulin tolerance tests are displayed in the Table below.

Patient	Day 0	Day 7	Change
1	22	27	5
2	23	24	1
3	22	26	4
4	31	**42**	**11**
5	22	24	2
6	21	23	2
7	20	25	5
8	22	20	-2
9	24	25	1
10	24	27	3
11	26	24	-2
12	23	26	3

Reviewer's comments: Patient 4 had a borderline glucose response to insulin on Day 7. This is probably of no clinical significance since it is very close to the desired goal. The remainder of the tests achieved a glucose <40 mg/dL during testing.

Changes in Plasma Glucose Levels (mg/dL) During the Insulin Tests					
Time (minutes)	Baseline (Day 0)		Endpoint (Day 7)		Change from baseline to endpoint p-value
	Mean (SEM)	95% CI of mean	Mean (SEM)	95% CI of mean	
-30	77.8 (1.7)	74.2, 81.5	79.6 (1.9)	75.3, 83.9	
-15	76.9 (1.5)	73.6, 80.3	75.8 (2.3)	70.7, 80.8	
0	74.9 (1.6)	71.4, 78.4	74.4 (1.9)	70.2, 78.6	
+10	45.8 (3.4)	38.4, 53.2	47.8 (2.7)	41.8, 53.8	
+20	25.1 (1.5)	21.7, 28.5	28.0 (1.7)	24.3, 31.7	
+30	25.3 (0.9)	23.4, 27.3	26.6 (1.5)	23.2, 30.0	
+60	35.8 (2.1)	31.2, 40.5	37.3 (1.8)	33.3, 41.2	
+90	45.8 (2.3)	40.8, 50.8	46.7 (2.1)	42.1, 51.3	
+120	58.5 (2.5)	53.1, 63.9	60.2 (2.2)	55.4, 64.9	
AUC	5008 (192)	4585, 5431	5150 (198)	4715, 5586	0.52
Cmax	79.9 (1.7)	76.2, 83.7	80.7 (2.0)	76.3, 85.1	0.97

A plot of plasma glucose levels in response to insulin provocation is shown below.



For the insulin provocation tests, the intention was to use the mean of the -15 and 0 minute concentrations as baseline. However, levels of all 5 variables decreased significantly during the observation period prior to insulin administration on both Days 0 and 7. Therefore, the 0 minute value was used as baseline.

ACTH: Peak ACTH levels occurred 40 minutes after the start of insulin administration. The AUC and C_{max} were slightly larger at endpoint than at baseline but these comparisons were not statistically significant.

Changes in Plasma ACTH (ng/L) During the Insulin Tests					
Time (minutes)	Baseline (Day 0)		Endpoint (Day 7)		Change from baseline to endpoint p-value
	Mean (SEM)	95% CI of mean	Mean (SEM)	95% CI of mean	
-30	**29.4 (6.6)**	15.0, 43.8	**17.6 (3.2)**	10.6, 24.6	
-15	**21.4 (3.9)**	12.8, 30.0	**15.4 (2.7)**	9.4, 21.4	
0	**19.7 (3.6)**	11.8, 27.6	**14.9 (2.3)**	10.0, 19.9	
+30	159.7 (37.6)	76.8, 242.5	162.3 (42.4)	69.0, 255.6	
+40	**238.0 (29.9)**	172.2, 303.9	**295.2 (35.7)**	216.6, 373.8	
+60	175.0 (22.0)	126.6, 223.3	175.4 (26.1)	117.9, 232.8	
+90	73.9 (11.7)	48.1, 99.6	78.1 (17.1)	40.5, 115.7	
+120	42.9 (8.1)	25.1, 60.6	38.6 (7.3)	22.6, 54.6	
AUC	12823 (1586)	9332, 16315	13703 (2009)	9282, 18124	0.73
Cmax	247.5 (31.4)	178.4, 316.7	295.8 (35.6)	217.5, 374.1	0.15