Table 131. Patient Disposition (All Screened) (NEB-203)

Study Status	Non-ITT	Atenolol 50 mg n (%)	Atenolol 100 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Total n (%)
Screened	139	24	21	23	23	24	254
Single-Blind	112	24	21	23	23	24	227
Randomized	0	24	21	23	23	24	115
ITT	0	24	21	23	23	24	115
PP	0	17	13	11	18	13	72
Completed	0 (0.0)	24 (100.0)	15 (71.4)	23 (100.0)	22 (95.7)	24 (100.0)	108 (93.9)
Discontinued	0 (0.0)	0 (0.0)	6 (28.6)	0 (0.0)	1 (4.3)	0 (0.0)	7 (6.1)
Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (0.9)
Lost to Follow-up	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Withdrew Consent	0 (0.0)	0 (0.0)	3 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.6)
Other	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

Data Source: Tables 1.1.2, 1.10, and 1.14.2

(Reproduced from Sponsor, NEB-203, Table 10.1-1, page 67)

In NEB-203, there were 254 patients screened with 227 patients entering the single-blind phase and 115 patients randomized (24 atenolol 50 mg, 21 atenolol 100 mg, 23 nebivolol 5 mg, 23 nebivolol 10 mg, and 24 nebivolol 20 mg). A total of 7 patients withdrew from the study, including 6 patients (28.6%) in the atenolol 100 mg group and 1 patient (4.3%) in the nebivolol 10 mg group. Of the 6 patients in the atenolol 100 mg group who withdrew, 3 withdrew consent, 2 were lost to follow-up, and 1 was withdrawn due to "other." The withdrawal in the nebivolol 10 mg group was due to the adverse event of a myocardial infarction.

The number of subjects completing the study through Day 28 was 69/70 (98.6%) for nebivolol and 39/45 (86.7%) for atenolol. The sponsor stated the number of patients completing the study was not the same as the number of patients completing the end-of-study submaximal ETTs. Of the patients randomized to nebivolol, 4% (1/23) and 9% (2/23) in the nebivolol 5 mg and 10 mg treatment groups, respectively, did not perform the final submaximal ETT. All patients in the nebivolol 20 mg treatment group completed the final submaximal ETT. Of the patients randomized to atenolol, 4% (1/23) and 38% (8/21) in the atenolol 50 mg and 100 mg treatment groups, respectively, did not perform the final submaximal ETT.

A total of 43/115 (37.4%) of patients had major protocol violations in NEB-203. The most common major protocol violations are listed in Table 132. In the nebivolol 5 mg treatment group, 10/23 (43.5%) of patients had an inappropriate workload used for baseline sub-maximal ETT per results of the maximal ETT.

Table 132. Most Common Major Protocol Violations (ITT Population) (NEB-203)

Criteria Violated	Atenolol 50mg n (%)	Atenolol 100mg n (%)	Nebivolol 5mg n (%)	Nebivolol 10mg n (%)	Nebivolol 20mg n (%)	Total n (%)
Inappropriate workload used for baseline sub-maximal ETT per results of the maximal ETT (i.e., range for sub-maximal ETT must be between 65% and 85% of maximal workload attained during the maximal ETT)						
	1 (4.2)	3 (14.3)	10 (43.5)	4 (17.4)	3 (12.5)	21 (18.3)
Baseline sub-maximal ETT #3 not performed and the difference in exercise duration was ≥15% between sub-maximal ETT #1 and #2						
	3 (12.5)	1 (4.8)	1 (4.3)	0 (0.0)	4 (16.7)	9 (7.8)
Hypertensive response to exercise (SBP ≥260 mmHg or diastolic BP ≥115 mmHg) during maximal ETT						
	2 (8.3)	1 (4.8)	3 (13.0)	0 (0.0)	1 (4.2)	7 (6.1)
Maximal achieved heart rate was <85% of age-predicted maximum heart rate calculated as [220-age] during maximal ETT						
	3 (12.5)	1 (4.8)	1 (4.3)	0 (0.0)	1 (4.2)	6 (5.2)
Sub-maximal ETT at Day 28 was performed outside the testing window of 1 to 5 hours following that day's dose of study medication						
	3 (12.5)	0 (0.0)	1 (4.3)	1 (4.3)	1 (4.2)	6 (5.2)

Data Source: Table 1.17

(Reproduced from Sponsor, NEB-203, Table 10.2-1, page 68)

Peak Sub-Maximal Exercise Duration at End of Study (NEB-203)

Patients randomized to atenolol 50 mg and 100 mg treatment groups increased their exercise duration by 3.7% and 9.2%, respectively, by the end of the study. Patients taking nebivolol 5 mg increased their exercise duration by 7.1%, while patients taking nebivolol 10 mg and 20 mg decreased their exercise duration by 10.4% and 8.9%, respectively. The results of the final submaximal ETT are listed in Table 133.

Table 133. Mean percent Change From Baseline to End of Study (Day 28) in Peak Sub-Maximal Exercise Duration (min) by Treatment: Primary Analysis (ITT OC Population)

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

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

(Reproduced from Sponsor, NEB-203, Table 11.4.1.1.1-1, page 74)

Final Rating of Perceived Exertion (RPE) (NEB-203)

Perceived exertion was unchanged in the nebivolol groups (-0.1 to 0.0) and increased in the atenolol groups (0.8 and 0.9). Pooled differences between nebivolol and atenolol treatment groups were statistically significant with a p-value of 0.004, as seen in Table 134.

Table 134. Mean Change From Baseline to End of Study (Day 28) in Final Rating of Perceived Exertion (RPE) by Treatment (ITT OC Population) (NEB-203)

Treatments	N	Baseline Mean	Treatment Mean	Change from Baseline[a] Mean (SD)	Change from Baseline[a] LS Mean (SE)[b]	Comparisons
Atenolol						**Atenolol vs. Nebivolol[b,c]**
50mg	24	17.8	18.7	0.9 (1.6)	0.8 (0.3)	(-1.5, -0.3)
100mg	14	17.5	18.6	1.1 (1.6)	0.9 (0.4)	0.004
Nebivolol						**Nebivolol Comparison[b]**
5mg	22	18.5	18.2	-0.2 (1.8)	-0.1 (0.3)	5mg vs. 20mg: 0.771
10mg	22	18.4	18.2	-0.1(1.1)	0.0 (0.3)	5mg vs. 10mg: 0.897*
20mg	24	18.3	18.3	0.0 (1.7)	0.0 (0.3)	10mg vs. 20mg: 0.874*

Data Source: Table 2.15
[a]RPE ranged from 6 to 20 where 6 and 20 represent the least and most amount of exertion and fatigue, respectively
[b]From an ANCOVA with factor treatment and covariate baseline value
[c]95% C.I. and p-value from the contrast of nebivolol vs. atenolol
* P-value is not applicable due to previous non-significant result in hierarchical testing scheme

(Reproduced from Sponsor, NEB-203, Table 11.4.1.2.2.1-1, page 80)

Systolic Blood Pressure and Heart Rate During Exercise (NEB-203)

During the final submaximal ETT, most patients were not able to exercise for 12 minutes, the protocol prespecified time for comparing systolic blood pressure and heart rate. Because less than 50% of subjects receiving nebivolol or atenolol exercised into Stage 4, the sponsor only discussed results through Stage 3. Nebivolol had a dose-dependent effect on systolic blood pressure and heart rate during exercise, as seen in Table 135 and Table 136. It also appeared that both doses of atenolol inhibited exercise induced increases in systolic blood pressure and heart rate better than all doses of nebivolol.

Table 135. Mean Percent Change and Change From Cycle Rest In Sub-Maximal Systolic Blood Pressure (mm Hg) During Exercise by Treatment (ITT OC Population) (Stage 3) (NEB-203)

Treatments	N	Cycle Rest Mean (SD)	Stage Mean (SD)	Percent Change Mean (SE)	Change Mean (SE)
			Stage 3		
Atenolol					
50mg	17	131.1 (18.7)	168.8 (19.9)	30.2 (4.4)	37.7 (4.8)
100mg	14	130.6 (8.6)	168.0 (21.1)	28.8 (4.1)	37.4 (5.3)
Nebivolol					
5mg	15	133.9 (15.9)	185.3 (17.6)	40.1 (5.4)	51.4 (6.3)
10mg	14	138.9 (20.9)	187.6 (20.8)	36.7 (4.5)	48.7 (5.3)
20mg	18	132.4 (11.1)	175.7 (26.0)	33.7 (5.4)	43.2 (6.9)

Data Source: Table 2.4

(Reproduced from Sponsor, NEB-203, Table 11.4.1.2.2.2.1-1, page 82)

Table 136. Mean Percent Change and Change From Cycle Rest In Sub-Maximal Heart Rate (bpm) During Exercise by Treatment (ITT OC Population) (NEB-203)

Treatments	N	Cycle Rest Mean (SD)	Stage Mean (SD)	Percent Change Mean (SE)	Change Mean (SE)
Stage 3					
Atenolol					
50mg	17	65.2 (10.5)	116.1 (9.6)	82.3 (7.7)	50.9 (2.5)
100mg	14	61.5 (10.3)	106.6 (15.5)	75.7 (7.1)	45.1 (3.7)
Nebivolol					
5mg	15	62.9 (9.7)	124.3 (19.2)	101.6 (10.5)	61.5 (5.6)
10mg	14	66.9 (15.8)	122.3 (14.2)	87.3 (7.2)	55.4 (2.8)
20mg	18	63.7 (11.1)	112.2 (17.5)	79.0 (7.3)	48.6 (3.5)

Data Source: Table 2.5

(Reproduced from Sponsor, NEB-203, Table 11.4.1.2.2.2.2-1, page 84)

Other Secondary Endpoints (NEB-203)

Blood Pressure

There were no significant differences between pooled nebivolol and atenolol treatment groups in mean percent change and change from baseline to end of treatment for the following parameters:

1. sitting diastolic blood pressure and systolic blood pressure at trough
2. sitting diastolic blood pressure and systolic blood pressure at peak
3. standing diastolic blood pressure and systolic blood pressure at trough
4. standing diastolic blood pressure and systolic blood pressure at peak
5. supine diastolic and systolic blood pressure at trough
6. supine systolic blood pressure at peak

For supine diastolic blood pressure at peak, there was a statistically significant difference between pooled atenolol and nebivolol treatment groups in reduction of peak diastolic blood pressure from baseline to end of study. Least squares mean changes from baseline were -18.3 and -13.5 for atenolol 50 mg and 100 mg, respectively, compared with -9.4, -13.6, and -13.2 for nebivolol 5 mg, 10 mg, and 20 mg, respectively, as shown in Table 137.

Table 137. Mean Percent Change and Change From Baseline in Peak Supine Blood Pressure (mm Hg) at End of Treatment (Day 28) (ITT OC Population) (NEB-203)

		Percent Change From Baseline			Change From Baseline	
Treatments	N	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]	N	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]
DBP						
Atenolol						
50mg	23	-19.1 (1.9)	(0.5, 7.8)	23	-18.3 (1.8)	(0.4, 7.4)
100mg	15	-14.0 (2.3)	0.027	15	-13.5 (2.2)	0.031
Nebivolol						
5mg	22	-9.7 (1.9)		22	-9.4 (1.8)	
10mg	22	-13.8 (1.9)		22	-13.6 (1.8)	
20mg	24	-13.7 (1.8)		24	-13.2 (1.8)	
SBP						
Atenolol						
50mg	23	-11.7 (1.9)	(-2.0, 5.6)	23	-17.3 (2.9)	(-3.2, 8.2)
100mg	15	-13.1 (2.4)	0.345	15	-19.8 (3.6)	0.390
Nebivolol						
5mg	22	-10.4 (2.0)		22	-15.4 (3.0)	
10mg	22	-9.4 (2.0)		22	-14.1 (3.0)	
20mg	24	-12.0 (1.9)		24	-18.7 (2.9)	

Data Source: Tables 2.8.2 and 2.9.2
[a] From an ANCOVA with factor treatment and covariate baseline value
[b] 95% C.I. and p-value from the contrast of nebivolol vs. atenolol

(Reproduced from Sponsor, NEB-203, Table 11.4.1.2.3.3.2-1, page 91)

Heart Rate (NEB-203)

Sitting heart rate at trough and peak decreased for all treatment groups in the ITT OC Population. There was no statistically significant difference between pooled atenolol and nebivolol treatment groups from baseline to end of treatment. At peak but not at trough, the comparison between nebivolol 5 mg and 20 mg was significant with p = 0.043 for percent change and p = 0.039 for change. Table 138 shows the changes in sitting heart rate from baseline to end of study.

Table 138. Mean Percent Change and Change From Baseline in Sitting Heart Rate (bpm) at End of Treatment (Day 28) (ITT OC Population) (NEB-203)

		Percent Change From Baseline			Change From Baseline	
Treatments	N	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]	N	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]
At Trough						
Atenolol						
50mg	24	-12.3 (1.7)	(-2.8, 3.9)	24	-9.3 (1.3)	(-2.1, 2.9)
100mg	17	-14.6 (2.0)	0.752	17	-10.9 (1.5)	0.759
Nebivolol						
5mg	23	-11.8 (1.8)		23	-8.9 (1.3)	
10mg	22	-12.5 (1.8)		22	-9.5 (1.4)	
20mg	24	-14.5 (1.7)		24	-10.8 (1.3)	
At Peak						
Atenolol						
50mg	24	-13.5 (2.0)	(-4.3, 3.7)	24	-10.5 (1.5)	(-2.9, 2.9)
100mg	15	-16.3 (2.6)	0.896	15	-12.4 (1.8)	0.985
Nebivolol						
5mg	22	-12.5 (2.1)		22	-9.6 (1.5)	
10mg	22	-14.3 (2.1)		22	-10.8 (1.5)	
20mg	24	-18.5 (2.0)		24	-14.0 (1.4)	

Data Source: Tables 2.6.2 and 2.7.2
[a]From an ANCOVA with factor treatment and covariate baseline value
[b]95% C.I. and p-value from the contrast of nebivolol vs. atenolol

(Reproduced from Sponsor, NEB-203, Table 11.4.1.2.3.4.1-1, page 92)

Standing heart rate at trough and peak decreased for all treatment groups in the ITT OC Population. There was no statistically significant difference between pooled atenolol and nebivolol treatment groups from baseline to end of treatment. Reductions in heart rate were dose-dependent. Comparisons between nebivolol treatment groups were not statistically significant.

Response Rates (NEB-203)

Responder rates for nebivolol 5 mg, 10 mg, and 20 mg ranged from 52.2% to 79.2%. Responder rates for atenolol 50 mg and 100 mg were 70.8% and 52.6%, respectively. There was no statistically significant difference in response rates between pooled nebivolol and pooled atenolol treatment groups.

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Table 139. Responder Rates by Treatment (ITT LOCF Population) (NEB-203)

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

Data Source: Table 2.12.1
[a]A subject is a responder if their average trough sitting DBP <90 mmHg at end of study or has decreased by ≥10 mmHg from baseline
[b]Percentage is the percentage of responders within that category
[c]Based on the Wald Chi-Square Test for trend form logistic regression with factor treatment and covariate baseline sitting DBP
[d]P-value from the contrast of nebivolol vs. atenolol
* P-value is not applicable due to previous non-significant result in hierarchical testing scheme
(Reproduced from Sponsor, NEB-203, Table 11.4.1.2.3.5-1, page 94)

Doppler Echocardiographic Measurements (NEB-203)

There was a statistically significant difference in Peak A Velocity at peak for pooled nebivolol and atenolol doses (p = 0.030), as seen in Table 140. There were no significant differences between pooled groups regarding LV end-diastolic dimension, Peak E Velocity, E/A Ratio, deceleration time of the mitral E-wave, and LV isovolumic relaxation time. At trough, left ventricular isovolumic relaxation time increased more from baseline in the atenolol groups than in the nebivolol groups, and this increase trended toward significance (p = 0.059).

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Table 140. Mean Change from Baseline in Trough and Peak Imaging and Doppler Echocardiographic Measurements of Left Ventricular Diastolic Performance at End of Treatment (ITT OC Population) (NEB-203)

	Trough			Peak		
		Change from Baseline			Change from Baseline	
Treatments	N	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]	N	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]
	LV End-Diastolic Dimension (short axis) (mm)					
Atenolol						
50mg	23	1.3 (0.5)	(-0.7, 1.2) 0.578	23	9.2 (3.9)	(-11.3, 4.1) 0.353
100mg	16	-0.1 (0.6)		15	-0.3 (4.8)	
Nebivolol						
5mg	23	0.7 (0.5)		21	1.2 (4.1)	
10mg	22	0.3 (0.5)		21	0.1 (4.1)	
20mg	24	1.5 (0.5)		23	1.3 (3.9)	
	Peak E Velocity (cm/sec)					
Atenolol						
50mg	19	7.5 (3.1)	(-5.0, 6.8) 0.759	21	25.3 (9.6)	(-29.8, 8.5) 0.273
100mg	15	2.0 (3.5)		14	3.9 (11.7)	
Nebivolol						
5mg	17	6.0 (3.3)		16	6.9 (10.9)	
10mg	20	4.8 (3.1)		18	0.4 (10.3)	
20mg	22	6.2 (2.9)		20	4.8 (9.8)	
	Peak A Velocity (cm/sec)					
Atenolol						
50mg	19	-3.3 (2.8)	(-6.9, 3.6) 0.524	21	-8.4 (2.5)	(0.6, 10.6) 0.030
100mg	15	-5.7 (3.1)		14	-11.3 (3.1)	
Nebivolol						
5mg	17	-4.3 (3.0)		16	-3.8 (2.9)	
10mg	20	-7.6 (2.7)		18	-3.4 (2.7)	
20mg	22	-6.7 (2.6)		20	-5.6 (2.6)	
	E/A Ratio					
Atenolol						
50mg	19	0.2 (0.1)	(-0.1, 0.2) 0.586	21	0.5 (0.2)	(-0.6, 0.1) 0.132
100mg	15	0.1 (0.1)		14	0.3 (0.2)	
Nebivolol						
5mg	17	0.2 (0.1)		16	0.2 (0.2)	
10mg	20	0.2 (0.1)		18	0.1 (0.2)	
20mg	22	0.2 (0.1)		20	0.2 (0.2)	

Data Source: Tables 2.13.3 and 2.13.4
[a]From an ANCOVA with factor treatment and covariate baseline value
[b]95% C.I. and p-value from the contrast of nebivolol vs. atenolol

(Reproduced from Sponsor, NEB-203, Table 11.4.1.2.4.1-1, page 95)

As shown in Table 141, there was a statistically significant difference in left ventricular end-systolic dimension at peak for pooled nebivolol doses versus pooled atenolol doses (p = 0.009), due primarily to a decrease in the atenolol 100 mg group.

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Table 141. Mean Change from Baseline in Trough and Peak Imaging and Doppler Echocardiographic Measurements of Left Ventricular Systolic Performance at End of Treatment (ITT OC Population) (NEB-203)

	Trough			Peak		
		Change from Baseline			Change from Baseline	
Treatments	N	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]	N	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]
	LV End-Systolic Dimension (short axis) (mm)					
Atenolol						
50mg	23	0.2 (0.4)	(-0.3, 1.3)	23	-0.5 (0.4)	(0.3, 2.0)
100mg	16	-0.6 (0.5)	0.182	15	-2.4 (0.5)	0.009
Nebivolol						
5mg	23	0.0 (0.4)		21	-0.2 (0.5)	
10mg	22	0.1 (0.4)		21	-0.7 (0.5)	
20mg	24	0.9 (0.4)		23	0.0 (0.4)	
	LV Ejection Time (msec)					
Atenolol						
50mg	23	34.5 (5.3)	(-5.6, 15.0)	23	44.6 (7.5)	(-23.9, 5.6)
100mg	16	31.4 (6.4)	0.369	15	40.8 (9.3)	0.220
Nebivolol						
5mg	23	33.3 (5.4)		23	21.6 (7.5)	
10mg	22	38.9 (5.5)		22	32.5 (7.7)	
20mg	24	40.7 (5.2)		23	46.7 (7.5)	
	LV Outflow Tract Velocity (cm)					
Atenolol						
50mg	22	3.7 (0.6)	(-1.3, 1.0)	21	4.4 (9.2)	(-12.6, 25.7)
100mg	14	2.3 (0.7)	0.745	11	3.4 (12.7)	0.499
Nebivolol						
5mg	21	1.5 (0.6)		20	22.6 (9.4)	
10mg	18	2.9 (0.6)		19	3.7 (9.7)	
20mg	20	4.1 (0.6)		19	5.1 (9.7)	
	LV Forward Stroke Volume (mL)					
Atenolol						
50mg	22	13.0 (2.2)	(-5.1, 3.7)	21	15.4 (2.6)	(-5.9, 4.9)
100mg	14	9.1 (2.7)	0.754	11	12.6 (3.5)	0.858
Nebivolol						
5mg	21	5.8 (2.2)		19	8.9 (2.7)	
10mg	18	10.4 (2.4)		19	13.9 (2.7)	
20mg	20	14.8 (2.3)		19	17.8 (2.7)	

Data Source: Tables 2.13.1 and 2.13.2
[a]From an ANCOVA with factor treatment and covariate baseline value
[b]95% C.I. and p-value from the contrast of nebivolol vs. atenolol

(Reproduced from Sponsor, NEB-203, Table 11.4.1.2.4.2-1, page 97)

The contrast between nebivolol 5 mg and 20 mg was statistically significant regarding dose-dependent increases in left ventricular ejection time at peak and forward stroke volume at peak ($p = 0.020$ for both), left ventricular outflow tract velocity-time integral at trough ($p = 0.003$), left ventricular forward stroke volume at trough ($p = 0.006$), and left ventricular forward stroke volume index at trough ($p = 0.008$).

Generalized Fatigue (NEB-203)

There was no significant difference in overall fatigue between pooled nebivolol and atenolol treatment groups from baseline to end of study ($p = 0.442$).

Table 142. Mean Change from Baseline in Fatigue Severity Scale (ITT OC Population) (NEB-203)

Treatments	N	Baseline Mean	Treatment Mean	Change from Baseline		
				Mean (SD)	LS Mean (SE)[a]	Atenolol vs. Nebivolol[a,b]
	Overall					
Atenolol						
50mg	24	3.3	3.7	0.4 (1.2)	0.4 (0.2)	(-0.7, 0.3) 0.442
100mg	15	3.0	3.3	0.2 (0.9)	0.2 (0.3)	
Nebivolol						
5mg	22	2.9	3.3	0.4 (1.1)	0.4 (0.3)	
10mg	22	2.7	3.1	0.3 (1.5)	0.2 (0.3)	
20mg	23	3.4	3.1	-0.3 (1.4)	-0.2 (0.2)	

Data Source: Table 2.14
[a]From an ANCOVA with factor treatment
[b]95% C.I. and p-value from the contrast of nebivolol vs. atenolol
[c]Overall is the average of the responses to the nine statements
(Reproduced from Sponsor, Table 11.4.1.2.5-1, page 99)

Correlation of Nebivolol Levels in Plasma with Change in Diastolic Blood Pressure and Heart Rate (NEB-203)

According to the sponsor, there were no statistically significant correlations between change in peak sitting diastolic blood pressure or heart rate and peak plasma levels of *d*-nebivolol, *l*-nebivolol, or *d,l*-nebivolol at end of study.

Table 143. Correlation of Reduction in Peak Sitting DBP (mm Hg) and Peak Plasma Levels (ng/mL) of Nebivolol at Day 28 (ITT LOCF Population) (NEB-203)

Nebivolol Treatment Group	Plasma Level		Blood Pressure Reduction		Correlation[a]	P-value[a]
	N	Mean (SD)	N	Mean (SD)		
d,l-Nebivolol						
5mg	22	1.7 (4.2)	22	-10.3 (7.9)	-0.135	0.550
10mg	22	4.7 (8.0)	22	-14.5 (8.3)	-0.103	0.648
20mg	21	3.4 (2.5)	21	-14.7 (8.4)	0.343	0.128
Overall	65	3.2 (5.5)	65	-13.2 (8.3)	-0.081	0.521
l-Nebivolol						
5mg	22	1.2 (3.6)	22	-10.3 (7.9)	-0.121	0.592
10mg	22	3.2 (6.3)	22	-14.5 (8.3)	-0.124	0.583
20mg	21	2.0 (1.5)	21	-14.7 (8.4)	0.381	0.088
Overall	65	2.1 (4.3)	65	-13.2 (8.3)	-0.087	0.491
d-Nebivolol						
5mg	22	0.5 (0.7)	22	-10.3 (7.9)	-0.188	0.402
10mg	22	1.5 (1.8)	22	-14.5 (8.3)	-0.022	0.921
20mg	21	1.4 (1.1)	21	-14.7 (8.4)	0.276	0.226
Overall	65	1.1 (1.4)	65	-13.2 (8.3)	-0.053	0.677

Data Source: Table 2.16.2
[a]From Pearson's Correlation
(Reproduced from Sponsor, Table 11.4.1.2.6.1-1; page 102)

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Table 144. Correlation of Reduction in Peak Sitting Heart Rate (bpm) and Peak Plasma levels (ng/mL) of Nebivolol at Day 28 (ITT LOCF Population) (NEB-203)

Nebivolol Treatment Group	Plasma Level		Heart Rate Reduction		Correlation[a]	P-value[a]
	N	Mean (SD)	N	Mean (SD)		
***d,l*-Nebivolol**						
5mg	22	1.7 (4.2)	22	-8.5 (8.5)	0.170	0.449
10mg	22	4.7 (8.0)	22	-10.8 (7.6)	0.213	0.341
20mg	21	3.4 (2.5)	21	-15.3 (7.0)	-0.032	0.890
Overall	65	3.2 (5.5)	65	-11.5 (8.1)	0.105	0.405
***l*-Nebivolol**						
5mg	22	1.2 (3.6)	22	-8.5 (8.5)	0.176	0.434
10mg	22	3.2 (6.3)	22	-10.8 (7.6)	0.228	0.307
20mg	21	2.0 (1.5)	21	-15.3 (7.0)	-0.057	0.808
Overall	65	2.1 (4.3)	65	-11.5 (8.1)	0.134	0.288
***d*-Nebivolol**						
5mg	22	0.5 (0.7)	22	-8.5 (8.5)	0.126	0.578
10mg	22	1.5 (1.8)	22	-10.8 (7.6)	0.144	0.522
20mg	21	1.4 (1.1)	21	-15.3 (7.0)	0.002	0.994
Overall	65	1.1 (1.4)	65	-11.5 (8.1)	0.002	0.986

Data Source: Table 2.17.2
[a]From Pearson's Correlation

(Reproduced from Sponsor, Table 11.4.1.2.6.2-1, page 103)

Statistical/Analytical Issues

There was no interaction between site and the primary and selected secondary blood pressure parameters ($p > 0.153$).

Subgroup Analyses

Due to small numbers of patients in the various subgroups, I cannot formulate any definitive conclusions from these analyses. Below, see the summary of percent change in sub-maximal exercise duration by subgroup in Table 145 and Table 146, as well as the summary of change in trough sitting diastolic blood pressure by subgroup in Table 147 and Table 148.

Table 145. Summary of Percent Change in Sub-Maximal Exercise Duration (min) from Baseline to End of Study by Subgroup at Trough (Baseline Sub-Maximal Exercise Duration, Age, and Gender; ITT OC) (NEB-203)

	Baseline Sub-Maximal Exercise Duration (Median)				Age (Years)				Gender			
	<10.13min		≥10.13min		<65		≥65		Male		Female	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Atenolol												
50mg	12	11.9 (31.6)	11	-4.0 (41.2)	19	7.5 (37.0)	4	-10.7 (35.1)	16	11.3 (40.9)	7	-11.8 (17.2)
100mg	6	22.7 (34.2)	7	-4.2 (29.5)	11	9.6 (36.4)	2	1.0 (4.2)	10	11.8 (36.6)	3	-3.6 (20.2)
Nebivolol												
5mg	14	5.5 (15.2)	8	10.8 (48.4)	22	7.4 (30.5)	0	NA	17	10.1 (33.9)	5	-1.8 (11.7)
10mg	13	-5.2 (15.3)	8	-16.0 (15.1)	19	-10.8 (15.8)	2	4.6 (6.5)	15	-7.8 (12.8)	6	-13.3 (22.7)
20mg	8	-14.8 (23.2)	16	-7.8 (32.9)	22	-10.8 (30.9)	2	-2.7 (11.7)	17	-5.6 (32.3)	7	-21.3 (19.9)

Data Source: Table 5.1

(Reproduced from Sponsor, Table 11.4.2.8.1-1, page 106)

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Table 146. Summary of Percent Change in Sub-Maximal Exercise Duration (min) from Baseline to End of Study by Subgroup at Trough (Baseline Sub-maximal Exercise Duration, Age, and Gender; ITT OC) (NEB-203)

	Race				BMI (kg/m²)*			
	Black		Non-Black		<30		≥30	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Atenolol								
50mg	4	3.8 (7.3)	19	4.4 (40.3)	14	11.0 (43.2)	9	-6.0 (21.1)
100mg	0	NA	13	8.2 (33.4)	8	6.9 (41.7)	5	10.4 (17.3)
Nebivolol								
5mg	4	10.2 (13.9)	18	6.8 (33.3)	13	7.2 (37.5)	9	7.7 (18.3)
10mg	3	-1.6 (25.3)	18	-10.6 (14.3)	12	-12.2 (14.1)	9	-5.5 (17.9)
20mg	3	-34.3 (25.6)	21	-6.7 (29.1)	15	-7.6 (34.0)	9	-14.4 (22.0)

Data Source: Table 5.1
*BMI is the baseline weight in kilograms divided by the square of the baseline height in meters

(Reproduced from Sponsor, Table 11.4.2.8.1-2, page 106)

Table 147. Summary of Change in Trough Sitting DBP (mm Hg) from Baseline to End of Study by Subgroup (Trough Sitting Diastolic Blood Pressure, Age, and Gender; ITT OC) (NEB-203)

	Baseline Trough Sitting Diastolic Blood Pressure (Median)				Age (Years)				Gender			
	<97mmHg		≥97mmHg		<65		≥65		Male		Female	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Atenolol												
50mg	9	-11.7 (9.9)	15	-15.4 (10.3)	19	-14.8 (10.3)	5	-10.8 (10.0)	17	-15.4 (11.3)	7	-10.6 (5.8)
100mg	4	-7.0 (5.0)	15	-9.7 (7.4)	16	-9.4 (7.3)	3	-7.3 (4.9)	15	-7.7 (4.0)	4	-14.3 (13.1)
Nebivolol												
5mg	6	-13.3 (7.5)	17	-7.5 (6.6)	22	-8.6 (7.1)	1	-17.0 (NA)	18	-8.4 (7.8)	5	-11.2 (3.8)
10mg	6	-12.5 (9.1)	17	-13.2 (5.9)	21	-13.3 (6.5)	2	-9.5 (10.6)	17	-13.3 (7.3)	6	-12.2 (5.0)
20mg	7	-11.0 (3.8)	17	-10.8 (7.8)	22	-10.9 (7.1)	2	-10.5 (2.1)	17	-11.7 (6.4)	7	-8.7 (7.6)

Data Source: Table 5.6

(Reproduced from Sponsor, Table 11.4.2.8.3-1, page 108)

Table 148. Summary of Change in Trough Sitting DBP from Baseline to End of Study by Subgroup (Trough Sitting Diastolic Blood Pressure, Age, and Gender; ITT OC) (NEB-203)

	Race				BMI (kg/m²)*			
	Black		Non-Black		<30		≥30	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Atenolol								
50mg	4	-11.5 (6.0)	20	-14.5 (10.8)	15	-15.3 (10.5)	9	-11.8 (9.7)
100mg	2	-18.5 (16.3)	17	-8.0 (5.0)	11	-10.6 (8.6)	8	-7.0 (3.3)
Nebivolol								
5mg	4	-11.0 (7.9)	19	-8.6 (7.2)	14	-8.9 (8.2)	9	-9.1 (5.7)
10mg	4	-12.0 (3.7)	19	-13.2 (7.2)	14	-12.4 (6.2)	9	-14.0 (7.6)
20mg	3	-5.7 (10.1)	21	-11.6 (6.2)	15	-10.1 (8.0)	9	-12.0 (4.2)

Data Source: Table 5.6
*BMI is the baseline weight in kilograms divided by the square of the baseline height in meters

(Reproduced from Sponsor, Table 11.4.2.8.3-2, page 108)

Response Rate by Subgroup (NEB-203)

Due to small numbers of patients in many of the subgroups, we cannot make any definitive statements about the following data in Table 149.

Table 149. Responder[a] Rates by Treatment and Baseline Characteristic at Day 28 (End of Study) (ITT LOCF) (NEB-203)

Characteristic Subgroup	Atenolol 50 mg n (%)[b]	Atenolol 100 mg n (%)[b]	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Total (%)[b]
Age Group						
< 65	14 (73.7)	8 (50.0)	11 (50.0)	19 (90.5)	17 (77.3)	69 (69.0)
≥ 65	5 (69.0)	2 (66.7)	1 (100.0)	1 (50.0)	2 (100.0)	9 (69.2)
Gender						
Male	12 (70.6)	7 (46.7)	9 (50.0)	14 (82.4)	14 (82.4)	56 (66.7)
Female	5 (71.4)	3 (75.0)	3 (60.0)	6 (100.0)	5 (71.4)	22 (75.9)
Race						
Black	3 (75.0)	1 (50.0)	3 (75.0)	4 (100.0)	2 (66.7)	13 (76.5)
Non-Black	14 (70.0)	9 (52.9)	9 (47.4)	16 (84.2)	17 (81.0)	65 (67.7)
Diabetes Status						
Yes	2 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	2 (100.0)	7 (100.0)
No	15 (68.2)	9 (50.0)	11 (50.0)	19 (86.4)	17 (77.3)	71 (67.0)
EM or PM Classification						
Poor	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	3 (60.0)
Extensive	16 (69.6)	10 (55.6)	11 (50.0)	19 (86.4)	19 (82.6)	75 (69.4)

(a) A subject is a responder if their average trough sitting diastolic blood pressure < 90 mmHg at end of study or has decreased by ≥ 10 mmHg from baseline
(b) Percentage is the percentage of responders within that category
Cross Reference: Data Listings 1, 11.1.1, 11.3.1, 11.5, and 16.3

(Reproduced from Sponsor, Table 2.12.5, page 331)

Although the sponsor performed post-hoc exploratory analyses in patients who maintained or increased their exercise capacity, these analyses were not prespecified in the protocol, and are of limited value. The overall interpretation of the exercise data in the nebivolol treatment groups did not change, even after excluding subjects in the atenolol 100 mg group.

Conclusions (NEB-203)

There were significant limitations regarding interpretation of the data in NEB-203, because 38% of the subjects in the atenolol 100 mg group did not complete the final sub-maximal ETT. There were also significant numbers of protocol violations, especially in the nebivolol 5 mg group (10/23 or 43.5%) regarding inappropriate workload used as a baseline in the initial submaximal ETT. Actual exercise duration is suspect, given the equations used to compare exercise duration between those groups which recorded exercise time in minutes alone and those groups which recorded exercise time in minutes and seconds. Nevertheless, from the data presented, nebivolol 5 mg increased exercise duration by 7.1%, and nebivolol 10 mg and 20 mg reduced exercise duration by 10.4% and 8.9%, respectively, at the end of the study. Atenolol 50 mg and 100 mg increased exercise duration by 3.7% and 9.2%, respectively. Atenolol appeared to inhibit increases in exercise heart rate and systolic blood pressure slightly better than nebivolol, although there was no statistical difference between pooled treatment groups. Both atenolol and nebivolol reduced trough sitting diastolic blood pressure, systolic blood pressure, and heart rate. At peak, atenolol significantly reduced supine diastolic blood pressure better than nebivolol ($p = 0.027$). Compared with nebivolol, atenolol significantly decreased peak A velocity at peak ($p = 0.030$) and decreased left ventricular end-systolic dimension at peak ($p = 0.009$).

11.5 NEB-321 (Pivotal) ("A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Nebivolol Added to Existing Antihypertensive Treatment in Patients with Mild to Moderate Hypertension")

Investigators

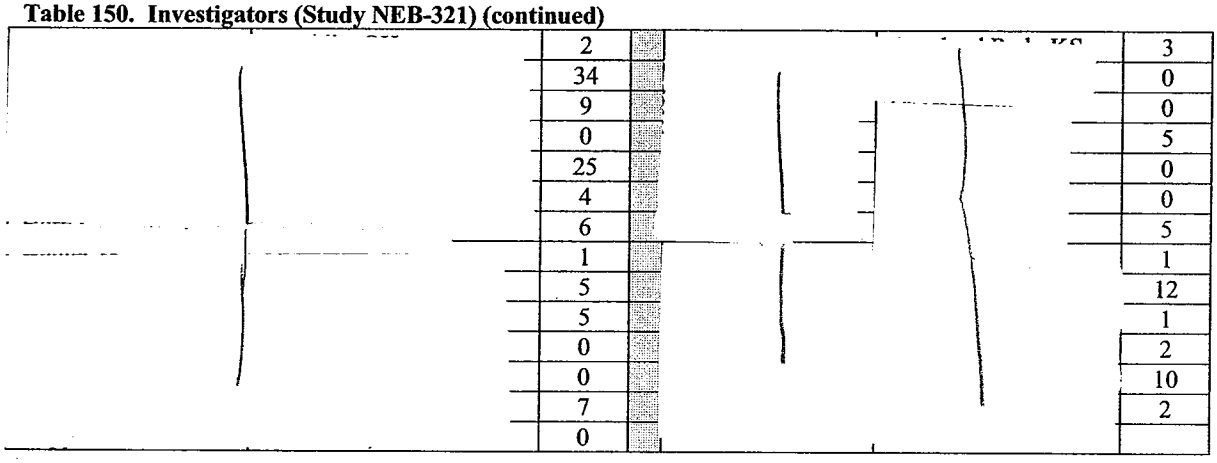
The 101 investigators are listed in Table 150 below. All 80 sites were in the US. Individual sites (n = 80) randomized between 0 and 46 patients.

Table 150. Investigators (Study NEB-321)

Investigator	Site	# Pts	Investigator	Site	# Pts
		2			27
		3			0
		25			2
		4			3
		13			8
		2			5
		0			9
		15			2
		2			25
		2			2
		2			5
		4			59
		2			4
		2			0
		1			3
		8			25
		0			3
		0			8
		3			0
		4			12
		6			9
		8			0
		5			46
		1			1
		1			11
		7			9
		2			3
		15			7
		0			0
		6			0
		3			10
		18			0
		6			11
		0			1
		1			12
		13			18
		4			0

(continued)

Table 150. Investigators (Study NEB-321) (continued)



2	3
34	0
9	0
0	5
25	0
4	0
6	5
1	1
5	12
5	1
0	2
0	10
7	2
0	

Study Dates
October 22, 2002 – October 18, 2003

Study Design
This study description was based upon the protocol dated July 19, 2002, an administrative change dated December 31, 2002,[34] and three amendments dated September 25, 2002,[35] April 4, 2003,[36] and July 2, 2003.[37]

This was a Phase III, double-blind, 12-week multi-center, randomized, placebo-controlled, parallel group study. The study had two phases. Phase I consisted of screening, followed by a 14 ± 3 day washout period of prior beta blockade, if necessary. Phase II consisted of baseline measurements, randomization, and double-blind treatment. Prior to randomization, patients underwent a medical history, physical examination, measurement of vital signs while supine, sitting, and standing, 12 lead ECGs, laboratory assessments, and genomics testing. Randomized to receive placebo or nebivolol 5, 10, or 20 mg once daily for 84 days, patients were stratified in all treatment arms by race, age, gender, diabetes status, metabolism of nebivolol, and use/non-use of an angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and diuretic. Following randomization on Day 1, there were three follow-up visits during Week 2 (14 ± 3 days), Week 6 (42 ± 5 days), and Week 12 (84 ± 7 days). The goal was to randomize 150 patients to each of the four treatment groups.

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[34] **Administrative Change 1, dated December 31, 2002, clarified the emergency unblinding procedure and asked the principal investigator to contact the unblinded independent TriaLine® staff to identify the study drug.**

[35] **Amendment 1, dated July 25, 2002, was applied to the original protocol dated July 19, 2002 prior to study initiation. The study began with this revised protocol on September 25, 2002. There was a "second" Amendment 1, dated July 25, 2002, which removed the Costa Rica site, allowed the use of particular antidepressants, clarified valid ambulatory blood pressure measurements, revised the screening period from 14-17 days to up to 17 days, and extended the safety follow-up period from 14 days to 30 days.**

[36] **Amendment 2, dated April 4, 2003, eliminated the use of ambulatory blood pressure monitoring at screening.**

[37] **Amendment 3, dated July 2, 2003, corrected the efficacy variable from DBP ≤ 90 mm Hg to DBP < 90 mm Hg.**

Patients took study drug between 7 a.m. and 10 a.m. each day with or without breakfast. On clinic days, study drug administration was deferred until the investigator obtained trough blood pressure and heart rate measurements. The investigator obtained three supine, sitting, and standing blood pressure and heart rate measurements at trough, which was 24 ± 3 hours after the previous morning's dose of study drug. The investigator measured trough vital signs during all 5 clinic visits and measured peak vital signs at baseline (days 0 and 1), Week 2, Week 6, and Week 12. Peak measurements were obtained 2-3 hours following dosing.

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

Inclusion Criteria for Study NEB-321 (Reproduced from Sponsor, page 28)[38]

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

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

In regards to prohibited medications, the list for NEB-321 was similar to the list for NEB-302, except ACE-I, ARBs, and diuretics were allowed. Compared to NEB-302, systemic steroids were not prohibited in NEB-321. Restricted medications in studies NEB-302 and NEB-321 were similar.

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

The primary analysis was intention-to-treat (ITT) with the last observation carried forward. A secondary population for efficacy analysis was the Per-Protocol (PP) population. The primary statistical method of treatment comparison was analysis of Covariance (ANCOVA) with factor treatment and covariates metabolism of nebivolol, diabetes status, ethnicity, age, gender, and use/non-use of ACEI, ARB, and diuretic. The sponsor used observed case and worst case analyses for the primary efficacy endpoint. Hochberg's step-up procedure was also used for

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

paired comparisons between treatment groups. For response rates, the sponsor used logistic regression analysis.

Secondary Endpoints in NEB-321 (Reproduced from Sponsor, page 43)

- change from baseline to Week 2 (Day 14) and Week 6 (Day 42) in the average sitting DBP taken at trough (24 ± 3 hours post-previous morning's dose of study drug), measured in the office using a sphygmomanometer
- change from baseline to Week 2 (Day 14), 6 (Day 42), and 12 (Day 84) in the average sitting systolic blood pressure (SBP) taken at trough (24 ± 3 hours post-previous morning's dose of study drug), measured in the office using a sphygmomanometer
- change of the average sitting SBP and average sitting DBP taken at peak (2 to 3 hours post-dose) at end of treatment (Week 12 [Day 84]) compared to baseline
- change from baseline to Week 12 (Day 84) in the average supine SBP and DBP taken at trough (24 ± 3 hours post-previous morning's dose of study drug), measured in the office using a sphygmomanometer. The change from baseline to Week 2 (Day 14) and Week 6 (Day 42) was also summarized
- change from baseline to Week 12 (Day 84) in the average supine SBP and DBP taken at peak (2 to 3 hours post-dose of study drug), measured in the office using a sphygmomanometer. The change from baseline to Week 2 (Day 14) and Week 6 (Day 42) was also summarized
- change from baseline to Week 12 (Day 84) in the average standing SBP and DBP taken at trough (24 ± 3 hours post-previous morning's dose of study drug), measured in the office using a sphygmomanometer
- change from baseline to Week 12 (Day 84) in the average standing SBP and DBP taken at peak (2 to 3 hours post-dose), measured in the office using a sphygmomanometer
- change from baseline to Week 12 (Day 84) in mean 24-hour SBP and DBP as measured by 24-hour ABPM
- change from baseline in trough sitting HR at Week 12 (Day 84)
- percent of patients with a reduction in sitting DBP to < 90 mm Hg or a reduction of at least 10 mm Hg from baseline at Week 12 (Day 84)

Investigators reported all serious adverse events t[redacted] within 24 hours.

Results (NEB-321)

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

Sites 652 and 721 had potential GCP guidelines violations. Either [redacted] or Bertek communicated with the FDA on September 26, 2003 regarding Site 652 (Niranjan Lal, M.D.).

Data from these sites were analyzed as described above. In Dr. Lal's case, his medical license had been suspended. Dr. Lal enrolled two patients in NEB-321. One patient, 6523210003, was discontinued from the study on January 9, 2003. Patient, 6523210002 completed the study on March 14, 2003. A monitoring and close-out visit was conducted at Dr. Lal's site on July 17, 2003. Dr. Lal's medical license was reinstated on September 17, 2003, and Kendle petitioned Bertek Pharmaceuticals to permit Dr. Lal to forward his study documentation. Bertek allowed Dr. Lal to forward all study related information. At Site 721, Dr. Selvaraj suffered a cerebrovascular accident. Many of the study responsibilities were transferred to the study coordinator. Six patients (7213210005, 7213210009, 7213210010, 7213210012, 7213210013, and 7213210014) completed the study after Dr. Selvaraj's cerebrovascular accident. On August 17, 2003, Dr. Selvaraj received permission from his neurologist to return to work. Dr. Selvaraj completed all outstanding work regarding NEB-321 and forwarded all results to the sponsor.

The demographic and baseline characteristics for patients in the ITT Population are shown in Table 151.

Table 151. Demographic and Baseline Characteristics of Subjects (Study NEB-321)

Variable	Placebo (N=167)	Nebivolol 5 mg (N=168)	Nebivolol 10 mg (N=168)	Nebivolol 20 mg (N=166)	Total (N=669)	p-value
Age (years)						
N	167	168	168	166	669	0.467 (a)
Mean (Standard Deviation)	54.3 (9.83)	53.5 (10.92)	54.0 (10.59)	52.6 (10.82)	53.6 (10.54)	
Median	54.0	54.0	54.0	52.0	53.0	
Range (Min, Max)	(25.0, 78.0)	(19.0, 80.0)	(26.0, 86.0)	(24.0, 76.0)	(19.0, 86.0)	
< 65	148 (83.8%)	142 (84.5%)	143 (85.1%)	141 (84.9%)	566 (84.6%)	
≥ 65	27 (16.2%)	26 (15.5%)	25 (14.9%)	25 (15.1%)	103 (15.4%)	
Gender						
Male	91 (54.5%)	94 (56.0%)	92 (54.8%)	91 (54.8%)	368 (55.0%)	0.994 (b)
Female	76 (45.5%)	74 (44.0%)	76 (45.2%)	75 (45.2%)	301 (45.0%)	
Race						
Black	48 (28.7%)	50 (29.8%)	51 (30.4%)	48 (28.9%)	197 (29.4%)	0.987 9b)
Non-Black	119 (71.3%)	118 (70.2%)	117 (69.6%)	118 (71.1%)	472 (70.6%)	
Diabetes Status						
Yes	26 (15.6%)	24 (14.3%)	22 (13.1%)	22 (13.3%)	94 (14.1%)	0.910 (b)
No	141 (84.4%)	144 (85.7%)	146 (86.9%)	144 (86.7%)	575 (85.9%)	
Metabolism of Nebivolol						
Poor	9 (5.4%)	10 (6.0%)	9 (5.4%)	8 (4.8%)	36 (5.4%)	0.972 (b)
Extensive	153 (91.6%)	154 (91.7%)	155 (92.3%)	156 (94.0%)	618 (92.4%)	
Missing	5 (3.0%)	4 (2.4%)	4 (2.4%)	2 (1.2%)	15 (2.2%)	
Use of ACE Inhibitor						
Use	82 (49.1%)	84 (50.0%)	82 (48.8%)	82 (49.4%)	330 (49.3%)	0.997 (b)
No Use	85 (50.9%)	84 (50.0%)	86 (51.2%)	84 (50.6%)	339 (50.7%)	

Variable	Placebo (N=167)	Nebivolol 5 mg (N=168)	Nebivolol 10 mg (N=168)	Nebivolol 20 mg (N=166)	Total (N=669)	p-value
Use of Angiotensin Receptor Blocker						
Use	58 (34.7%)	52 (31.0%)	54 (32.1%)	51 (30.7%)	215 (32.1%)	0.855 (b)
No Use	109 (65.3%)	116 (69.0%)	114 (67.9%)	115 (69.3%)	454 (67.9%)	
Use of Diuretic						
Use	72 (43.1%)	72 (42.9%)	77 (45.8%)	72 (43.4%)	293 (43.8%)	0.943 (b)
No Use	95 (56.9%)	96 (57.1%)	91 (54.2%)	94 (56.6%)	376 (56.2%)	
Combined ACEI and ARB Use	0 (0.0%)	2 (1.2%)	0 (0.0%)	1 (0.6%)	3 (0.4%)	0.299 (b)
Combined ACEI and Diuretic Use	23 (13.8%)	22 (13.1%)	25 (14.9%)	19 (11.4%)	89 (13.3%)	0.826 (b)
Combined ARB and Diuretic Use	22 (13.2%)	17 (10.1%)	23 (13.7%)	22 (13.3%)	84 (12.6%)	0.744 (b)
No ACEI, ARB, or Diuretic Use	0 (0.0%)	1 (0.6%)	3 (1.8%)	3 (1.8%)	7 (1.0%)	0.271 (b)
Sitting Diastolic Blood Pressure (Baseline) (Day 1)						
Trough						
N	167	168	168	166		0.594
Mean (SD)	96.4 (4.57)	96.4 (4.55)	95.8 (5.07)	96.5 (5.22)		
Peak						
N	167	168	168	166		0.147
Mean	89.2 (7.54)	89.3 (7.86)	87.7 (8.60)	87.9 (8.27)		
Sitting Systolic Blood Pressure (Baseline) (Day 1)						
Trough						
N	167	168	168	166		0.281
Mean (SD)	146.5 (13.95)	147.4 (13.44)	145.3 (14.26)	144.8 (13.16)		
Peak						
N	167	168	168	166		0.005
Mean	140.4 (15.05)	138.5 (14.12)	137.0 (15.03)	135.0 (13.70)		
Sitting Heart Rate (Baseline) (Day 1)						
Trough						
N	167	168	168	166		0.977
Mean	74.5 (9.93)	74.3 (8.94)	74.6 (8.36)	74.2 (8.39)		
Peak						
N	167	168	168	166		< 0.001
Mean	74.1 (9.66)	72.0 (8.57)	71.3 (7.79)	68.9 (8.11)		

Missing values not used in p-value computations
(a) From ANOVA with treatment as factor
(b) From Chi-square Test

(Reproduced from Sponsor, Table 4 and Table 6.2, pages 122, 123, 133, and 134)

Subject disposition is shown in Table 152.

Table 152. Patient Disposition (ITT Population) in Study NEB-321

	Placebo (N=167)	Nebivolol 5 mg (N=168)	Nebivolol 10 mg (N=168)	Nebivolol 20 mg (N=166)	All (N=669)
Completed Study	146 (87.4%)	152 (90.5%)	150 (89.3%)	150 (90.4%)	598 (89.4%)
Early Termination	21 (12.6%)	16 (9.5%)	18 (10.7%)	16 (9.6%)	71 (10.6%)
Primary Reason for Discontinuation					
Adverse Event	4 (2.4%)	9 (5.4%)	5 (3.0%)	7 (4.2%)	25 (3.7%)
Treatment Failure	3 (1.8%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	5 (0.7%)
Lost to Follow-up	4 (2.4%)	0 (0.0%)	5 (3.0%)	1 (0.6%)	10 (1.5%)
Protocol Deviation	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)	2 (0.3%)
Withdrew Consent	10 (6.0%)	7 (4.2%)	7 (4.2%)	3 (1.8%)	27 (4.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	2 (0.3%)

Four patient whose primary reason for withdrawal was reported as Withdrew Consent also cited adverse event as a primary reason for withdrawal but were only classified into adverse event as their primary reason for discontinuation

(Reproduced from Sponsor, Table 3, page 121)

From baseline to Week 6, compliance > 90% ranged from 84.5% to 88.6% in the nebivolol treatment groups, compared with 82.0% in the placebo group. From Week 6 to Week 12, compliance > 90% ranged from 82.5% to 86.9% in the nebivolol treatment groups, compared with 79.0% in the placebo group.

Primary Efficacy Endpoint (NEB-321)

All nebivolol doses significantly reduced sitting trough diastolic blood pressure in a dose-dependent fashion from baseline to end of study, as shown in Table 153.

Table 153. Change from Baseline to Week 12 in Sitting DBP at Trough (ITT LOCF) (NEB-321)

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

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

[c] LS mean difference from pairwise comparison of nebivolol treatment vs. placebo.
(Reproduced from Sponsor, Table 11-1, page 58)

Secondary Efficacy Endpoints (NEB-321)

Sitting Systolic Blood Pressure at Trough

At end of study, all nebivolol doses significantly reduced sitting systolic blood pressure at trough, as shown in Table 154.

Table 154. Change from Baseline to Week 12 in Sitting SBP at Trough (ITT LOCF) (NEB-321)

Treatment	N	Treatment Mean (SD) (mm Hg)	Mean Change from Baseline (SD)	LS Mean Change from Baseline (SE)[a]	Hochberg's Adjusted p-value[a,b]	LS mean Difference (95% CI)[a,c]
Placebo						
Baseline	167	146.5 (13.95)	-	-	-	-
Week 12		143.9 (16.26)	-2.6 (13.12)	-0.1 (1.71)	-	-
Nebivolol						
5 mg						
Baseline	168	147.4 (13.44)	-	-	-	-
Week 12		139.2 (17.37)	-8.2 (13.68)	-5.7 (1.71)	$p < 0.001$	-5.7 (-8.6, -2.7)
10 mg						
Baseline	168	145.3 (14.26)				
Week 12		139.3 (17.48)	-6.0 (15.95)	-3.7 (1.71)	$p = 0.015$	-3.7 (-6.6, -0.7)
20 mg						
Baseline	166	144.8 (13.16)	-	-	-	-
Week 12		136.2 (17.27)	-8.6 (15.24)	-6.3 (1.72)	$p < 0.001$	-6.2 (-9.2, -3.3)

Source: Table 10.1.
Baseline=Last value prior to dosing on Day 1. SD=Standard Deviation. SE=Standard Error.
[a] From an ANCOVA model with treatment, race, age, gender, diabetes status, nebivolol metabolism, use of ACE inhibitors, use of ARBs, use of diuretics as factors, and baseline measurement as a covariate.
[b] Level of significance: $p \leq 0.05$; p-values obtained from the pairwise comparisons between each of the 3 nebivolol dose groups and placebo were placed in ascending order and adjusted as described in Section 9.7.1.3.1.
[c] LS mean difference from pairwise comparison of nebivolol treatment vs. placebo.
(Reproduced from Sponsor, Table 11-4, page 63)

Other Secondary Efficacy Endpoints (NEB-321)

Nebivolol was statistically significant for all secondary efficacy endpoints except nebivolol 10 mg did not significantly reduce standing and supine systolic blood pressure at trough from baseline to end of study ($p = 0.176$ for standing and $p = 0.055$ for supine). In Tables 144 and 145, I compiled a summary of results for all primary and secondary endpoints.

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Table 155. Summary of Results of LS Mean Change in DBP, SBP, and HR from Baseline to End of Study (Day 84) at Trough (ITT LOCF) (NEB-321)

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

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

p-value is Hochberg's adjusted p-value

(Compiled by Hicks K)

Table 156. Summary of Results of LS Mean Change in DBP, SBP, and HR from Baseline to End of Study (Day 84) at Peak (ITT LOCF) (NEB-321)

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

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

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

In the ITT OC Population, all doses of nebivolol significantly reduced diastolic blood pressure by ambulatory blood pressure monitoring, as seen in Table 157 ($p \leq 0.003$). Additionally, all doses of nebivolol significantly reduced heart rate measured by ABPM ($p < 0.001$). Reductions in heart rate were dose-dependent.

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Table 157. Change from Baseline to Week 12 in DBP by ABPM (ITT OC)

Treatment	N	24-hour BP (mmHg)	Morning BP While Awake (mmHg)	Evening BP While Awake (mmHg)	BP While Asleep (mmHg)
Placebo					
Baseline (Mean [SD])	167	87.7 (9.71)	94.0 (9.69)	89.9 (11.33)	76.6 (11.65)
Week 12 (Mean [SD])		86.2 (9.23)	91.7 (10.27)	88.4 (10.33)	75.9 (10.80)
Mean Change from Baseline (SD)		-1.4 (6.57)	-3.2 (8.47)	-2.0 (7.71)	-0.7 (8.49)
LS Mean Change from Baseline (SE)[a]		-0.9 (0.90)	-3.5 (1.33)	-1.3 (1.39)	0.8 (1.34)
Nebivolol 5 mg					
Baseline (Mean [SD])	168	87.7 (9.34)	93.3 (9.18)	89.2 (10.78)	76.2 (10.77)
Week 12(Mean [SD])		81.1 (9.04)	86.6 (10.06)	81.9 (10.27)	71.7 (10.44)
Mean Change from Baseline (SD)		-6.2 (6.80)	-6.2 (8.03)	-7.5 (8.88)	-4.1 (7.88)
LS Mean Change from Baseline (SE)[a]		-5.8 (0.89)	-7.3 (1.34)	-7.3 (1.40)	-3.2 (1.35)
Hochberg's adjusted p-value		p< 0.001	p= 0.003	p< 0.001	p= 0.001
LS Mean Difference (95% CI)[a,c]		-5.0 (-6.5, -3.4)	-3.8 (-6.0, -1.6)	-6.0 (-8.3, -3.6)	-4.0 (-6.2, -1.7)
Nebivolol 10 mg					
Baseline (Mean [SD])	168	87.1 (9.54)	93.1 (9.89)	89.0 (11.07)	76.4 (10.94)
Week 12(Mean [SD])		80.1 (10.56)	87.1 (11.28)	82.0 (11.42)	71.8 (12.53)
Mean Change from Baseline (SD)		-6.1 (8.16)	-5.6 (9.45)	-6.6 (10.67)	-3.9 (10.68)
LS Mean Change from Baseline (SE)[a]		-5.7 (0.92)	-6.1 (1.40)	-5.9 (1.46)	-1.9 (1.41)
Hochberg's adjusted p-value		p< 0.001	p= 0.030	p< 0.001	p= 0.022
LS Mean Difference (95% CI)[a,c]		-4.8 (-6.4, -3.2)	-2.5 (-4.8, -0.2)	-4.6 (-7.0, -2.2)	-2.7 (-5.0, -0.4)
Nebivolol 20 mg					
Baseline (Mean [SD])	166	87.4 (8.87)	92.9 (8.99)	89.7 (9.91)	76.6 (10.92)
Week 12 (Mean [SD])		80.6 (9.61)	86.7 (10.74)	81.8 (10.54)	71.4 (10.80)
Mean Change from Baseline (SD)		-6.9 (7.34)	-6.2 (8.66)	-8.1 (9.65)	-5.9 (9.11)
LS Mean Change from Baseline (SE)[a]		-6.3 (0.92)	-7.1 (1.34)	-7.4 (1.40)	-4.2 (1.35)
Hochberg's adjusted p-value		p< 0.001	p= 0.003	p< 0.001	p< 0.001
LS Mean Difference (95% CI)[a,c]		-5.4 (-7.0, -3.8)	-3.5 (-5.7, -1.4)	-6.0 (-8.3, -3.7)	-5.0 (-7.2, -2.9)

Source: Tables 26.1-26.4.
[a]From an ANCOVA model with treatment, race, age, gender, diabetes status, nebivolol metabolism, use of ACE inhibitors, use of ARBs, and use of diuretics as factors, and baseline measurement as a covariate.
[b]Level of significance: $p \leq 0.05$; p-values obtained from the pairwise comparisons between each of the 3 nebivolol dose groups and placebo were placed in ascending order and adjusted as described in Section 9.7.1.3.1.
[c]LS mean difference from pairwise comparison of nebivolol treatment vs. placebo

(Reproduced from Sponsor, Table 11-16, page 82)

Response Rate (NEB-321)

The response rate was dose-dependent and ranged from 53.0% to 65.1% in the nebivolol treatment groups, as shown in Table 158.

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Table 158. Percent of Patients with a Reduction in Sitting Diastolic Blood pressure to < 90 mm Hg at Day 84 or a Reduction of at least 10 mm hg from Baseline to Day 84 ITT Population, Last Observation Carried Forward (NEB-321)

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

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

(Reproduced from Sponsor, Table 28.1, page 267)

Subgroups

For the primary efficacy endpoint, there was no significant treatment interaction by gender, age, race, race adjusting for BMI, diabetes status, nebivolol metabolism, use of ACE inhibitor, use of ARB, and use of diuretic.

Interaction by Site

There was no significant interaction by study site for the primary efficacy endpoint.

Trough to Peak Ratios (NEB-321)

Using placebo-subtracted LS mean changes from baseline, ratios for sitting DBP reduction were 1.046, 0.884, and 1.078 for nebivolol 5 mg, 10 mg, and 20 mg, respectively. For sitting SBP reduction, placebo-subtracted LS mean changes from baseline were 0.993, 0.654, and 1.055 for nebivolol 5 mg, 10 mg, and 20 mg, respectively.

Summary (NEB-321)

Compared to placebo, nebivolol 5, 10, and 20 mg doses significantly reduced trough sitting DBP and SBP in patients on background antihypertensive therapy. Nebivolol 10 mg did not significantly reduce supine and standing SBP at trough. Using placebo-subtracted LS mean changes, ratios for sitting SBP reduction were lower than for DBP reduction. Some patients may require twice daily dosing of nebivolol.

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11.6 NEB-306 (Pivotal) ("A Multicenter, Parallel Group Extension Study to Determine the Safety and Efficacy of Long-Term Nebivolol Exposure in Patients With Mild to Moderate Hypertension (Final Report)")

Investigators

The 115 investigators are listed in Table 159 below. The sites were in the US, United Kingdom, the Netherlands, and Belgium. Individual sites (n=115) randomized between 0 and 38 patients in the extension phase and between 0 and 8 patients in the follow-up phase.

Table 159. Investigators (Study NEB-306)

Investigator	Site	# Patients		Investigator	Site	# Patients	
		Extension Phase	Follow-up Phase			Extension Phase	Follow-up Phase
		4	0			3	0
		11	0			1	0
		7	0			3	0
		18	0			3	0
		8	0			6	0
		2	0			5	3
		0	0			1	0
		9	0			1	0
		1	0			5	0
		4	0			4	0
		9	0			15	0
		4	0			6	0
		5	0			1	0
		1	0			10	1
		9	0			2	0
		4	0			9	0
		5	0			7	0
		4	0			1	0
		15	0			3	0
		8	0			24	0
		25	3			3	0
		4	0			5	2
		5	0			1	0
		8	0			12	0
		1	0			4	0
		12	0			38	0
		4	0			38	0
		5	0			5	0
		8	0			5	0
		15	0			5	0
		26	0			5	0

Investigator	Site	# Patients		Investigator	Site	# Patients	
		Extension Phase	Follow-up Phase			Extension Phase	Follow-up Phase
		28	0			18	0
		24	0			10	0
		1	0			7	0
		2	0			4	0
		15	2			6	0
		7	0			12	0
		8	0			3	0
		11	0			4	1
		7	1			2	?
		3	0			6	0
		1	0			2	0
		17	0			12	0
		18	0			6	1
		15	0			2	0
		2	0			5	0
		4	0			1	0
		13	0			13	0
		5	0			3	0
		2	0			6	0
		3	1			10	8
		8	0			5	0
		2	0			3	0
		7	0			11	2
		18	0			28	3
		2	0			3	0
		3	0			1	0
		8	0			1	0
		2	0				

Study Dates
March 8, 2002 – September 25, 2003

Study Design
The study description was based upon the protocol dated November 12, 2001 and Amendment 1 dated March 4, 2003.[39]

This was a Phase III double-blind, multicenter, parallel group, 9-month extension study with an optional 4 week randomized withdrawal phase. In response to discussions with the FDA on October 9, 2002,[40] Mylan added the 4 week follow-up phase to assess rebound effects from the abrupt withdrawal of nebivolol. The 9-month extension study did not include a control group. Only the 4 week follow-up phase was double-blind and placebo-controlled, and patients were randomized in a 2:1 fashion to placebo or nebivolol 5, 10, or 20 mg.

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

An overview of the study is shown in Figure 20.

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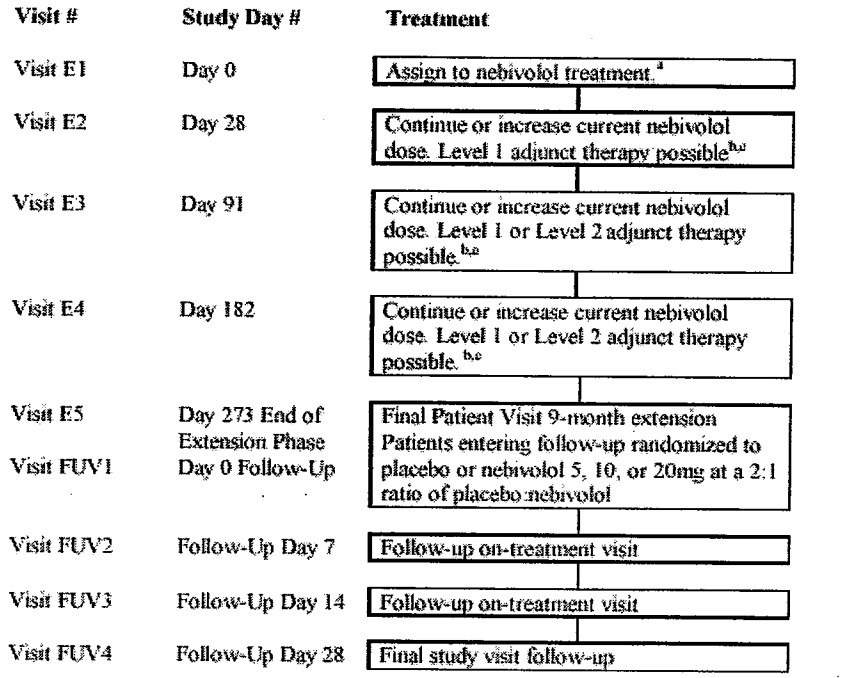
[39] **The first amendment allowed patients to also use open-label amlodipine 5 or 10 mg. Prior to Amendment 1, in the double blind randomization phase, patients received either nebivolol monotherapy (5, 10, or 20 mg) or nebivolol (5, 10, or 20 mg) in conjunction with Level 1 and 2 adjunct therapies consisting of open-label thiazide/thiazide-like diuretic or thiazide/thiazide-like diuretic with triamterene, respectively. After the approval of Amendment 1, patients received either nebivolol monotherapy (5, 10, or 20 mg) or nebivolol (5, 10, or 20 mg) in conjunction with Level 1 and 2 adjunct therapies consisting of open-label amlodipine 5 or 10 mg, respectively. The first amendment allowed for the 4-week follow-up phase. NEB-306 concluded early to include this data in the NDA 21,742 dossier. Patients were allowed to continue nebivolol in NEB-323, a long-term, open-label study. Amendment 1 used the same definition for a responder as NEB-202, NEB-302, and NEB-305 and added descriptive summaries by race.**

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

Figure 20. Study Design (NEB-306)



[a] Nebivolol dose based on average sitting heart rate and DBP and dose in previous study.
[b] Prior to Amendment 1, Level 1 and 2 adjunct therapies were thiazide or thiazide-like diuretic and thiazide or thiazide-like diuretic with triamterene, respectively; after Amendment 1, Level 1 and 2 adjunct therapies were amlodipine 5 and 10mg, respectively.
[c] Nebivolol dose and addition of Level 1 or 2 adjunct therapy based on average sitting heart rate and DBP and dose assigned at previous study visit.

(Reproduced from Sponsor, Figure 9.1-1, page 31)

In the 9-month extension phase, patients received one of four possible treatments based on the average sitting heart rate and diastolic blood pressure measured at the study visit and the therapy they were already receiving. After the investigator recorded this data in the TeleTrial® system, Teletrial® instructed the investigator to assign adjunct therapy, if necessary, according to the detailed algorithm shown in Table 160.

The four possible treatments were

- nebivolol once daily monotherapy (5 mg, 10 mg, or 20 mg)
- nebivolol once daily (5 mg, 10 mg, or 20 mg) plus Level 1 adjunct therapy
- nebivolol once daily (5 mg, 10 mg, or 20 mg) plus Level 2 adjunct therapy
- nebivolol once daily (5 mg, 10 mg, or 20 mg) plus another antihypertensive medication ("other")[41]

[41] **The "other" category consisted of patients receiving nebivolol in conjunction with an antihypertensive in a different class other than a diuretic or calcium channel blocker. Similarly, patients in the "other" category could also be on nebivolol plus adjunct therapy in addition to an additional antihypertensive medication which could be a diuretic, calcium channel blocker or other type of antihypertensive.**

Table 160. Study Medication Administered: Algorithm for Assignment of Nebivolol Study Medication and Adjunctive Therapy During the 9-Month Extension Phase (NEB-306)

	Study Medications at Previous Clinic Visit	Diastolic BP <90mmHg		Diastolic BP ≥90mmHg	
		HR ≥55BPM	HR <55BPM	HR ≥55BPM	HR <55BPM
Visit E1 (Study Day 0)	Placebo	Neb 5mg	Ineligible	Neb 5mg	Ineligible
	Neb 1.25mg	Neb 5mg	Ineligible	Neb 5mg	Ineligible
	Neb 2.5mg	Neb 5mg	Ineligible	Neb 5mg	Ineligible
	Neb 5mg	Neb 5mg	Neb 5mg	Neb 10mg	Neb 5mg
	Neb 10mg	Neb 10mg	Neb 5mg	Neb 20mg	Neb 5mg
	Neb 20mg	Neb 20mg	Neb 10mg	Neb 10mg	Neb 10mg
	Neb 30/40mg	Neb 30mg	Neb 10mg	Neb 200mg	Neb 20mg
Visit E2 (Study Day 28)	Neb 5mg	Neb 5mg	Neb 5mg	Neb 10mg	Neb 5mg + Level 1[a]
	Neb 10mg	Neb 10mg	Neb 10mg	Neb 20mg	Neb 5mg + Level 1[a]
	Neb 20mg	Neb 20mg	Neb 20mg	Neb 10mg	Neb 10mg
Visit E3 (Study Day 91)	Neb 5mg	Neb 5mg	Neb 5mg	Neb 10mg	Neb 5mg + Level 1[a]
	Neb 5mg + Level 1[a]	Neb 5mg + Level 1[a]	Neb 5mg + Level 1[a]	Neb 5mg + Level 1[a]	Neb 5mg + Level 2[b]
	Neb 10mg	Neb 10mg	Neb 5mg	Neb 10mg + Level 1[a]	Neb 5mg + Level 1[a]
	Neb 20mg	Neb 20mg	Neb 10mg	Neb 20mg + Level 1[a]	Neb 10mg + Level 1[a]
Visit E4 (Study Day 182)	Neb 5mg	Neb 5mg	Neb 5mg	Neb 5mg + Level 1[a]	Neb 5mg + Level 1[a]
	Neb 5mg + Level 1[a]	Neb 5mg + Level 1[a]	Neb 5mg + Level 1[a]	Neb 5mg + Level 2[b]	Neb 5mg + Level 2[b]
	Neb 5mg + Level 2[b]	Neb 5mg + Level 2[b]	Neb 5mg + Level 2[b]	Neb 10mg + Level 2[b]	Neb 5mg + Level 2[b]
	Neb 10mg	Neb 10mg	Neb 10mg	Neb 10mg+ Level 1[a]	Neb 5mg + Level 1[a]
	Neb 10mg + Level 1[a]	Neb 10mg + Level 1[a]	Neb 10mg + Level 1[a]	Neb 10mg + Level 2[b]	Neb 5mg + Level 2[b]
	Neb 20mg	Neb 20mg	Neb 20mg	Neb 20mg+ Level 1[a]	Neb 10mg+ Level 1[a]
	Neb 20mg + Level 1[a]	Neb 20mg + Level 1[a]	Neb 20mg + Level 1[a]	Neb 20mg + Level 2[b]	Neb 10mg + Level 2[b]
Visit E5 (Study Day 273)	Neb 5mg	End of Treatment 9-month Extension Phase	End of Treatment 9-month Extension Phase	End of Treatment 9-month Extension Phase	End of Treatment 9-month Extension Phase
	Neb 5mg + Level 1[a]				
	Neb 5mg + Level 2[b]				
	Neb 10mg				
	Neb 10mg + Level 1[a]				
	Neb 10mg + Level 2[b]				
	Neb 20mg				
	Neb 20mg + Level 1[a]				
	Neb 20mg + Level 2[b]				

[a] thiazide/thiazide-like diuretic without triamterene (original Protocol) and amlodipine 5mg (after Amendment 1)
[b] thiazide/thiazide-like diuretic with triamterene(original Protocol) and amlodipine 10mg (after Amendment 1).
Note: BP = blood pressure; HR = heart rate; Neb = nebivolol

(Reproduced from Sponsor, Table 9.4.1-1, page 37)

The study permitted titration of nebivolol during Visit E2 through E4. At study Visit E2 and study Visits E3 and E4, Level 1 and Level 2 adjunct therapy was allowed, respectively. As shown in Table 161, adjunctive therapy consisted of the open-label use of the following medications:

Table 161. Adjunctive Therapy (NEB-306)

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

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

Based on the diastolic blood pressure-heart rate algorithm, Teletrial® assigned the patient's nebivolol dose. Although the investigators and patients knew patients were receiving nebivolol, they were blinded to the actual dose. Two patients were unblinded during NEB-306. One patient was unblinded after he experienced the adverse events of bronchitis, drowsiness, nausea, and stopped transpiration on October 23, 2002. The other patient was unblinded on the last day of the study, because he strongly insisted on being continued on the same nebivolol dose.

There were five study visits in the Extension Phase and four follow-up visits in the randomized withdrawal phase. Investigators measured trough supine, sitting, and standing blood pressure and heart rate at Visits E1 through E4 and at follow-up visits 2 through 4. At Visits E1, E3, E4, and E5, investigators measured peak supine, sitting, and standing blood pressure and heart rate.

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

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

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

Prohibited medications in NEB-306 were similar to those in NEB-302, except the previously described adjunctive medications were allowed.

Restricted medications in NEB-306 were similar to those described in NEB-302, with the following exceptions:

- NEB-306 prohibited antihistamine use within 24 hours of clinic visits, compared to NEB-302 which prohibited antihistamine use within 3 days of Visits 3 and 7.
- NEB-306 did not allow NSAID use exceeding a total of 2 days within 2 weeks prior to Study Day 273. NEB-302 did not permit NSAID use exceeding 5 consecutive days or within 3 days prior to Visits 3 and 7.

As stated on page 57 of the protocol, major protocol violations in NEB-306 included

- lack of informed consent
- baseline protocol violations in the feeder study
- presence of exclusion criterion
- trough blood pressure measurements taken < 22 or > 28 hours post-dosing at last visit
- peak blood pressure measurements taken < 2 or > 3 hours post-dosing at last visit
- prohibited concomitant medication (defined as medication received 14 days prior to first dose and any time after the first dose in NEB-306)
- receipt of incorrect treatment or non-receipt of an assigned bottle

The objectives of NEB-306 were to determine the long-term efficacy and safety profile of nebivolol for the treatment of elevated blood pressure in patients with mild to moderate hypertension.

The primary efficacy endpoint was the change in average sitting diastolic blood pressure taken at trough drug effect (approximately 24 ± 2 hours post previous morning's dose) at end of treatment compared to baseline of NEB-202, NEB-302, or NEB-305.

Because the population in NEB-306 was self-selected, the sponsor did not perform formal statistical analyses. The primary population for analysis was intention-to-treat, observed cases. The secondary population for analysis was intention-to-treat, last observation carried forward, and the Per-Protocol (PP) Population.

As reproduced from the sponsor on page 49, secondary efficacy endpoints for NEB-306 include the following parameters:

- the change of the average sitting SBP taken at trough drug effect (approximately 24 ± 2 hours post-previous morning's dose) at end of treatment compared to baseline of NEB-202, NEB-302, or NEB-305
- the change of the average sitting SBP and DBP taken at peak drug effect (approximately 2-3 hours post-dose) at end of treatment compared to baseline of NEB-202, NEB-302, or NEB-305
- the change of the average supine SBP and DBP taken at trough drug effect (approximately 24 ± 2 hours post-previous morning's dose) at end of treatment compared to baseline of NEB-202, NEB-302, or NEB-305
- the change of the average supine SBP and DBP taken at peak drug effect (approximately 2-3 hours post-dose) at end of treatment compared to baseline of NEB-202, NEB-302, or NEB-305)
- the change of the average standing SBP and DBP taken at trough drug effect (approximately 24 ± 2 hours post-previous morning's dose) at end of treatment compared to baseline of NEB-202, NEB-302, or NEB-305
- the change of the average standing SBP and DBP taken at peak drug effect (approximately 2-3 hours post-dose) at end of treatment compared to baseline of NEB-202, NEB-302, or NEB-305
- the response rates of treatment groups. A responder was defined in 2 ways: (1) a patient whose sitting DBP (trough) at end of study was < 90 mm Hg, or had decreased by ≥ 10 mm Hg from baseline (baseline of NEB-202, NEB-302, and NEB-305) to end of study or (2) a patient whose average sitting DBP (trough) at end of extension phase was < 90 mm Hg. To be consistent with NEB-202, NEB-302, and NEB-305, the primary definition was the former.
- effect of nebivolol over time. Blood pressure parameters and percent of responders were plotted over time.
- Incidence of patients who received rescue medication for elevated blood pressure. If a patient was prescribed 2 adjunct medications concurrently, the second adjunct medication was considered a rescue medication.

Investigators reported serious adverse events to [redacted] within 24 hours of the investigator's first knowledge of the event.

Results (NEB-306)

Out of 2,016 ITT patients from the feeder studies, 845 patients entered the 9-month extension phase. NEB-302, NEB-305, and NEB-202 enrolled 129, 366, and 350 patients, respectively. By the end of the extension phase or at early termination, there were 607, 206, 21, and 11 patients receiving nebivolol, nebivolol + diuretic, nebivolol + calcium channel blocker (CCB), and nebivolol + "other" regimen, respectively. The number of subjects completing the study through Day 273 was 393/845 (46.5%), including 268/607 (44.2%) nebivolol, 110/206 (53.4%) nebivolol + diuretic, 7/21 (33.3%) nebivolol + CCB, and 8/11 (72.7%) nebivolol + other patients.

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

Subject disposition is shown in Table 162 and Table 163 below.

Table 162. Patient Disposition by Treatment, 9-Month Extension Phase (ITT Population) (NEB-306)

	Nebivolol n (%)	Nebivolol + Diuretic n (%)	Nebivolol + CCB[a] n (%)	Nebivolol + Other n (%)	Total N(%)
ITT Extension Population	607	206	21	11	845
Completed	268 (44.2)	110 (53.4)	7 (33.3)	8 (72.7)	393 (46.5)
Discontinued	339 (55.8)	96 (46.6)	14 (66.7)	3 (27.3)	452 (53.5)
Adverse Event	26 (4.3)	4 (1.9)	1 (4.8)	0	31 (3.7)
Treatment Failure	13 (2.1)	4 (1.9)	0	0	17 (2.0)
Lost to Follow-Up	32 (5.3)	6 (2.9)	0	0	38 (4.5)
Protocol Deviation	7 (1.2)	1 (0.5)	0	1 (9.1)	9 (1.1)
Withdrew Consent	47 (7.7)	8 (3.9)	1 (4.8)	0	56 (6.6)
Other	214 (35.3)	73 (35.4)	12 (57.1)	2 (18.2)	301 (35.6)

Data Source: Table 1.1.1 and Table 1.7.1
Note: Treatment classification was based on the treatment at the end of study participation.
[a] CCB = Calcium Channel Blocker

(Reproduced from Sponsor, Table 10.1-1, page 59)

Table 163. Patient Disposition by Treatment, 4-Week Follow-Up Phase (ITT Population) (NEB-306)

	Placebo n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Total N (%)
ITT Follow-Up Population	18	5	4	1	28
Completed	18 (100)	5 (100)	4 (100)	1 (100)	28 (100)
Data Source: Table 1.7.2					

(Reproduced from Sponsor, Table 10.1-2, page 59)

Table 164 summarizes patient enrollment by feeder study and nebivolol dose at time of entry.

Table 164. Patient Enrollment by Feeder Study and Nebivolol Dose at Time of Entry to NEB-306[a]

Study	Placebo n (%)	Nebivolol 1.25 mg n (%)	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 30/40 mg n (%)	Total N (%)
NEB-202								
Entered NEB-306	18 (43.9)	0 (0.0)	26 (61.9)	15 (36.6)	25 (53.2)	26 (57.8)	19 (44.2)	129 (49.8)
Did Not Enter NEB-306	23 (56.1)	0 (0.0)	16 (38.1)	26 (63.4)	22 (46.8)	19 (42.2)	24 (55.8)	130 (50.2)
NEB-302								
Entered NEB-306	29 (43.3)	32 (47.1)	27 (39.7)	67 (45.3)	65 (48.9)	74 (51.4)	72 (48.3)	366 (47.1)
Did Not Enter NEB-306	38 (56.7)	36 (52.9)	41 (60.3)	81 (54.7)	68 (51.1)	70 (48.6)	77 (51.7)	411 (52.9)
NEB-305								
Entered NEB-305	34 (55.7)	0 (0.0)	0 (0.0)	109 (50.0)	98 (47.6)	109 (50.2)	0 (0.0)	350 (49.9)
Did Not Enter NEB-306	27 (44.3)	0 (0.0)	0 (0.0)	109 (50.0)	108 (52.4)	108 (49.8)	0 (0.0)	352 (50.1)
(a) Only subjects who completed the NEB-302, NEB-305, or NEB-202 were included in this table. **Cross Reference: NEB-306 Data Listing 1 and Data Listing 1 and 5 in NEB-302, NEB-305, and NEB-202**								

(Reproduced from Sponsor, Table 1.9, page 352)

The demographic and baseline characteristics of the subjects in the Extension Phase are presented in Table 165.

Table 165. Baseline[a] Patient Characteristics by Treatment[b] (Extension Phase) (ITT) (NEB-306)

Parameter	Nebivolol n (%)	Nebivolol + Diuretic n (%)	Nebivolol + Calcium Channel Blocker n (%)	Nebivolol + Other n (%)	Total N (%)
Age					
N	607	206	21	11	845
Mean (SD)	52.7 (11.5)	54.1 (10.1)	48.5 (9.7)	62.4 (7.6)	53.0 (11.2)
Age Group					
< 65	503 (82.9)	172 (83.5)	21 (100.0)	6 (54.5)	702 (83.1)
≥ 65	104 (17.1)	34 (16.5)	0 (0.0)	5 (45.5)	143 (16.9)

(continued)

Parameter	Nebivolol n (%)	Nebivolol + Diuretic n (%)	Nebivolol + Calcium Channel Blocker n (%)	Nebivolol + Other n (%)	Total N (%)
Age Group					
< 75	591 (97.4)	203 (98.5)	21 (100.0)	10 (90.9)	825 (97.6)
≥75	16 (2.6)	3 (1.5)	0 (0.0)	1 (9.1)	20 (2.4)
Gender					
Male	311 (51.2)	125 (60.7)	9 (42.9)	6 (54.5)	451 (53.4)
Female	296 (48.8)	81 (39.3)	12 (57.1)	5 (45.5)	394 (46.6)
Race[b]					
Black	133 (21.9)	54 (26.2)	8 (38.1)	2 (18.2)	197 (23.3)
Non-Black	474 (78.1)	152 (73.8)	13 (61.9)	9 (81.8)	648 (76.7)
Caucasian	423 (69.7)	136 (66.0)	11 (52.4)	8 (72.7)	578 (68.4)
Asian	2 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)	3 (0.4)
Hispanic	46 (7.6)	13 (6.3)	2 (9.5)	1 (9.1)	62 (7.3)
Other	3 (0.5)	2 (1.0)	0 (0.0)	0 (0.0)	5 (0.6)
Diabetes Status					
Yes	39 (6.4)	12 (5.8)	0 (0.0)	2 (18.2)	53 (6.3)
No	568 (93.6)	194 (94.2)	21 (100.0)	9 (81.8)	792 (93.7)
EM or PM Classification					
Poor	43 (7.1)	16 (7.8)	1 (4.8)	1 (9.1)	61 (7.2)
Extensive	564 (92.9)	190 (92.2)	20 (95.2)	10 (90.9)	784 (92.8)
BMI[c] (kg/m^2)					
< 30	358 (59.0)	116 (56.3)	8 (38.1)	8 (72.7)	490 (58.0)
≥ 30	249 (41.0)	90 (43.7)	13 (61.9)	3 (27.3)	355 (42.0)
Sitting Heart Rate (bpm) (Baseline)					
N	607	206	21	11	845
Mean (SD)	72.7 (8.4)	72.9 (8.8)	73.4 (8.5)	71.2 (8.7)	72.7 (8.5)
Sitting DBP (mm Hg) (Baseline)					
N	607	206	21	11	845
Mean (SD)	98.6 (3.3)	100.4 (4.1)	100.8 (4.4)	99.1 (2.0)	99.1 (3.6)
Sitting SBP (mm Hg) (Baseline)					
N	607	206	21	11	845
Mean (SD)	150.9 (13.7)	154.2 (15.5)	152.6 (15.2)	160.2 (9.1)	151.8 (14.2)

(a) Baseline represents the baseline value at the start of NEB-302, NEB-305, or NEB-202
(b) Treatment Classification was based on the treatment at the end of study.
(c) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
Cross Reference: NEB-306 Data Listing 1

(Reproduced from Sponsor, Tables 1.1.1 and 1.2.1, pages 144-145 and 150-152)

The baseline and demographic characteristics for the patients in the four-week follow-up phase are presented in Table 166.

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Table 166. Baseline[a] Patient Characteristics by Treatment (Four-Week Follow-up Phase) (ITT) (NEB-306)

Parameter	Placebo n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Total N (%)
Age					
N	18	5	4	1	28
Mean	50.3 (9.0)	52.8 (11.0)	45.8 (16.0)	67.0 (NA)	50.7 (10.6)
Age Group					
< 65	16 (88.9)	4 (80.0)	3 (75.0)	0 (0.0)	23 (82.1)
≥ 65	2 (11.1)	1 (20.0)	1 (25.0)	1 (100.0)	5 (17.9)
Age Group					
< 75	18 (100.0)	5 (100.0)	4 (100.0)	1 (100.0)	28 (100.0)
Gender					
Male	3 (16.7)	2 (40.0)	2 (50.0)	0 (0.0)	7 (25.0)
Female	15 (83.3)	3 (60.0)	2 (50.0)	1 (100.0)	21 (75.0)
Race[b]					
Black	4 (22.2)	2 (40.0)	1 (25.0)	0 (0.0)	7 (25.0)
Non-Black	14 (77.8)	3 (60.0)	3 (75.0)	1 (100.0)	21 (75.0)
Caucasian	12 (66.7)	2 (40.0)	3 (75.0)	1 (100.0)	18 (64.3)
Hispanic	2 (11.1)	1 (20.0)	0 (0.0)	0 (0.0)	3 (10.7)
Diabetes Status					
No	18 (100.0)	5 (100.0)	4 (100.0)	1 (100.0)	28 (100.0)
EM or PM Classification					
Poor	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Extensive	17 (94.4)	5 (100.0)	4 (100.0)	1 (100.0)	27 (96.4)
BMI[c] (kg/m^2)					
< 30	10 (55.6)	2 (40.0)	3 (75.0)	1 (100.0)	16 (57.1)
≥ 30	8 (44.4)	3 (60.0)	1 (25.0)	0 (0.0)	12 (42.9)
Sitting Heart Rate (bpm) (Baseline)					
N	18	5	4	1	28
Mean (SD)	70.2 (8.1)	64.4 (7.4)	74.5 (19.8)	73.0 (NA)	69.9 (10.1)
Sitting DBP (mm Hg) (Baseline)					
N	18	5	4	1	28
Mean (SD)	97.5 (1.9)	97.2 (2.7)	97.8 (3.6)	97.0 (NA)	97.5 (2.2)
Sitting SBP (mm Hg) (Baseline)					
N	18	5	4	1	28
Mean (SD)	150.8 (11.3)	147.2 (12.1)	142.8 (13.3)	165.0 (NA)	149.5 (11.8)

(a) Baseline represents the baseline value at the start of NEB-302, NEB-305, or NEB-202
(b) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
Cross Reference: NEB-306 Data Listing 1
(Reproduced from Sponsor, Tables 1.1.2 and 1.2.2, pages 146-147 and 154-156)

Common coexisting medical conditions in the ITT 9-month extension population included essential hypertension (99.8%), hypercholesterolemia (17.8%), hyperlipidemia (10.2%), hysterectomy (10.2%), seasonal allergies (6.0%), tubal ligation (5.7%), depression (5.7%), gastroesophageal reflux disease (5.4%), allergic rhinitis (5.1%), and headaches (5.1%).

In the 4-week follow-up phase, common coexisting medical conditions in ≥ 10% of the ITT Population included essential hypertension (100%), hysterectomy (32.1%), gastroesophageal

reflux disease (21.4%), hypercholesterolemia (14.3%), hyperlipidemia (10.7%), myopia (10.7%), postmenopausal status (10.7%), seasonal allergies (10.7%), and anemia (10.7%).

In the 9-month extension phase, a total of 74.9% of patients used concomitant medications. Concomitant medications used in ≥ 2.0% of patients included acetylsalicylic acid (15.9%), multivitamins (13.7%), acetaminophen/paracetamol (9.9%), atorvastatin (86%), ibuprofen (6.4%), tocopherol (5.8%), conjugated estrogens (4.1%), ascorbic acid (4.0%), simvastatin (3.8%), levothyroxine sodium (3.6%), calcium (3.3%), esomeprazole (3.1%), fexofenadine hydrochloride (2.4%), rofecoxib (2.4%), metformin (2.2%), celecoxib (2.1%), and sildenafil citrate (2.1%). In the nebivolol and nebivolol and diuretic groups, 5.1% and 10.2% of patients, respectively, used ibuprofen, which was markedly different.

Enrollment status by efficacy in NEB-202, NEB-302, and NEB-305 is shown in Table 167.

Table 167. Summary of Change From Baseline[a] in Efficacy Endpoints by Enrollment Status into NEB-306 (ITT) (NEB-306)

Parameter/ Treatment Group[b]	Patient Cohort	N	Baseline[a] Mean	Day 84		
				Day 84 Mean	Change From Baseline[a]	SE
Sitting Diastolic Blood Pressure (mm Hg)						
Placebo	Patients not entering NEB-306	88	99.98	94.15	-5.83	0.80
	Patients entering NEB-306	81	99.10	92.94	-6.16	0.91
Nebivolol 1.25 mg	Patients not entering NEB-306	36	99.67	91.61	-8.06	1.15
	Patients entering NEB-306	32	98.31	90.13	-8.19	1.32
Nebivolol 2.5 mg	Patients not entering NEB-306	57	99.91	90.82	-9.09	0.97
	Patients entering NEB-306	53	99.13	91.57	-7.57	1.05
Nebivolol 5 mg	Patients not entering NEB-306	216	99.77	89.73	-10.04	0.56
	Patients entering NEB-306	191	98.99	88.83	-10.17	0.49
Nebivolol 10 mg	Patients not entering NEB-306	198	99.80	88.53	-11.27	0.56
	Patients entering NEB-306	188	98.94	87.95	-10.99	0.54
Nebivolol 20 mg	Patients not entering NEB-306	197	99.71	89.33	-10.38	0.62
	Patients entering NEB-306	209	99.43	86.90	-12.53	0.57

(continued)

Table 156. Summary of Change From Baselinea in Efficacy Endpoints by Enrollment Status into NEB-306 (ITT) (continued)

Parameter/ Treatment Group[b]	Patient Cohort	N	Baseline[a] Mean	Day 84		
				Day 84 Mean	Change From Baseline[a]	SE
Nebivolol 30/40 mg	Patients not entering NEB-306	101	99.54	90.22	-9.33	0.77
	Patients entering NEB-306	91	99.02	86.09	-12.93	0.82
Sitting Systolic Blood Pressure (mm Hg)						
Placebo	Patients not entering NEB-306	88	151.45	147.03	-4.42	1.49
	Patients entering NEB-306	81	153.31	146.90	-6.41	1.55
Nebivolol 1.25 mg	Patients not entering NEB-306	36	152.67	145.64	-7.03	2.13
	Patients entering NEB-306	32	149.19	142.72	-6.47	1.92
Nebivolol 2.5 mg	Patients not entering NEB-306	57	148.70	140.95	-7.75	1.87
	Patients entering NEB-306	53	149.55	143.02	-6.53	2.03
Nebivolol 5 mg	Patients not entering NEB-306	216	151.96	140.84	-11.12	0.97
	Patients entering NEB-306	191	151.61	141.38	-10.23	0.99
Nebivolol 10 mg	Patients not entering NEB-306	198	152.99	140.69	-12.30	0.99
	Patients entering NEB-306	188	152.43	141.26	-11.18	0.99
Nebivolol 20 mg	Patients not entering NEB-306	197	151.75	141.26	-10.49	1.13
	Patients entering NEB-306	209	152.43	137.27	-15.16	1.03
Nebivolol 30/40 mg	Patients not entering NEB-306	101	153.86	144.41	-9.46	1.60
	Patients entering NEB-306	91	150.79	136.67	-14.12	1.44

(a) Refers to change from baseline (baseline value at the start of NEB-302, NEB-305, or NEB-202) to Day 84 (of NEB-302, NEB-305, or NEB-202 respectively)
(b) Treatment group is the treatment group that patients were on at the start of NEB-302, NEB-305, or NEB-202
Cross Reference: NEB-306 Data Listing 1 and Data Listings 1 and 10.1.1-10.1.3, 10.2.1-10.2.3, 10.3.1-10.3.3 from NEB-302, NEB-305, or NEB-202

(Reproduced from Sponsor, Table 1.11, pages 355 and 356)

Compliance

During the 9-month extension phase, noncompliance was 5.2%, 8.0%, 0.0%, and 0.0% in the nebivolol, nebivolol + diuretic, nebivolol + calcium channel blocker, and nebivolol + other groups, respectively.

In the 4-week follow-up phase, noncompliance was 0.0% in all groups.

Results

Primary Efficacy Endpoint (NEB-306)

The primary efficacy endpoint was the change in average sitting DBP taken at trough at end of treatment compared to baseline of NEB-202, NEB-302, or NEB-305.

The primary efficacy results for the ITT OC Population are shown in Table 168.

Table 168. Mean Change From Baseline in Sitting Diastolic Blood Pressure (mm Hg) at Trough by Treatment (ITT OC, 9-Month Extension Phase)

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

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

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

For the primary efficacy endpoint in the ITT LOCF secondary population, results were similar except the mean decrease in the nebivolol + calcium channel blocker group at the end of the 9-month extension phase was significant. These results are shown in Table 169.

Table 169. Mean Change from Baseline[a] in Sitting Diastolic Blood Pressure (mm Hg) at Trough by Treatment (ITT LOCF, 9-Month Extension Phase) (NEB-306)

Treatment by Visit[a]	N	Baseline Mean[b]	Treatment Mean	Change From Baseline		
				Mean	SE	95% CI
Day 273 (Visit E5)						
Nebivolol	607	98.6	85.6	-13.0	0.3	(-13.6, -12.3)
Nebivolol + Diuretic	206	100.4	89.2	-11.2	0.5	(-12.2, -10.2)
Nebivolol + CCB[c]	21	100.8	93.0	-7.9	2.5	(-13.1, -2.6)
Nebivolol + Other	11	99.1	85.4	-13.7	3.3	(-21.1, -6.4)

(a) Baseline represents the baseline in the feeder study (NEB-302, NEB-305, or NEB-202)
Cross Reference: NEB-306 Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, and Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, 10.3.1-10.3.3 in NEB-302, NEB-305, or NEB-202.
(Reproduced from Sponsor, Table 2.1.2, page 370)

Sites with GCP Issues (NEB-306)

There were several sites with GCP issues. The sponsor terminated Site 117 from feeder Study NEB-305 due to inadequate safety monitoring. Site 117 also participated in Study 202 as Site 324. At Site 263 from feeder Study NEB-305, 3 medication bottles were returned with tablets which were not from a nebivolol study. These tablets were hydrochlorothiazide, and were thought to be from a prior study conducted at the site. Sites 145, 223, and 233 from feeder Study NEB-302 were potential GCP violators prior to unblinding. At Sites 145 and 233, investigators used electronic data capture which was difficult to access. Site 223 [redacted] contained conflicting information regarding procedure times on multiple patients. The primary efficacy results excluding Sites with potential GCP issues are shown in Table 170.

Table 170. Mean Change from Baseline[a] in Sitting Diastolic Blood Pressure (mm Hg) at Trough by Treatment Excluding Problem Sites[b] (ITT OC) (NEB-306)

Treatment by Visit[a]	N	Baseline Mean[b]	Treatment Mean	Change From Baseline		
				Mean	SE	95% CI
Day 273 (Visit E5)						
Nebivolol	238	97.7	83.2	-14.5	0.5	(-15.4, -13.6)
Nebivolol + Diuretic	114	99.9	88.2	-11.7	0.6	(-13.0, -10.4)
Nebivolol + CCB[c]	7	102.0	95.3	-6.7	4.3	(-17.1, 3.7)
Nebivolol + Other	9	99.0	84.3	-14.7	3.1	(-21.8, -7.6)

(a) Baseline represents the baseline in the feeder study (NEB-302, NEB-305, or NEB-202)
(b) Excludes sites 324, 145, 223, 233, 117, 263
Cross Reference: NEB-306 Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3.
(Reproduced from Sponsor, Table 2.1.5, page 376)

There was no significant difference in the primary efficacy analysis when the potential GCP violators were removed.

Secondary Efficacy Endpoints

Table 171 shows the overall results of the secondary efficacy endpoints.

Table 171. Mean Change From Baseline by Treatment (ITT OC, 9-Month Extension Phase) (NEB-306)

Treatment by Visit[a]	N	Baseline Mean[b]	Treatment Mean	Change From Baseline		
				Mean	SE	95% CI
Sitting Systolic Blood Pressure (mm Hg) at Trough (Day 273) (Visit E5)						
Nebivolol	266	148.2	133.4	-14.8	0.9	(-16.6, -13.1)
Nebivolol + Diuretic	125	153.2	137.0	-16.2	1.4	(-19.0, -13.4)
Nebivolol + CCB[c]	7	151.9	148.3	-3.6	8.3	(-23.9, 16.8)
Nebivolol + Other	9	159.8	141.2	-18.6	6.5	(-33.7, -3.5)

(continued)

Treatment by Visit[a]	N	Baseline Mean[b]	Treatment Mean	Change From Baseline		
				Mean	SE	95% CI
Sitting Diastolic Blood Pressure (mm Hg) at Peak (Day 273) (Visit E5)						
Nebivolol	256	97.8	79.5	-18.4	0.5	(-19.3, -17.4)
Nebivolol + Diuretic	120	100.3	85.2	-15.1	0.6	(-16.3, -13.8)
Nebivolol + CCB[c]	7	102.0	90.6	-11.4	4.0	(-21.2, -1.7)
Nebivolol + Other	9	99.0	80.1	-18.9	2.8	(-25.3, -12.4)
Sitting Systolic Blood Pressure (mm Hg) at Peak (Day 273) (Visit E5)						
Nebivolol	256	148.4	128.9	-19.6	0.9	(-21.3, -17.8)
Nebivolol + Diuretic	120	153.6	133.7	-20.0	1.4	(-22.8, -17.1)
Nebivolol + CCB[c]	7	151.9	141.7	-10.1	7.7	(-19.0, 8.7)
Nebivolol + Other	9	159.8	130.8	-29.0	6.2	(-43.2, -14.8)
Standing Diastolic Blood Pressure (mm Hg) at Trough (Day 273) (Visit E5)						
Nebivolol	266	97.8	84.8	-13.0	0.5	(-14.0, -12.0)
Nebivolol + Diuretic	125	101.6	89.9	-11.7	0.7	(-13.1, -10.3)
Nebivolol + CCB[c]	7	103.0	95.7	-7.3	4.3	(-17.9, 3.3)
Nebivolol + Other	9	98.8	84.1	-14.7	3.3	(-22.2, -7.1)
Standing Systolic Blood Pressure (mm Hg) at Trough (Day 273) (Visit E5)						
Nebivolol	266	148.4	133.5	-14.9	1.0	(-16.7, -13.0)
Nebivolol + Diuretic	125	154.5	137.0	-17.5	1.4	(-20.3, -14.8)
Nebivolol + CCB[c]	7	148.0	146.4	-1.6	7.3	(-19.3, -16.2)
Nebivolol + Other	9	157.9	143.2	-14.7	6.4	(-29.4, 0.1)
Standing Diastolic Blood Pressure (mm Hg) at Peak (Day 273) (Visit E5)						
Nebivolol	256	97.8	81.3	-16.5	0.5	(-17.4, -15.5)
Nebivolol + Diuretic	120	101.5	87.5	-14.0	0.7	(-15.4, -12.7)
Nebivolol + CCB[c]	7	103.0	88.9	-14.1	4.4	(-24.9, -3.4)
Nebivolol + Other	9	98.8	79.9	-18.9	2.3	(-24.3, -13.5)
Standing Systolic Blood Pressure (mm Hg) at Peak (Day 273) (Visit E5)						
Nebivolol	256	148.8	129.7	-19.1	0.9	(-21.0, -17.3)
Nebivolol + Diuretic	120	155.0	135.0	-19.9	1.4	(-22.7, -17.2)
Nebivolol + CCB[c]	7	148.0	139.0	-9.0	7.9	(-28.3, -10.3)
Nebivolol + Other	9	157.9	132.7	-25.2	5.5	(-37.8, -12.6)
Supine Diastolic Blood Pressure (mm Hg) at Trough (Day 273) (Visit E5)						
Nebivolol	266	95.4	82.9	-12.5	0.5	(-13.5, -11.6)
Nebivolol + Diuretic	125	98.7	87.7	-11.0	0.7	(-12.3, -9.7)
Nebivolol + CCB[c]	7	103.0	94.1	-8.9	5.1	(-21.3, 3.6)
Nebivolol + Other	9	96.8	84.2	-12.6	2.8	(-19.0, -6.1)
Supine Systolic Blood Pressure (mm Hg) at Trough (Day 273) (Visit E5)						
Nebivolol	266	148.6	134.4	-14.2	0.9	(-16.0, -12.5)
Nebivolol + Diuretic	125	153.8	139.2	-14.6	1.4	(-17.4, -11.8)
Nebivolol + CCB[c]	7	152.7	149.0	-3.7	6.4	(-19.4, 12.0)
Nebivolol + Other	9	162.4	148.9	-13.6	6.7	(-29.1, 2.0)
Supine Diastolic Blood Pressure (mm Hg) at Peak (Day 273) (Visit E5)						
Nebivolol	256	95.4	79.7	-15.6	0.5	(-16.6, -14.6)
Nebivolol + Diuretic	120	98.7	84.7	-14.0	0.7	(-15.4, -12.6)
Nebivolol + CCB[c]	7	103.0	89.1	-13.9	5.1	(-26.3, -1.4)
Nebivolol + Other	9	96.8	82.0	-14.8	3.3	(-22.4, -7.1)

(continued)

Treatment by Visit[a]	N	Baseline Mean[b]	Treatment Mean	Change From Baseline		
				Mean	SE	95% CI
Supine Systolic Blood (mm Hg) at Peak (Day 273) (Visit E5)						
Nebivolol	256	148.7	129.6	-19.1	0.9	(-20.9, -17.3)
Nebivolol + Diuretic	120	154.1	135.0	-19.1	1.5	(-22.0, -16.2)
Nebivolol + CCB[c]	7	152.7	140.9	-11.9	7.4	(-30.1, 6.3)
Nebivolol + Other	9	162.4	135.7	-26.8	8.2	(-45.8, -7.8)

Data Source: Tables 2.2.1, 2.3, 2.4, 2.9.1, 2.10.1, 2.11, 2.5, 2.6.1, 2.7, 2.8
[a]See Table 9.7.1.5-1 for the relative day ranges for each visit
[b]Baseline represents the baseline in the feeder study (NEB-202, NEB-302, or NEB-305)
[c]CCB = Calcium channel blocker
(Compiled by Hicks K, pages 392, 398, 400, 408, 414, 418, 424, and 430)

There were statistically significant mean changes from baseline to Day 273 in all treatment groups for the following secondary endpoints:

- sitting diastolic blood pressure at peak
- standing diastolic blood pressure at peak
- supine diastolic blood pressure at peak

There were statistically significant mean changes from baseline to Day 273 in all treatment groups except for nebivolol + calcium channel blocker for the following secondary endpoints:

- sitting systolic blood pressure at trough
- sitting systolic blood pressure at peak
- standing diastolic blood pressure at trough
- standing systolic blood pressure at trough
- standing systolic blood pressure at peak
- supine diastolic blood pressure at trough
- supine systolic blood pressure at trough
- supine systolic blood pressure at peak

Response Rate: 9-Month Extension Phase (NEB-306)

The primary method of defining a responder was the achievement of a diastolic blood pressure < 90 mm Hg or decreased by ≥ 10 mm Hg from baseline to end of study for the ITT OC Population in the 9-month extension phase. Nebivolol + calcium channel blocker had the lowest responder rate (40.0%), as seen in Table 172.

Table 172. Responder Rates by Treatment–Primary Method (Intent-to-Treat Observed Cases, 9-Month Extension Phase) (NEB-306)

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

(continued)

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

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

Using the secondary method of a responder, defined as a diastolic blood pressure < 90 mm Hg for the ITT OC Population at the end of the 9-month extension phase, the nebivolol + calcium channel blocker treatment group still had the lowest response rate (30.0%), as shown in Table 173.

Table 173. Responder[a] Rates by Treatment--Secondary Method (Intent-to-Treat Observed Cases, 9-Month Extension Phase) (NEB-306)

Treatment[b]	Total	Responders[a]	
		N	(%)
Nebivolol	583	435	(74.6)
Nebivolol + Diuretic	206	111	(53.9)
Nebivolol + CCB[c]	20	6	(30.0)
Nebivolol + Other	11	8	(72.7)
Total	820	560	(68.3)

Data source: Table 2.13.2.1
[a] A responder was defined as a patient whose average trough sitting diastolic blood pressure was < 90 mm Hg at the end of the study
[b] Treatment classification was based on the treatment being received at the end of the study
[c] CCB=Calcium Channel Blocker

(Reproduced from Sponsor, Table 11.4.1.1.2.4-2, page 79)

Frequency of Adjunct Therapy Use (NEB-306)

For the ITT OC Population in the 9-month extension phase, 29.0% of patients received adjunct therapy. During the extension phase, 26.8% (226/842) of patients received nebivolol + diuretic and 2.5% (21/842) received nebivolol + calcium channel blocker.

Rescue Therapy (NEB-306)

Rescue medication, defined as antihypertensive therapy in addition to nebivolol once daily plus one adjunct therapy (diuretic (or diuretic-like), calcium channel blocker, or one other antihypertensive medication), was used in 1.1% (9/845) patients in the ITT OC Population in the 9-month extension phase. No patients in the nebivolol or in the nebivolol + diuretic treatment groups required rescue therapy. In the nebivolol + calcium channel blocker and nebivolol + other treatment groups, 9.5% (2/21) and 63.6% (7/11), respectively, required rescue therapy.

Efficacy in the 4-Week Follow-Up Phase (NEB-306)

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

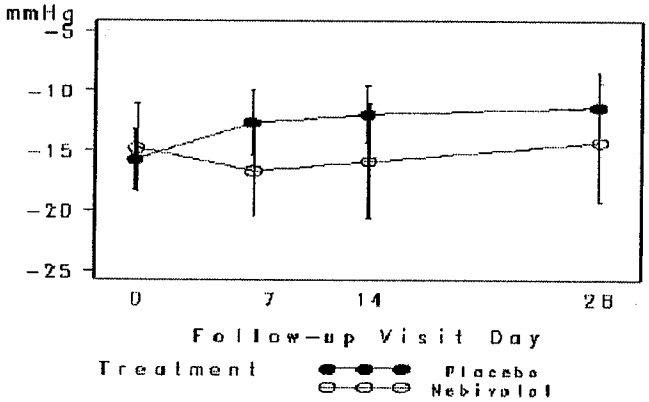
value at baseline of the feeder studies. For sitting diastolic blood pressure at trough, Table 174 and Figure 21 show the change from baseline for the placebo and combined nebivolol treatment groups in the 4-week follow-up phase.

Table 174. Sitting Diastolic Blood Pressure at Trough (Raw Mean Change-from-Baseline During Follow-up) (4-Week Follow-Up Phase) (NEB-306)

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

(Reproduced from Sponsor, Table 7.1, page 464)

Figure 21. Mean Change from Baseline in Sitting Diastolic Blood Pressure (mm Hg) at Trough by Visit and Treatment (95% Confidence Interval) in Follow-Up Phase (ITT OC) (NEB-306)



(Reproduced from Sponsor, Figure 11.4.1.2-1, page 80)

At the end of the 4-week follow-up phase, the placebo group had a 72.2% response rate, defined as a trough sitting diastolic blood pressure < 90 mm Hg. Although there were only 18 patients in the placebo group, the available data suggest nebivolol does not result in rebound hypertension.

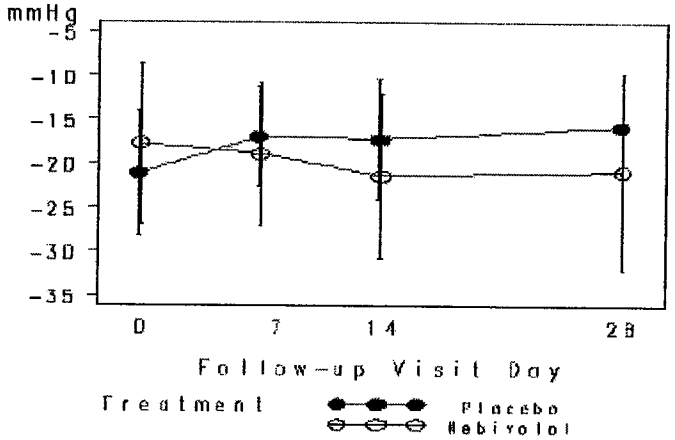
Similarly, from the end of the extension phase to Days 7, 14, and 28 of the follow-up study, the mean sitting systolic blood pressure at trough in the placebo patients increased by 5.2, 4.3, and 7.4 mm, respectively. According to the sponsor, at Day 28, the sitting systolic blood pressure at trough for the placebo patients was -15.8 (95% Confidence Interval: -21.3, -10.2), which was below the baseline value of the feeder studies. Table 175 and Figure 22 show the change in sitting systolic blood pressure at trough for the placebo and combined nebivolol treatment in the 4-week follow-up phase.

Table 175. Sitting SBP at Trough (Raw mean Change-from-Baseline During Follow-Up) (NEB-306)

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

(Reproduced from Sponsor, Table 7.2, page 465)

Figure 22. Mean Change from Baseline in Sitting Systolic Blood pressure (mm Hg) at Trough by Visit and Treatment (95% Confidence Interval) in Follow-Up Phase (ITT OC) (NEB-306)



(Reproduced from Sponsor, Figure 11.4.1.2-2, page 81)

Response Rate: 4-Week Follow-Up Phase (NEB-306)

Table 176 shows responder rates by treatment for the ITT Follow-up Population using the primary method and the baseline from the feeder study.

Table 176. Responder[a] Rates by Treatment–Primary Method (Population: Intent-to-Treat Follow-Up) (NEB-306)

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

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

(Reproduced from Sponsor, Table 2.13.1.2, page 434)

Using the last non-missing post-baseline average trough sitting diastolic blood pressure and the primary method, Table 177 shows the responder rates by treatment for the follow-up phase.

Table 177. Responder[a] Rates by Treatment--Primary Method (Population: Intent-to-Treat Follow-up) (NEB-306)

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

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

(Reproduced from Sponsor, Table 2.13.1.3, page 435)

Table 178 shows the responder rates by treatment for the ITT Follow-up Population using the secondary method.

Table 178. Responder[a] Rates by Treatment--Secondary Method (Population: Intent-to-Treat Follow-up) (NEB-306)

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

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

(Reproduced from Sponsor, Table 2.13.2.2, page 437)

The response rates using primary and secondary methods are identical, as seen in the above Tables. Although only a small number of patients participated in the randomized withdrawal study, the placebo response rate of 72.2% suggests nebivolol did not cause rebound

hypertension. Nebivolol 10 mg had the lowest response rate of 50.0%, while Nebivolol 20 mg had the highest response rate at 100.0%.

Subgroup Analysis 9-Month Extension Phase (NEB-306)

I compiled the results for the mean change from baseline in sitting diastolic blood pressure at trough by treatment and subgroup in Table 179 for the ITT OC Population for the 9-month extension phase. Although there were only two Blacks in the nebivolol + calcium channel blocker treatment group, this therapy did not appear to be effective, because sitting diastolic blood pressure actually increased 4.5 mm Hg from baseline. Overall it appeared nebivolol + calcium channel blocker in the subgroups had the least favorable effect on sitting diastolic blood pressure in the 9-Month Extension Phase.

Table 179. Mean Change from Baseline[a] in Sitting Diastolic Blood Pressure (mm Hg) at Trough by Treatment and Subgroup (ITT OC) (9-Month Extension Phase) (NEB-306)

Day 273	N	Baseline Mean	Treatment Mean	Change from Baseline		
				Mean	SE	95% C.I.
BMI < 30						
Nebivolol	153	97.5	82.6	-14.9	0.6	(-16.1, -13.7)
Nebivolol + Diuretic	66	99.7	87.3	-12.4	0.9	(-14.3, -10.5)
Nebivolol + Calcium Channel Blocker	3	98.0	89.7	-8.3	6.0	(-34.2, 17.5)
Nebivolol + Other	6	98.7	83.7	-15.0	4.3	(-26.1, -3.9)
BMI ≥ 30						
Nebivolol	113	98.2	83.1	-15.1	0.6	(-16.3, -13.9)
Nebivolol + Diuretic	59	100.9	89.3	-11.6	0.8	(-13.2, -10.0)
Nebivolol + Calcium Channel Blocker	4	105.0	99.5	-5.5	6.7	(-26.7, 15.7)
Nebivolol + Other	3	99.7	85.7	-14.0	4.5	(-33.4, 5.4)
Black						
Nebivolol	16	98.5	85.9	-12.6	2.1	(-17.1, -8.0)
Nebivolol + Diuretic	26	100.2	88.6	-11.6	1.5	(-14.7, -8.4)
Nebivolol + Calcium Channel Blocker	2	98.5	103.0	**4.5**	9.5	(-116, 125.2)
Nebivolol + Other	2	97.0	76.5	-20.5	11.5	(-167, 125.6)
Non-Black						
Nebivolol	250	97.8	82.6	-15.1	0.4	(-16.0, -14.3)
Nebivolol + Diuretic	99	100.3	88.2	-12.1	0.7	(-13.5, -10.7)
Nebivolol + Calcium Channel Blocker	5	103.4	92.2	-11.2	3.4	(-20.6, -1.8)
Nebivolol + Other	7	99.6	86.6	-13.0	2.8	(-19.8, -6.2)
Male						
Nebivolol	127	97.7	83.0	-14.7	0.6	(-15.9, -13.4)
Nebivolol + Diuretic	73	101.2	88.6	-12.6	0.8	(-14.2, -11.0)
Nebivolol + Calcium Channel Blocker	3	105.3	101.0	-4.3	9.3	(-44.3, 35.6)
Nebivolol + Other	6	99.3	84.2	-15.2	4.3	(-26.3, -4.1)
Female						
Nebivolol	139	97.9	82.7	-15.3	-.6	(-16.5, -14.0)
Nebivolol + Diuretic	52	98.9	87.7	-11.2	1.0	(-13.2, -9.2)
Nebivolol + Calcium Channel Blocker	4	99.5	91.0	-8.5	4.3	(-22.0, 5.0)
Nebivolol + Other	3	98.3	84.7	-13.7	4.4	(-32.6, 5.3)

(continued)

Day 273	N	Baseline Mean	Treatment Mean	Change from Baseline		
				Mean	SE	95% C.I.
Diabetes						
Nebivolol	9	97.6	83.8	-13.8	2.1	(-18.7, -8.8)
Nebivolol + Diuretic	7	97.7	85.0	-12.7	3.2	(-20.5, -5.0)
Nebivolol + Calcium Channel Blocker	0	N/A	N/A	N/A	N/A	(N/A, N/A)
Nebivolol + Other	1	97.0	88.0	-9.0	N/A	(N/A, N/A)
No Diabetes						
Nebivolol	257	97.8	82.8	-15.0	0.5	(-15.9, -14.1)
Nebivolol + Diuretic	118	100.4	88.4	-11.9	0.6	(-13.2, -10.7)
Nebivolol + Calcium Channel Blocker	7	102.0	95.3	-6.7	4.3	(-17.1, 3.7)
Nebivolol + Other	8	99.3	83.9	-15.4	3.4	(-23.4, -7.4)
Poor Metabolizer						
Nebivolol	28	97.2	87.0	-10.3	1.4	(-13.1, -7.4)
Nebivolol + Diuretic	11	101.6	86.1	-15.5	1.8	(-19.5, -11.6)
Nebivolol + Calcium Channel Blocker	0	N/A	N/A	N/A	N/A	(N/A, N/A)
Nebivolol + Other	1	99.0	89.0	-10.0	N/A	(N/A, N/A)
Extensive Metabolizer						
Nebivolol	238	97.9	82.4	-15.5	0.5	(-16.4, -14.6)
Nebivolol + Diuretic	114	100.1	88.5	-11.6	0.7	(-13.0, -10.3)
Nebivolol + Calcium Channel Blocker	7	102.0	95.3	-6.7	4.3	(-17.1, 3.7)
Nebivolol + Other	8	99.0	83.8	-15.3	3.4	(-23.3, -7.2)
< 65 years old						
Nebivolol	224	98.0	82.7	-15.3	0.5	(-16.3, -14.4)
Nebivolol + Diuretic	105	100.3	89.0	-11.3	0.7	(-12.6, -9.9)
Nebivolol + Calcium Channel Blocker	7	102.0	95.3	-6.7	4.3	(-17.1, 3.7)
Nebivolol + Other	5	99.2	86.6	-12.6	2.8	(-20.5, -4.7)
≥ 65 years old						
Nebivolol	42	97.0	83.7	-13.3	1.1	(-15.5, -11.1)
Nebivolol + Diuretic	20	100.1	84.4	-15.8	1.4	(-18.7, -12.8)
Nebivolol + Calcium Channel Blocker	0	N/A	N/A	N/A	N/A	(N/A, N/A)
Nebivolol + Other	4	98.8	81.5	-17.3	6.3	(-37.2, 2.7)

(a) Baseline represents the baseline in the feeder study (NEB-302, NEB-305, or NEB-202)
Cross Reference: NEB-306 Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, and Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, 10.3.1-10.3.3 in NEB-302, NEB-305, or NEB-202)

(Compiled by Hicks K from Sponsor, Table 2.1.7.1, Table 4.1, Table 4.2, Table 4.3, Table 4.4, and Table 4.5; pages 384, 445, 449, 453, 457, and 461)

Subgroup Analysis 4-Week Follow-Up Phase (NEB-306)

Table 180 shows the mean change from the feeder study baseline at trough to Day 28 of the follow-up phase for sitting diastolic blood pressure at trough.

Table 180. Mean Change from Baseline[a] in Sitting Diastolic Blood Pressure (mm Hg) at Trough by Treatment and Subgroup (ITT Follow-Up Phase) (NEB-306)

Day 28	N	Baseline Mean[a]	Treatment Mean	Change from Baseline		
				Mean	SE	95% C.I.
BMI < 30						
Nebivolol	10	97.4	87.5	-9.9	2.1	(-14.7, -5.1)
Nebivolol + Diuretic	2	95.5	83.0	-12.5	7.5	(-108, 82.8)
Nebivolol + Calcium Channel Blocker	3	98.0	88.7	-9.3	5.9	(-34.7, 16.0)
Nebivolol + Other	1	97.0	76.0	-21.0	N/A	(N/A, N/A)
BMI ≥ 30						
Nebivolol	8	97.6	84.4	-13.3	1.9	(-17.8, -8.7)
Nebivolol + Diuretic	3	98.3	78.7	-19.7	2.2	(-29.1, -10.3)
Nebivolol + Calcium Channel Blocker	1	97.0	87.0	-10.0	N/A	(N/A, N/A)
Nebivolol + Other	0	N/A	N/A	N/A	N/A	(N/A, N/A)

(a) Baseline represents the baseline in the feeder study (NEB-302, NEB-305, or NEB-202)
Cross Reference: NEB-306 Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, and Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, 10.3.1-10.3.3 in NEB-302, NEB-305, or NEB-202.

(Reproduced from Sponsor, Table 2.1.7.2, page 387)

Table 181 shows the mean change from baseline (last visit in the NEB-306 Extension Phase) to Day 28 of the follow-up phase for sitting diastolic blood pressure at trough.

Table 181. Mean Change from End of NEB-306 Extension Phase[a] in Sitting Diastolic Blood pressure (mm Hg) at Trough by Treatment and Subgroup (ITT Follow-up) (NEB-306)

Day 28	N	Baseline Mean[a]	Treatment Mean	Change from Baseline		
				Mean	SE	95% C.I.
BMI < 30						
Nebivolol	10	82.8	87.5	4.7	1.6	(1.0, 8.4)
Nebivolol + Diuretic	2	82.0	83.0	1.0	6.0	(-75.2, 77.2)
Nebivolol + Calcium Channel Blocker	3	82.7	88.7	6.0	7.0	(-24.1, 36.1)
Nebivolol + Other	1	79.0	76.0	-3.0	N/A	(N/A, N/A)
BMI ≥ 30						
Nebivolol	8	80.4	84.4	4.0	2.0	(-0.8, 8.8)
Nebivolol + Diuretic	3	82.7	78.7	-4.0	1.5	(-10.6, 2.6)
Nebivolol + Calcium Channel Blocker	1	88.0	87.0	-1.0	N/A	(N/A, N/A)
Nebivolol + Other	0	N/A	N/A	N/A	N/A	(N/A, N/A)

(a) Baseline represents the last visit in the NEB-306 extension phase.
Cross Reference: NEB-306 Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, and Data Listings 1, 10.1.1-10.1.3, 10.2.1-10.2.3, 10.3.1-10.3.3 in NEB-302, NEB-305, or NEB-202.

(Reproduced from Sponsor, Table 2.1.7.3, page 390)

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Summary (NEB-306)
Nebivolol monotherapy significantly decreased sitting diastolic (-15.0 mm Hg) and systolic blood pressure (-14.8 mm Hg) at trough from baseline to end of treatment in the 9-month extension phase. For sitting diastolic and systolic blood pressure at trough, the nebivolol + calcium channel blocker treatment group appeared to be least effective. Although only 28 patients participated in the 4-week follow-up phase (randomized withdrawal trial), nebivolol did not appear to cause rebound hypertension.

11.7 Supportive Studies

The Agency reviewed all supportive studies submitted by the sponsor. None of these studies altered the efficacy results of the Pivotal studies. Table 182 provides a list of the supportive studies. The reviews for the nitric oxide and hemodynamic studies referred to in Section 5.2, Pharmacodynamics, may be found in the section following Table 182. The number prior to the study title corresponds to # in the Table.

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Table 182. List of Supportive Studies (all reviewed)

#	LMD No.	Study ID	Title	Study Category/ Type/Design
1	N/A	1270_01_00	Comparative Effects of Nebivolol, Nebivolol Enantiomers, Atenolol, Metoprolol, Carvedilol and Bucindolol on Human Endothelial Cell Nitric Oxide Release Following Acute Treatment	Molecular pharmacology, Nitric oxide effects, In vitro
2	N/A	1273_01_00	Comparative Effects of Nebivolol, Nebivolol Enantiomers, and Six Nebivolol Metabolites on Endothelial Nitric oxide Release from Human Endothelial Cells following Acute Treatment	Molecular pharmacology, Nitric oxide effects, In vitro
3	N/A	1332_01_00 Same as 1332_00_00	Comparative Effects of Nebivolol Metabolites 4,5'-dihydroxy, 4,8'-dihydroxy, Glucuronide, Nebivolol and Nebivolol Enantiomers on Endothelial Cells following Acute Treatment	Molecular pharmacology, Nitric oxide effects, In vitro
4	N/A	1333_00_00	Comparative Effects of Nebivolol and Atenolol on Nitric Oxide Release from Human Endothelial Cells following Chronic Treatment	Molecular pharmacology, Nitric oxide effects, In vitro
5	N/A	1334_00_00	Comparative Effects of Nebivolol and Atenolol on Nitric Oxide Release in Black and Caucasian Endothelial Cells following Chronic Treatment	Molecular pharmacology, Nitric oxide effects, In vitro
6	N/A	1271_01_00	Effects of Nebivolol and ACE-Inhibitors on Endothelial Nitric Oxide Release in Black and Caucasian Donor Endothelial Cells following Chronic Treatment	Molecular pharmacology, Nitric oxide effects, In vitro
7	N/A	1269_01_00	Separate and Combined Effects of Nebivolol and ACE-Inhibitors on Human Endothelial Cell Nitric Oxide Release following Acute Treatment	Molecular pharmacology, Nitric oxide effects, In vitro
8	N/A	1268_01_00	Effects of Acute Nebivolol Treatment on Nitric Oxide Release and Vascular Function in Normal versus Diseased Mesenteric Arteries	Molecular pharmacology, Nitric oxide effects, In vitro
9	N/A	1312_01_00	Adrenergic Receptor Pharmacology of Nebivolol in the Human Heart	Molecular Pharmacology, Beta adrenergic receptor affinity, In vitro
10	N/A	1311_01_00	Adrenergic Receptor Pharmacology of Nebivolol, its Enantiomers and Nine Metabolites in the Human heart	Molecular pharmacology, Beta adrenergic receptor affinity, In vitro
11	59897	N/A	Response to Isoprenaline after Single Intravenous and Oral Application of Nebivolol: Time Course. Clinical Research Report. January 1988.	Pharmacodynamics, Beta blockade, Open-label
12	59988	NED-6	Isoprenaline Dose-Response in Man after a Single 5 mg Intravenous dose of Nebivolol and after Oral Application of Nebivolol 5 mg Once Daily for One Week. Clinical Research Report NEB-NED-6. February 1988.	Pharmacodynamics, Beta blockade, Open-label

#	LMD No.	Study ID	Title	Study Category/ Type/Design
13	84265 92890 106646	GBR-20	Clinical Pharmacology of Nebivolol (Drug Investigation; 3 (suppl. 1): 31-32, 1991) A Comparative Study of the Relative Beta-Blocking Potency, and Beta-1 selectivity of Nebivolol, Propranolol and Atenolol in Healthy Volunteers. A Comparative Study of the Potency and Relative Beta-1 Selectivity of Nebivolol, Propranolol and Atenolol in a Group of Healthy Volunteers. Clinical Research Report NEB-GBR-20, May 1994	Pharmacodynamics, Beta blockade, Single-blind, placebo-controlled
14	108078	BEL-20	Determination of the Acute and Subacute Beta-Sympathicolytic Activity of d-, l-, and dl Nebivolol compared to Atenolol and Placebo, in Inhibiting Exercise-Induced Tachycardia. Synoptic Clinical Research Report NEB-BEL-20. April 1994	Pharmacodynamics, Beta blockade, Double-blind, placebo-controlled
15	108084	NED-5	Time Course of Beta-Blockade with Nebivolol. Synoptic Clinical Research Report NEB-NED-5. January 1988	Pharmacodynamics, Beta blockade, Open-label
16	106922	GBR-29	A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol Isomers on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-29.	Pharmacodynamics, Vasodilation, Double-blind, cross-over
17	107421	GBR-23	A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol Isomers on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-23.	Pharmacodynamics, Vasodilation, Open-label
18	107422	GBR-25	A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-25.	Pharmacodynamics, Vasodilation, Open-label, cross-over
19	107423	GBR-28	A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-28.	Pharmacodynamics, Vasodilation, Open-label, cross-over
20	107424	GBR-27	A Study to Compare the Effect of Nebivolol and Atenolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-27.	Pharmacodynamics, Vasodilation, Open-label, cross-over
21	136347	GBR-31	A Study to Investigate the Vasodilator Effect of Nebivolol Racemate and Isomers on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-31. July 1997.	Pharmacodynamics, Vasodilation, Double-blind, cross-over
22	101180	SWE-5	Nebivolol—Effects on Peripheral Arterial and Venous Blood Flow. Clinical Research Report NEB-SWE-5. November 1993.	Pharmacodynamics, Vasodilation, Double-blind, placebo-controlled, cross-over

#	LMD No.	Study ID	Title	Study Category/ Type/Design
23	49278	N/A	Effect of a Single Oral Intake of R67555 (5 mg and 10 mg) and of a 7-Day Intake of R67555 (5 mg/day) on ECG. Clinical Research Report. February 1986.	Pharmacodynamic, Hemodynamic, Open-label, cross-over
24	59987	N/A	Invasive Haemodynamics of Nebivolol: Effects of a Single 5 mg Intravenous Injection and a 5 mg Oral Dose of Nebivolol Once Daily for 1 week on Blood Pressure, Heart Rate, Central Venous Pressure, Cardiac Output, Stroke Volume and Total Peripheral Resistance. Clinical Research Report. February 1988.	Pharmacodynamic, Hemodynamic, Open-label
25	64808	BEL-19	Effect of Nebivolol 10 mg and 20 mg versus Placebo on Heart Rate, Blood Pressure, Systolic Time Intervals and Side Effects. A Double-Blind Placebo-Controlled Cross-Over Study in Healthy Volunteers. Clinical Research Report NEB-BEL-19. January 1989.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, cross-over
26	65661	BEL-17	Phase I Study: Effect of Nebivolol on Dopamine Related Phenomena. Part II: Haemodynamic Effects. Clinical Research Report NEB-BEL-17. February 1989.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled cross-over
27	65662 65669	BEL-32	Cardiac Haemodynamic effects of d-, l-, dl-Nebivolol and Atenolol during a 7-day Double-Blind Cross-Over Study in Healthy Volunteers. Clinical Research Report NEB-BEL-32. March 1989. Effects of Isometric Handgrip on Blood Pressure and Heart Rate during a 7-day Double-Blind Cross-Over Treatment with dl-, d-, and l-Nebivolol and Atenolol in Healthy Volunteers. Clinical Research Report NEB-BEL-32, January 1989.	Pharmacodynamic, Hemodynamic, Double-blind, active-controlled
28	68085	BEL-21	Phase I Study: Comparison of the Subacute Haemodynamic Effects of l-nebivolol versus a Combination of l-Nebivolol and Atenolol in Healthy Volunteers. Clinical Research Report NEB-BEL-21. March 1989.	Pharmacodynamic, Hemodynamic, Double-blind, active-controlled, parallel groups
29	108085 106560	NED-7	Invasive Hemodynamics of Nebivolol in Hypertensive Patients. Synoptic Clinical Research Report NEB-NED-7. April 1994. Invasive Hemodynamics of Nebivolol in Hypertensive Patients.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, cross-over
30	107433	USA-2	Evaluation of Left Ventricular Function Assessed with Doppler Echocardiography and Radionuclide Ventriculography in Hypertensive Patients after Chronic Treatment with Nebivolol and Atenolol. Clinical Research Report NEB-USA-2, April 1994.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, active-controlled, cross-over

#	LMD No.	Study ID	Title	Study Category/ Type/Design
31	54549 45715	BEL-30	Haemodynamic Effects of a Single Oral Administration of R 65824, a New Selective Beta-1-Adrenoceptor Blocking Agent in Human Volunteers as compared to the Effects of Atenolol, Pindolol and Propranolol. Clinical Research Report NEB-BEL-30, September 1985. Haemodynamic Effects in Man During Exercise of a Single Oral Dose of Nebivolol (R67555), a New Beta-1-Adrenoceptor Blocking Agent: a Comparative Study with Atenolol, Pindolol and Propranolol. (Drug Development Research; 8: 109-117, 1986)	
32	56952	BEL-1/Part I	Hematological, Biochemical and Urinary Safety during Subacute Treatment with Nebivolol in a Double-Blind Placebo-Controlled Study. Part I, Clinical Research Report NEB-BEL-1. August 1987.	Pharmacodynamic, Safety, Double-blind, placebo-controlled, cross-over
33	59056	BEL-1/Part II	Double-Blind Placebo-Controlled Study Comparing the Haemodynamic Effects of Various Doses of Nebivolol during Subacute Treatment. Clinical Research Report NEB-BEL-1. June 1987.	Pharmacodynamic, Hemodynamic, double-blind, placebo-controlled, cross-over
34	59580	N/A	Randomized Cross-Over Study Comparing the Haemodynamic Effects during Exercise of a Single Administration of Nebivolol 0.5 mg I.V., 5 mg Tablet and 5 mg Solution in Healthy Volunteers. Clinical Research Report. March 1987.	Pharmacodynamic, Hemodynamic, Open-label, placebo-controlled, cross-over
35	59899	BEL-35	Acute Haemodynamic Effects of Various Doses of Nebivolol in a Placebo-Controlled Cross-Over Study in Healthy Volunteers. Clinical Research Report NEB-BEL-35. February 1988.	Pharmacodynamic, Hemodynamic, Open-label, placebo-controlled, cross-over
36	59922	BEL-38	Acute hemodynamic Effects of 2 Enantiomers of Nebivolol (R 67138 and R 67145) in Men at Rest and During Exercise. Clinical Research Report NEB-BEL-38. March 1988.	Pharmacodynamic, Hemodynamic, Open-label, cross-over
37	59970	BEL-36	Double-Blind Study Comparing the Subacute Hemodynamic Effects in Men at Rest and During Exercise of the 2 Enantiomers of dl-Nebivolol, d-Nebivolol (R67138) and l-Nebivolol (R67145). Clinical Research Report NEB-BEL-36. March 1988.	Pharmacodynamic, Hemodynamic, Double-blind, cross-over
38	64858	RSA-1	The Effects of Nebivolol on Heart Rate and Blood Pressure at Rest and During Exercise. A Dose Finding Study. Clinical Research Report NEB-RSA-1.	Pharmacodynamic, Hemodynamic, Open-label, cross-over

#	LMD No.	Study ID	Title	Study Category/ Type/Design
39	65577 69017	BEL-9	Effects of Isometric Handgrip on Blood Pressure and Heart Rate During a 14-day Double-Blind Cross-Over Treatment with Nebivolol and Atenolol in Healthy Volunteers. Clinical Research Report NEB-BEL-9. January 1989. Non-Invasive Cardiac Haemodynamics of Nebivolol in Man. (Acta Antwerpiensa; 6(2): 2-21, 1989)	Pharmacodynamic, Hemodynamic, Double-blind, active-controlled, cross-over
40	106561	NED-11	Pharmacological Properties of Nebivolol in Man	Hemodynamic, Single-blind, cross-over
41	65660	BEL-15	Double-Blind Placebo-Controlled Cross-Over Study Evaluating the Acute Haemodynamic Effects of dl-Nebivolol 5 mg, d-Nebivolol 2.5 mg and l-Nebivolol 2.5 mg in Healthy Volunteers. Clinical Research Report NEB-BEL-15. February 1989.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, cross-over
42	68099	RSA-5	The Effects of Nebivolol on Heart Rate and Blood Pressure at Rest and During Exercise. A Sub-Acute Dose Finding Study. Clinical Research Report NEB-RSA-5.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, parallel groups
43	88216	SWE-1	Nebivolol—Blockade of Exercise Induced Tachycardia. Clinical Research Report NEB-SWE-1. March 1991.	Pharmacodynamic, Hemodynamic, Single-blind, placebo-controlled, active-controlled, cross-over
44	88260	GBR-19	The Effect of Nebivolol on Heart Rate, Blood Pressure and Cardiac Output at Rest and During Exercise in Healthy Volunteers. February 1991.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled
45	106914	BEL-26	Cardiovascular and Metabolic Effect of d-, l- and dl-Nebivolol. Synoptic Clinical Research Report NEB-BEL-26. September 1994.	Pharmacodynamic, Hemodynamic, Double-blind, cross-over, placebo-controlled, parallel group
46	106917	BEL-25(a)	Comparison of the Metabolic Effects of Nebivolol and Atenolol During Dynamic Exercise Part 1: Healthy Volunteers. Synoptic Clinical Research Report NEB-BEL-25(a). September 1994.	Pharmacodynamic, Hemodynamic, Double-blind, active-controlled, cross-over
47	106918	BEL-25(b)	Comparison of the Metabolic Effect of Nebivolol and Atenolol During Dynamic Exercise Part 2: in Patients with Borderline HT and/or Abnormally Quick Rise of BP During Exercise. Synoptic Clinical Research Report-NEB-BEL-25(b). September 1994.	Pharmacodynamic, Hemodynamic, Double-blind, active-controlled, cross-over
48	108077	BEL-16	Comparative Study on the Effects of Nebivolol (2.5 and 5 mg) and Atenolol (50 mg) on Renal Blood Flow at Rest and on Energy Liberation During One Hour Submaximal Dynamic Exercise in Normal Individuals. A Pilot Study. Synoptic Clinical Research Report NEB-BEL-16. June 1994.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, cross-over

#	LMD No.	Study ID	Title	Study Category/ Type/Design
49	92970	INT-2	Effect of Nebivolol (5 mg) on Exercise Induced Tiredness in Essential Hypertension. A Double-Blind, Randomized Comparison with Atenolol (50 mg) and Placebo, After a 4-week Placebo Run-In Period. Clinical Research Report NEB-INT-2. August 1993.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, active-controlled, cross-over
50	107426	GBR-4	A Comparison of the Haemodynamics of Nebivolol and Atenolol in Hypertensive Patients. Clinical Research Report NEB-GBR-4. December 1993.	Pharmacodynamic, Hemodynamic, Double-blind, placebo-run in, active-controlled, cross-over
51	59898	N/A	Haemodynamic Effects of Subacute Treatment with Nebivolol: A Comparison Between Poor and Normal Metabolizers. February 1988.	Pharmacodynamic, Hemodynamic, Open-label, parallel group
52	62826	BEL-4/Part I	Comparison of the Subacute Haemodynamic Effects of Nebivolol in Poor and Normal Metabolizers. Part I. Clinical Research Report NEB-BEL-4. May 1988.	Pharmacodynamic, Hemodynamic, Open-label, parallel group
53	62269	BEL-4/Part II	Effect of an 8-day Intake of Nebivolol 5 mg/day on ECG in 6 poor and 6 Normal Metabolizers. Part II. Clinical Research Report NEB-BEL-4. May 1988.	Pharmacodynamic, Hemodynamic, Open-label, parallel group
54	62270	BEL-4/Part III	Multiple Dose Study of Nebivolol in Poor and Normal Metabolizers. Analysis of the Safety Data. Part III. Clinical Research Report NEB-BEL-4. May 1988.	Pharmacodynamic, Hemodynamic, Open-label, parallel group
55	69145	BEL-17/Part I	Effect of Nebivolol on Dopamine Related Phenomena. Part I: Hormonal Effects. Clinical Research Report NEB-BEL-17. June 1989.	Pharmacodynamic, metabolic/endocrine, Double-blind, placebo-controlled, cross-over
56	101048	BEL-52	Effects of Nebivolol on Hormonal Responses to Insulin Induced Hypoglycaemia. Clinical Research Report NEB-BEL-52. December 1993.	Pharmacodynamic, Metabolic/endocrine, Open-label
57	107434	BEL-39	The Influence of Chronic Treatment with Nebivolol or Atenolol on the Control of Glucose Levels in Diabetic Patients. Clinical Research Report NEB-BEL-39. August 1994.	Pharmacodynamic, Metabolic/endocrine, Double-blind, placebo-controlled, cross-over
58	106748	ITA-5	Efficacy and Tolerance of Nebivolol Compared to Atenolol in Non-Insulin Dependent Diabetics with Essential Hypertension. Clinical Research Report NEB-ITA-5. October 1994.	Pharmacodynamic, Metabolic/endocrine, Double-blind, placebo-run in, active-controlled, parallel groups
59	125153	CAN-7	Clinical Evaluation of the Effects of Nebivolol vs. Atenolol on Plasma Lipid Profile and Carbohydrate Metabolism in Normometabolic Patients with Mild-to-Moderate Hypertension. Clinical Research Report NEB-CAN-7.	Pharmacodynamic, Metabolic/endocrine, Double-blind, active-controlled, parallel groups

#	LMD No.	Study ID	Title	Study Category/ Type/Design
60	126525	CAN-8	A Prospective Comparison of the Effects of Nebivolol and Atenolol on Glucose, Insulin and Lipid Metabolism During Long-Term Treatment in Patients with Mild to Moderate Essential Hypertension and Impaired Glucose Intolerance. Clinical Research Report NEB-CAN-8. February 1998.	Pharmacodynamic, Metabolic/endocrine, Double-blind, active-controlled, cross-over
61	92864	N/A	A Study to Assess the Effects of Nebivolol on Sedation and Psychomotor Performance.	Pharmacodynamic, Psychomotor/sedation, Double-blind, placebo-controlled, cross-over
62	107425	GBR-14	A Study of the Possible Pharmacokinetic and Psychomotor Interactions of Alcohol and Nebivolol in Healthy Volunteers. Clinical Research Report NEB-GBR-14. March 1994.	Pharmacodynamic, Psychomotor/sedation, Double-blind, placebo-controlled, cross-over
63	106642	GBR-22	Effect of Nebivolol on Lung Function in Normal Subjects: A Comparison with Atenolol and Propranolol. Clinical Research Report NEB-GBR-22. December 1989.	Pharmacodynamic, Pulmonary, Double-blind, placebo-controlled, active-controlled, cross-over
64	92579	ITA-2	Open Trial with Nebivolol 5 mg Once Daily in Hypertension with Renal Artery Stenosis. Clinical Research Report NEB-ITA-2. March 1993.	Pharmacodynamic, Renal, Open-label, placebo-run in
65	49643	N/A	Randomized Double-Blind Cross-Over Study of the Effects of Topical R67555 as Compared with Timolol on the Intraocular Pressure, Blood Pressure and Heart rate in Human Healthy Volunteers. April 1986.	Pharmacodynamic, Ophthalmic, Double-blind, active-controlled, cross-over
66	51686	N/A	Randomized Double-Blind Cross-Over Study of the Effects of Topical R67555 as Compared with R67555 Solvent and Timolol, on the Intraocular Pressure, Blood Pressure and Heart Rate in Human Healthy Volunteers. July 1986	Pharmacodynamic, Ophthalmic, Double-blind, active-controlled, cross-over
67	46816	N/A	Safety Data after Oral Administration of R65824 5 mg/day for 7 Consecutive Days in 6 Human Volunteers. December 1985.	Pharmacodynamic, Safety, Open-label
68	46817	N/A	Safety Data After a Single Oral Administration of 5 mg and 10 mg of R65824 in 8 Human Volunteers. December 1985.	Pharmacodynamic, Safety, Open-label

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Studies Sponsored by Janssen

	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
69	88035	INT-1 US Study Results	Report of U.S. Study Results in an International Trial: Nebivolol in the Treatment of Essential Hypertension (A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study). Clinical Research Report NEB-INT-1. March 1992.	Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups	Sample size/Mean change from baseline at endpoint intent-to-treat (supine or sitting DBP at trough mm Hg)^ Placebo: 42/ -3.0 0.5 mg: 42/-5.4 1 mg: 42/-4.7 2.5 mg: 43/-5.5 5 mg: 44/-9.1 10 mg: 41/-8.7 ^ unless otherwise noted
70	101220	INT-1 Non-US	The Effect of Nebivolol (0.5, 1, 2.5, 5, and 10 mg) in the Treatment of Essential Hypertension. A Double-Blind, Randomized Comparison with Placebo in an International Dose-Finding Trial. Clinical Research Report NEB-INT-1. March 1992.	Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups	Placebo: 84/-3.3 0.5 mg: 83/-4.0 1 mg: 87/-6.0 2.5 mg: 85/-7.1 5 mg: 86/-9.2 10 mg: 84/-10.1
71	106572 92891	USA-1	A Pilot Study to Compare the Cardiac Effects of Nebivolol and Atenolol. Synoptic Clinical Research Report NEB-USA-1. April 1994. Comparison of Antihypertensive and Beta-1-Adrenoceptor Antagonist Effect of Nebivolol and Atenolol in Essential Hypertension. (Clinical and Experimental Hypertension; 15(3): 501-509, 1993).	Janssen, Hypertension Double-blind, Placebo-controlled, Parallel group, Active-controlled, Cross-over	1. Diastolic and systolic blood pressures were reduced to the same extent by nebivolol and atenolol; 2. PEP/LVET as an indirect measure for left ventricular performance shows a favorable decrease in the nebivolol 10 mg group compared to the unchanged value after atenolol.
72	84315	USA-3	Double-Blind, Placebo-Controlled Study of Nebivolol 30 mg in Hypertensive Patients. Clinical Research Report NEB-USA-3. February 1991.	Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups	N=8 nebivolol, N=4 placebo. See complete review for full details.
73	88185	USA-4	Nebivolol in the Treatment of Essential Hypertension (A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study). Clinical Research Report NEB-USA-4. May 1992.	Janssen Double-blind, Placebo-controlled, Parallel groups	Placebo: 46/-3.7 2.5 mg: 46/-6.4 5 mg: 44/-7.2 30 mg: 44/-10.1

	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
74	106916	USA-6	Nebivolol in Congestive Heart Failure: a Placebo-Controlled, Double-Blind, Dose-Titration, Pilot Study. Clinical Research Report NEB-USA-4. November 1994.	Janssen, Other cardiovascular condition Double-blind, Placebo-controlled, Parallel groups	Placebo: 19 Nebivolol: 19 6-Minute Walk Test At the overall endpoint, the walking distance for subjects on placebo was significantly increased compared to baseline ($p \leq 0.04$), whereas there was no significant increase in subjects on nebivolol.
75	101044	BEL-3/6	Double-Blind, Placebo-Controlled, Multicentre Trial with Oral Nebivolol 2.5, 5 and 10 mg Once Daily in Essential Hypertension, Followed by An Open Nebivolol 5 mg Treatment for Up to 4 Years. Clinical Research Report NEB-BEL-3/6. November 1993.	Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups	Placebo: 35/-11.3 2.5 mg: 35/-15.7 5 mg: 34/-16.1 10 mg: 32/-15.7
76	101219	BEL-12/18	The Effect of Nebivolol (0.5, 1, 2.5 and 5 mg) in the Treatment of Essential Hypertension. A Double-Blind, Randomized Comparison with Placebo in a Dose Finding Trial Followed by an Open Long-Term Follow-Up. Clinical Research Report NEB-BEL-12/18. June 1994.	Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups, Open-label	Placebo: 41/-9.4 0.5 mg: 37/-12.5 1 mg: 41/-10.6 2.5 mg: 42/-17.0 5 mg: 42/-14.4
77	122133	FRA-6	Comparison of Efficacy and Tolerability of Nebivolol Combined with Nitrendipine and Placebo Combined with Nitrendipine in the Treatment of Hypertension Resistant to Nitrendipine. Clinical Research Report NEB-FRA-6. June 1998.	Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups	Nebivolol + nit: 12/-12.4 Placebo + nit: 12/-9.4
78	92707	GBR-1	Effect of Nebivolol (5 mg) in Essential Hypertension. A Double-Blind, Randomized Comparison with Atenolol (50 mg) and Placebo. Clinical Research Report NEB-GBR-1. April 1994.	Janssen, Hypertension Double-blind, Placebo-controlled, Active-controlled, Parallel groups	Nebivolol: 119/-12.6 Atenolol: 121/-12.2 Placebo: 124/-4.9
79	111607	GER-12	Clinical Evaluation of the Antihypertensive Efficacy and Safety of Nebivolol versus Amlodipine in Elderly Patients with Confirmed Mild to Moderate Essential Hypertension. Clinical Research Report NEB-GER-12. May 1995.	Janssen, Hypertension Double-blind, Active-controlled, Parallel groups	Nebivolol: 41/-13.4 Amlodipine: 27/-14.6

	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
80	101221	INT-3	Nebivolol versus Enalapril in the Treatment of Essential Hypertension. Multicenter International Nebivolol Trial. Clinical Research Report NEB-INT-3. May 1994.	Janssen, Hypertension Double-blind, Active-controlled Parallel groups	5 mg Nebivolol: 205/-12.3 10 mg Enalapril: 205/-9.8
81	92909 109101	INT-4	Effect of Nebivolol and its Enantiomers in Hypertensive Patients. Comparison with Placebo and Atenolol. Clinical Research Report NEB-INT-4. June 1993. Nebivolol Long-Term Treatment in Patients with Essential Hypertension. Synoptic Clinical Research Report NEB-INT-4. December 1994.	Janssen, Hypertension Double-blind, Placebo-controlled, Active-controlled, Cross-over, Open-label	N=30 d,l nebivolol: -11.8 d nebivolol: -11.5 Atenolol: -11.5 l nebivolol: -2.1 Placebo: -4.3
82	106562	INT-7	Nebivolol versus Enalapril in the Treatment of Essential Hypertension. Multicenter International Long-Term Follow-Up Nebivolol Trial. Clinical Research Report NEB-INT-7. November 1994.	Janssen, Hypertension Double-blind, Active-controlled, Parallel groups	Nebivolol: 31/-1.2 Enalapril: 32/-0.3
83	10122	INT-5	Nebivolol versus Nifedipine in the Treatment of Essential Hypertension. Multicenter International Nebivolol Trial. Clinical Research Report NEB-INT-5. July 1994.	Janssen, Hypertension Double-blind, Active-controlled, Parallel groups	Nebivolol: 92/1.3 Nifedipine: 90/0.3
84	129816	INT-8	Nebivolol versus Nifedipine in the Treatment of Essential Hypertension (Long-Term Extension). Clinical Research Report NEB-INT-8. June 1998.	Janssen, Hypertension Double-blind, Active-controlled, Parallel groups	Nebivolol: 91/-11.2 Nifedipine: 85/-10.6
85	101182	ITA-3	Left Ventricular Hypertrophy and Systolic Function in Hypertensive Patients During Long-Term Treatment with Nebivolol. A Randomized, Double-Blind Trial versus Atenolol. Clinical Research Report NEB-ITA-3. June 1998.	Janssen, Hypertension Double-blind, Active-controlled Parallel groups	**Primary parameter:** Left ventricular mass index, g/m^2: Mean at Baseline/endpoint Nebivolol: 162.7/147.3 (n=24*) Atenolol: 168.0/149.9 (n=24*) * End systolic values for secondary echocardiography parameters were available in only half of the patients

	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
86	101224	TCH-1/2	A Double-Blind Comparative Trial of the Effects of Metoprolol and Nebivolol in Hypertensive patients. Clinical Research Report NEB-TCH-1/2. December 1993.	Janssen, Hypertension Double-blind, Active-controlled, Parallel groups	See Table below.

Therapeutic results (n = number of patients with efficacy data)	Double-blind phase	
	nebivolol (n=82)	metoprolol (n=73)
Primary parameters • Supine DBP, mm Hg mean at baseline/endpoint	102.6/85.3*	102.8/87.5

(Reproduced from Sponsor, Study ID TCH 1/2, page 8)

87	107416	CAN-9	Protocol for the Clinical Evaluation of the Antihypertensive Efficacy and Safety of Nebivolol (R67555) and d-Nebivolol (R85547) in Patients with Confirmed Mild to Moderate Essential Hypertension. Clinical Research Report NEB-CAN-9. October 1994.	Janssen, Hypertension Double-blind, Cross-over	DBP trough sitting (Mean at Baseline/Last Available Visit) Nebivolol: 30 (99/91) d-nebivolol: 30 (99/90) Hormones (renin, progesterone, testosterone, ACTH, aldosterone, cortisol, LH, FSH, estradiol): no clinically significant between treatment changes. Significant decrease from baseline in plasma renin concentration following nebivolol and d-nebivolol.

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	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
88	108086	RSA-6	A Comparison of the Effects of Nebivolol and Atenolol Against Placebo and Nitrates on Venous Tone Using Plethysmography. A Double-Blind Cross-Over Controlled Study with Hypertensive Patients. Synoptic Clinical Research Report NEB-RSA-6. March 1994.	Janssen, Hypertension Double-blind, Placebo-controlled, Active-controlled, Cross-over	See Table below.

Pharmacodynamic and clinical results		end of run-in	nebivolol (n = 21)	atenolol (n=20)	placebo (n=21)
Plethysmography					
• maximum venous outflow, ml/min/100 ml: mean ± SEM					
- arm	pre nitro	41.2±1.63	39.9±1.77	42.1±2.08	40.4±2.01
	post-pre nitro	5.7±0.80	4.6±0.89	5.7±0.81	6.3±0.84
- leg	pre-nitro	40.7±2.23	39.2±1.90	41.0±1.81	40.1±2.33
	post-pre nitro	6.5±0.82	4.9±0.88	6.0±0.81	6.0±0.65
• venous volume, ml/100 ml					
- arm	pre nitro	2.4±0.08	2.5±0.07	2.6±0.07	2.6±0.05
	post-pre nitro	0.3±0.02	0.3±0.02 *	0.3±0.03 **	0.2±0.03
- leg	pre nitro	2.6±0.14	2.6±0.12	2.7±0.10	2.7±0.08
	post-pre nitro	0.1±0.03	0.2±0.05	0.2±0.03	0.2±0.02

(Reproduced from Sponsor, Study ID RSA-6, page 2)

89	101046	NED-12/8	Nebivolol in the Treatment of Essential Hypertension. A Multicenter, Double-Blind, Cross-Over, and Single-Treatment Trial with An Open Long-Term Follow-Up. Clinical Research Report NEB-NED-12/8. April 1994.	Janssen, Hypertension Double-blind, Placebo-controlled, Cross-over	Placebo: 80/-2.3 Nebivolol: 80/-10.6
90	92691	NED-13/10	The Efficacy and Safety of Nebivolol in Severe Hypertension. A Randomized, Placebo-Controlled Cross-Over Trial Followed by 11 Months of Open Nebivolol Treatment. Clinical Research Report NEB-NED-13/10. September 1993.	Janssen, Hypertension Double-blind, Placebo-controlled, Cross-over	Placebo: 19/-5.3 Nebivolol: 19/-14.4

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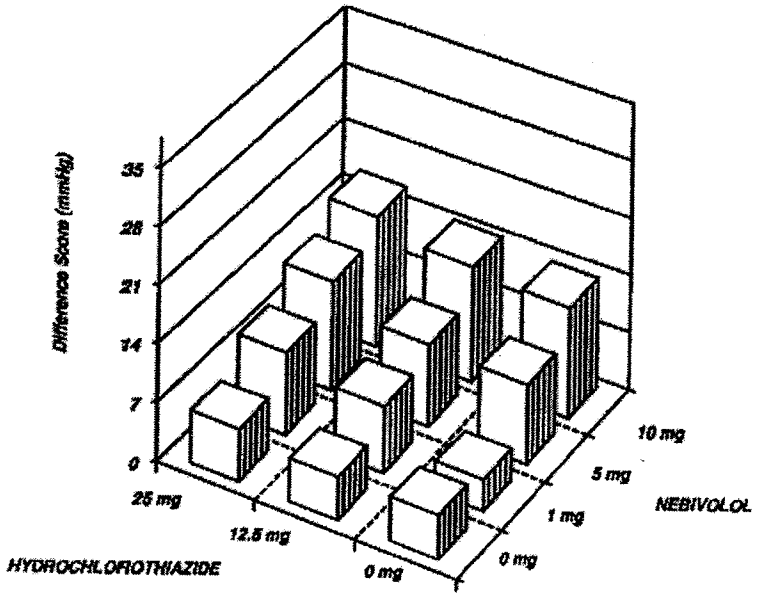
	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
91	107414	CAN-3	Multicentre Clinical Evaluation of Antihypertensive Efficacy and Safety of the Combination of Nebivolol and Hydrochlorothiazide: HANS (Hydrochlorothiazide and Nebivolol Study). Clinical Research Report NEB-CAN-3. October 1994.	Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups	See Figure below.

Display 5c: Mean Difference from Baseline Scores for Trough Sitting Diastolic Blood Pressure (mmHg) - Week 4



(Reproduced from Sponsor, Study ID CAN-6, Display 5c, page 62)

92	107415	CAN-6	Clinical Evaluation of the Antihypertensive Efficacy and Safety of Nebivolol versus Lisinopril in Patients with Confirmed Mild to Moderate Essential Hypertension. Clinical Research Report NEB-CAN-6. July 1994.	Janssen, Hypertension Double-blind, Active-controlled, Cross-over	(Clinic BP: A responder is defined as patients having a sitting DBP < 90 mm Hg or decrease ≥ 10 mm Hg) **% Responders:** Lisinopril: 29/52% Nebivolol 29/41%

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	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
93	101047	POR-1/5	Nebivolol in the Treatment of Essential Hypertension. A Multicenter Open and Double-Blind Trial with An Open Long-Term Follow-up. Clinical Research Report NEB-POR-1/5. December 1993.	Hypertension Double-blind, Placebo-controlled, Open-label	2.5 mg: 133/-12.2 Placebo: 46/+8.2 2.5 mg: 47/+3.6
94	109042	BEL-23	Tolerability of Nebivolol in Patients with Essential Hypertension. Synoptic Clinical Research Report NEB-BEL-23. November 1994.	Hypertension Open-label, Dose-escalation	Week 1: 22/10 mg; Week 2: 22/15 mg; Week 3-6: 22/20 mg. No DBP results, dosage-dependent AEs
95	108081	GER-5	Double-Blind Trial of Nebivolol versus Placebo in the Treatment of Essential Hypertension. Synoptic Clinical Research Report NEB-GER-5. September 1994.	Hypertension Double-blind, Placebo-controlled, Parallel groups	Placebo: 15/-1.7 2.5 mg: 15/-3.6 5.0 mg: 15/-11.0
96	108083	NED-4	Efficacy, Pharmacodynamics, Pharmacokinetics and Safety of Open Nebivolol Treatment (2.5 mg and 7.5 mg) in Hypertensive patients. Synoptic Clinical Research Report NEB-NED-4. December 1993.	Hypertension Open-label	2.5 mg: 6/-9.0 7.5 mg: 6/-16.0
97	109089	NED-9	Tolerability of Nebivolol in Patients with Essential Hypertension. Synoptic Clinical Research Report NEB-NED-9. November 1994.	Hypertension Open-label	Week 1: 10/10 mg; Week 2: 10/15 mg; Week 3-4: 10/20 mg. No DBP results, dosage-dependent AEs
98	84288	MEX-1	Long-Term Therapy with Nebivolol in Patients with Hypertension. (Drug Investigation; 3 (suppl. 1): 180-182, 1991).	Hypertension Open-label	5.0 mg (3 mos.): 40/-13.1 5.0 mg (6 mos.): 35/-15.2
99	84283	NED-1	Nebivolol. An Acute and Long Term Study in Essential Hypertension. (Drug Investigation;(suppl. 1): 152-154, 1991).	Hypertension Single-blind, Placebo-controlled	Placebo: 9/+7.0 5.0 mg (4 wks.): 9/-18.0
100	108082	NED-2	Effect of a Single Dose of Nebivolol in Hypertensive Patients: Dose-Finding. Synoptic Clinical Research Report NEB-NED-2. December 1987.	Hypertension Open-label	Single dose 10 mg (n=5), BP ↓ > with nebivolol vs. placebo
101	109065	AUS-3	A Study to Establish the Acute Effects of Nebivolol on Blood Pressure and Whether or Not There are First Dose Postural Effects in Middle Aged and Elderly patients. Synoptic Clinical Research Report NEB-AUS-3. October 1994.	Hypertension Double-blind, Placebo-controlled, Active-controlled, Cross-over	(n=11) Efficacy data not reported
	111589		A Study to Establish the Acute Effects of Nebivolol on Blood Pressure and Whether or Not There are First Dose Postural Effects in Middle Aged and Elderly patients. Clinical Research Report NEB-AUS-3. March 1995.		1st dose effect on BP & postural change (n=12): placebo, nebivolol 5 mg, labetalol 200 mg, atenolol 50 mg. Nebivolol = atenolol, labetalol worse

	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
102	106715	AUS-5	Effect of Single and Combination Therapy with Nebivolol and Enalapril and Comparison with Placebo in the Treatment of Essential Hypertension. Clinical Research Report NEB-AUS-5. October 1994.	Hypertension Double-blind, Placebo-controlled, Active-controlled, Cross-over	Placebo: 16 Nebivolol 5 mg: 19 Enalapril 10 mg: 17 Neb+Enal: 20 Neb > effect on BP Placebo & Enalapril.
103	76693	ARG-1	Effects of Nebivolol on Left Ventricular Function in Patients with Essential hypertension. (Drug Investigation; 3 (suppl. 1): 155-160, 1991).	Hypertension Double-blind, Active-controlled, Parallel groups	Nebivolol 5 mg: 15/-15.1 Atenolol 100 mg: 15/-11.4
104	107413	FRA-5	Effect of Nebivolol on Arterial Hemodynamics and Compliance in Patients with Essential Hypertension. Clinical Research Report NEB-FRA-5. October 1994.	Hypertension Double-blind, Active-controlled, Parallel groups	Nebivolol 5 mg:12/-15.7 Atenolol 100 mg: 12/-12.4
105	106599	GER-9	Double-Blind Placebo-Controlled Phase II Study of dl-Nebivolol and its d- and l-Enantiomers in Patients with Mild to Moderate Hypertension. Clinical Research Report NEB-GER-9. April 1994.	Hypertension Double-blind, Placebo-controlled, Parallel groups	Placebo: 8/+5.1 Nebivolol-dl 5 mg: 8/-7.9 Nebivolol-l 2.5 mg: 8/+1.1 Nebivolol-d 2.5 mg: 7/-16.4
106	106921	MEX-2	Nebivolol in Hypertensives; Diastolic Function. Synoptic Clinical Research Report NEB-MEX-2. October 1994.	Hypertension Double-blind, Active-controlled, Cross-over	Nebivolol 5 mg: 14/-12 Atenolol 100 mg: 14/-13
107	64696	BEL-10	Double-Blind, Placebo-Controlled Cross-Over Study with Nebivolol in Hypertensive Patients. Analysis in Haematological and Biochemical Safety Data. Clinical Research Report NEB-BEL-10. December 1988.	Hypertension Double-blind, Placebo-controlled, Cross-over	Placebo: 23/0.0 Nebivolol 5 mg: 23/-10.0
108	84062	HKG-2	The application of Nebivolol in Essential Hypertension: A Double-Blind, Randomized, Placebo-Controlled Study. (International J. Cardiology; 35: 387-395, 1992).	Hypertension Double-blind, Placebo-controlled, Parallel groups	Placebo: 14/0.0 Nebivolol 5 mg: 18/-5.0
109	109079 106927	GBR-2	Nebivolol and 24 Hour Blood Pressure Monitoring: A Comparison with Placebo. Synoptic Clinical Research Report NEB-GBR-2. December 1994. Nebivolol and 24 Hour Blood Pressure Monitoring: A Comparison with Placebo. Clinical Research Report NEB-GBR-2. September 1993.	Hypertension Double-blind, Placebo-controlled, Cross-over	Placebo: 14/-16.6 Nebivolol 5 mg: 14/-14.7 Placebo: 14/-4.5 Nebivolol 5 mg: 14/-11.6

	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
110	153127	CAN-10	Evaluation of the Safety of Nebivolol 5 mg o.d. in Mild to Moderate Hypertensive Subjects Characterized as Poor Metabolizers for Debrisoquine, in Comparison to Extensive Metabolizers. Clinical Research Report NEB-CAN-10. May 2000.	Hypertension Open-label, Parallel groups	Nebivolol 5 mg: EM 23/-10.2 Nebivolol 5 mg: PM 14/-9.3
111	106923	BEL-11	Open Long-Term Treatment with 5 mg Nebivolol in Patients with Essential Hypertension. Synoptic Clinical Research Report NEB-BEL-11. November 1994.	Hypertension Open-label	Nebivolol 5 mg 1 yr: 37/-10.0 Nebivolol 5 mg 2 yr: 28/-10.0
112	108080	GER-2	Oral Treatment with Nebivolol in Hospitalized Patients with Essential Hypertension. An Open Pilot Study. Synoptic Clinical Research Report NEB-GER-2. September 1988.	Hypertension Open-label	Nebivolol 1 mg: 22/-33.5
113	92596	RSA-8	Long-Term (3-month) Effects of A New Beta-Blocker (Nebivolol) on Cardiac Performance in Dilated Cardiomyopathy. (JACC; 21(5): 1094-1100, 1993)	Other cardiovascular condition, Double-blind, Placebo-controlled, Parallel groups	Placebo: 13/+1.0 Nebivolol 1-5 mg: 11/-6.0 Nebivolol +chronotropic & -inotropic effect
114	106915	BEL-46	Long-Term Effects of Nebivolol on Ischaemic Left Ventricular Dysfunction. Clinical Research Report NEB-BEL-46. October 1994.	Other cardiovascular condition, Double-blind, Placebo-controlled, Parallel groups	Placebo: 10/? Nebivolol 2.5 mg: 10/? Nebivolol 5 mg: 10/? Atenolol 50 mg: 10/? Nebivolol > exercise tolerance than atenolol
115	101223	TCH-4	Clinical and Haemodynamic Effects of Nebivolol in Patients with Mild to Moderate Congestive Heart Failure. Clinical Research Report NEB-TCH-4. April 1994.	Other cardiovascular condition, Double-blind, Placebo-controlled, Parallel groups	Placebo: 29/+2.1 Nebivolol 2.5 mg: 29/-2.4 Nebivolol 5 mg: 33/-3.1
116	106563	BEL-42	Postoperative Haemodynamic Effects of Racemic Nebivolol Compared to d- and l-Nebivolol in Patients with Coronary Artery Bypass Grafting. Synoptic Clinical Research Report NEB-BEL-42. January 1994.	Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups	Nebivolol-dl 5 mg: 17/-1.3 Nebivolol-l 2.5 mg: 16/+1.8 Nebivolol-d 2.5 mg: 16/-0.2

	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
117	76730	ITA-1	Antianginal and anti-ischaemic activity of nebivolol in stable angina of effort. (Drug Investigation; 3 (suppl. 1): 86-96, 1991).	Other cardiovascular condition Double-blind, placebo-controlled, parallel groups	Placebo: 16/? Nebivolol 5 mg: 16/?
118	84268	FRA-3	Pilot Study of Cardiovascular Effects of Nebivolol in Congestive Heart Failure. (Drug Investigation; 3 (suppl. 1): 69-81, 1991).	Other cardiovascular condition, Double-blind, Placebo-controlled, Parallel groups	Placebo: 6/+6 Nebivolol 1,2.5,5 mg: 6/-1
119	92860	GER-7	Determination of the Anti-Ischemic Activity of Nebivolol in Comparison with Atenolol. (International J. Cardiology; 43: 279-289, 1994).	Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups	Nebivolol 5 mg: 12/? Atenolol 100 mg: 12/?
120	106920	TCH-3	Effect of Nebivolol and Metoprolol in Patients with Coronary Artery Disease and Depressed Left Ventricular Function. Synoptic Clinical Research Report NEB-TCH-3. October 1994.	Other cardiovascular condition, Double-blind, Parallel groups	Nebivolol 5 mg: 18/-4.8 Metoprolol 50 mg: 18/-4.8
121	79247	BEL-14	Comparison of Left Ventricular Haemodynamics of Nebivolol and Metoprolol in Patients with Acute Myocardial Infarction. (Drug Investigation; 3 (suppl. 1): 140-141, 1991).	Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups	Nebivolol 5 mg: 40/-5.0 Metoprolol 100 mg: 40/-3.0
122	154909 107432	NED-14	Nebivolol versus Atenolol in Postinfarction Patients with Left Ventricular Dysfunction. Analysis Tables and Graphs. June 1993.	Other cardiovascular condition, Active-controlled, Parallel groups	Nebivolol 5 mg: 13/-7.0 Atenolol 100 mg: 15/-8.0
123	92597	BEL-28	Administration of Nebivolol after Coronary Artery Bypass in Patients with Altered Left Ventricular Function. (J. Cardiovascular Physiology; 22: 253-258, 1993)	Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups	Nebivolol 5 mg: 15/? Atenolol 50 mg: 15/?
124	109097	FRA-7	Comparative Study of Intravenous Nebivolol, Propranolol and Labetalol in Obese Subject: Part I-Hemodynamics. Synoptic Clinical Research Report NEB-FRA-7. November 1994.	Other cardiovascular condition, Double-blind, Active-controlled, Cross-over	Nebivolol 0.07mg/kg: 19/-6 Propanolol 0.1mg/kg: 19/-4 Labetalol 0.9mg/kg: 19/-8

	LMD No.	Study ID	Title	Disease State/ Design	Efficacy Results*
125	106528	SWE-2	Nebivolol – The effect on anginal Attacks and Exercise Tolerance in Patients with Stable Effort Induced Angina Pectoris. Clinical Research Report NEB-SWE-2. January 1994.	Other cardiovascular condition, Open-label, Placebo-controlled, Cross-over	Placebo: 10/-2 Nebivolol 2.5 mg: 10/-3 Nebivolol 5 mg: 10/-2 Nebivolol 10 mg: 10/-8
126	109017	GER-10	The Influence of Nebivolol on Haemodynamics and the Pressure-Volume Relationship in Patients with Coronary Artery Disease Undergoing Diagnostic Cardiac Catheterization. Synoptic Clinical Research Report NEB-GER-10. October 1994.	Other cardiovascular condition, Open-label	Nebivolol 2.5 mg: 7/?
127	82501	BEL-33	The Effect of Nebivolol in Patients with Left Ventricular Diastolic Dysfunction. (Acta Anterwerpiensia; 1991).	Other cardiovascular condition, Open-label	Nebivolol 5 mg: 12/?
128	80800	BEL-24/41	Effects of d-Nebivolol and l-Nebivolol on Left Ventricular Systolic and Diastolic Function: Comparison with d-l-Nebivolol and Atenolol. (J. Cardiovascular Pharmacology; 22: 183-190, 1993)	Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups	Nebivolol-dl 2.5 mg: 9/? Nebivolol-l 1.25-2.5 mg: 22/? Nebivolol-d 1.25-2.5 mg: 22/? Atenolol 15 mg: 9/?
129	108079	BEL-34	An Open Pilot Study on the Hemodynamic Effects of Nebivolol in Patients with Acute Congestive Heart Failure. Clinical Research Report NEB-BEL-34. February 1994.	Other cardiovascular condition, Open-label	Nebivolol 5 mg: 5/+4
130	72317	GER-1	Hemodynamic Effects of Nebivolol at Rest and On Exertion in Patients with Heart Failure. (Angiology; 41: 696-701, 1990).	Other cardiovascular condition, Open-label	Nebivolol 5 mg: 10/?

[*Sample size/Mean change from baseline at endpoint intent-to-treat (supine DBP at trough mmHg). ?denotes data not available.]

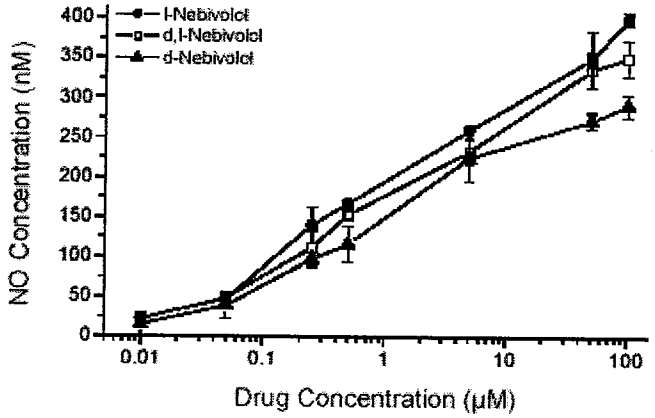
Studies Sponsored by A. Menarini Ltd

	Study ID	Title	Sponsor/Design	Efficacy Results
131	NAP 01	Randomized, Multicenter, Multinational, Dose Ranging Placebo-Controlled Comparative Study of Nebivolol, 2.5, 5, 10 and 20 mg / day in Patients with Stable Angina Pectoris	Double-Blind, Placebo-Controlled, Parallel groups	Data not available
132	MR/01-99/01-Nhf	Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure	Multi-Centre, Multi-National, Randomized, Parallel group, Placebo-Controlled, Double-Blinded Study, Phase III	Ongoing

11.8 1. Report Number: 1270_01_00. ("Comparative Effects of Nebivolol, Nebivolol Enantiomers, Atenolol, Metoprolol, Carvedilol, and Bucindolol on Human Endothelial Cell Nitric Oxide Release Following Acute Treatment") (June 25, 2002)

Study 1270.01.00 compared the effects of nebivolol, nebivolol enantiomers, atenolol, metoprolol, carvedilol, and bucindolol on the release of nitric oxide from human umbilical vein endothelial cells (HUVEC) following acute treatment. The concentrations of nebivolol and its enantiomers ranged from 100 nM to 100 μM. HUVEC released 400 nM, 300 nM, and 350 nM of nitric oxide in response to 100 μM concentrations of *l*-nebivolol, *d*-nebivolol, and racemic mixture of nebivolol, respectively, as seen in Figure 23.

Figure 23. Nitric Oxide Release from Endothelial Cells Following Acute Treatment with Nebivolol and Its Enantiomers



(Reproduced from Sponsor, Report Number 1270.01.00, Figure 1A, page 9)

The racemic mixture of nebivolol and its enantiomers increased NO release from HUVEC and were superior to the other agents tested. At a 5 μM concentration of study drug, HUVEC released 40 nM of nitric oxide for atenolol, over 200 nM for *d*-nebivolol and the racemic mixture, and over 250 nM for *l*-nebivolol. At 500 nM, HUVEC released over 160 nM of nitric oxide for racemic nebivolol, compared to slightly over 85 nM of nitric oxide for bucindolol, and less than 85 nM of nitric oxide for metoprolol and carvedilol. Nitric oxide release for this compound is shown in Figure 24 below.

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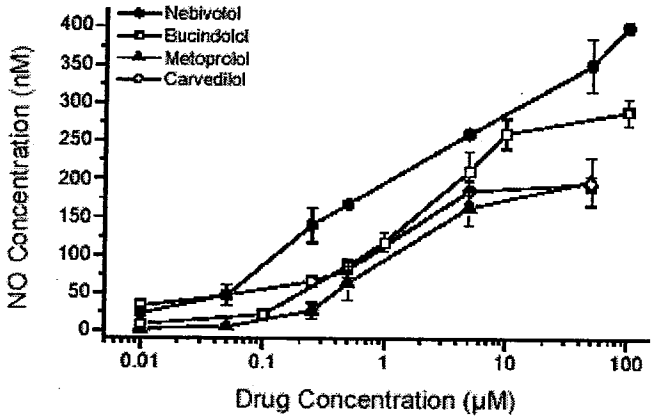
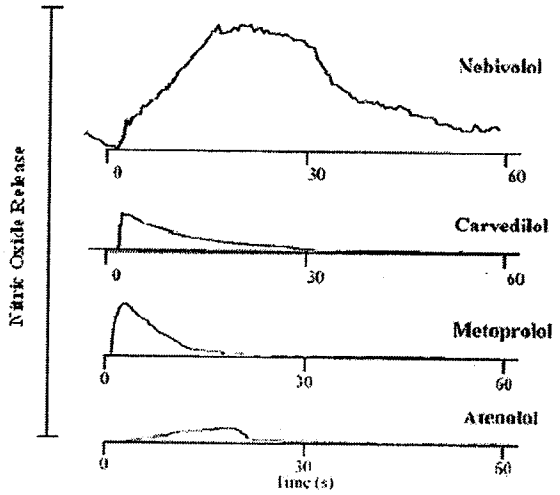
Figure 24. Nitric Oxide Release Following Acute Treatment with Nebivolol, Bucindolol, Metoprolol, and Carvedilol



(Reproduced from Sponsor, Report Number 1270.01.00, Figure 4A, page 12)

Following nebivolol, nitric oxide release from HUVEC occurred gradually over 15 seconds and then plateaued for an additional 15 seconds, prior to declining over the subsequent 30 seconds, as seen in Figure 25. The release kinetics for carvedilol,metoprolol, and bucindolol, however, were different, and were marked by a rapid onset and shorter plateau phase. The release kinetics for atenolol were not sufficiently studied. It is not known whether or not rapid release kinetics increase the concentration of superoxide and free radical formation, thereby depleting nitric oxide and resulting in cellular toxicity.

Figure 25. Nitric Oxide Releasing Effect of Various Beta-Blockers on Human Endothelial Cells



(Reproduced from Sponsor, Report Number 1270.01.00, Figure 5, page 13)

X-ray diffraction analyses found that nebivolol was located in the membrane hydrocarbon core, as were carvedilol and metoprolol, two compounds which also increased nitric oxide release. Atenolol, a hydrophilic compound, however, had its equilibrium location in the charged

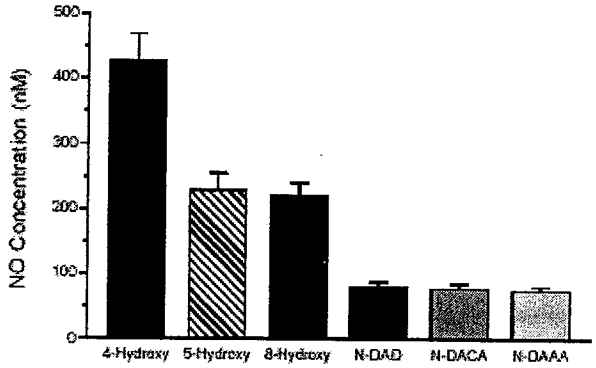
headgroup. It is not known whether or not the location of electron density for the compounds affects the amount of nitric oxide released.

Conclusions: Nebivolol, and especially *l*-nebivolol, stimulated NO release from HUVEC. Peak nitric oxide release from HUVEC following acute treatment with nebivolol appeared to be greater than nitric oxide release following acute treatment with atenolol, metoprolol, carvedilol, or bucindolol. The activity of *d*-nebivolol was approximately 70% of that measured for *l*-nebivolol. The racemic mixture of nebivolol demonstrated NO effects similar to the *l*-enantiomer alone.

11.9 2. Report Number: 1273_01_00. ("Comparative Effects of Nebivolol, Nebivolol Enantiomers, and Six Nebivolol Metabolites on Endothelial Nitric Oxide Release from Human Endothelial Cells following Acute Treatment") (July 25, 2002)

Study 1273.01.00 compared the effects of nebivolol, nebivolol enantiomers, and six nebivolol metabolites (4-hydroxy nebivolol, 5-hydroxy nevibolol, 8-hydroxy nebivolol, N-dealkylated carboxylic acid (N-DACA), N-dealkylated diol (N-DAD), and N-dealkylated amino alcohol (N-DAAA) on nitric oxide release from human endothelial cells following acute treatment. At concentrations of 10 μM of 4-hydroxy nebivolol, 5-hydroxy nebivolol, and 8-hydroxy nebivolol, HUVEC released nitric oxide at concentrations of 420 nM, 230 nM, and 230 nM, respectively. The remaining three metabolites resulted in peak NO levels less than 90 nM. At concentrations of 5 μM, 4-hydroxy nebivolol and nebivolol resulted in peak NO concentrations of greater than 400 nM and of 225 nM, respectively. Additionally, the peak NO concentration achieved after 4-hydroxy nebivolol approximated the concentration usually measured with acetylcholine, and both agents demonstrated rapid early release kinetics.

Figure 26. Peak NO Release Following Acute Treatment with Nebivolol Metabolites (10μM)



(Reproduced from Sponsor, Report Number 1273.01.00, Figure 1, page 9)

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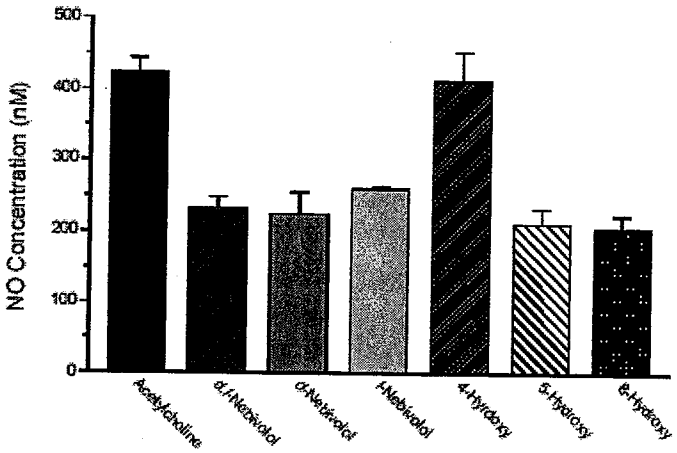
Figure 27. Peak NO Release Following Treatment with Acetylcholine, Nebivolol, and Nebivolol Metabolites (5 µM Treatment)



(Reproduced from sponsor, Report Number 1273.01.00, Figure 2, page 10)

Conclusions: Peak NO release from HUVEC following acute treatment with 4-hydroxy nebivolol approximated that seen with acetylcholine, and was higher than *d*-nebivolol, *l*-nebivolol, and *d,l*-nebivolol.

11.10 4. Report Number: 1333_00_00. ("Comparative Effects of Nebivolol and Atenolol on Nitric Oxide Release from Human Endothelial Cells following Chronic Treatment") (August 2, 2002)

Human endothelial cells were chronically treated for twenty-four hours with either a 10 µM concentration of atenolol or nebivolol. After study drug washout, the investigator reintroduced study drug and determined the concentration-dependent effects of nebivolol and atenolol on NO releasing capacity following stimulation with calcium ionophore at 1 µM. Nebivolol significantly increased nitric oxide release from HUVEC, while atenolol, had no effect, as seen in Figure 28. Additionally, at increasing concentrations of nebivolol from 0.1 µM to 10 µM, NO peak release also increased from approximately 25 nM to 120 nM. This study did not appear to test increasing concentrations of atenolol above 10 µM to see if there was a response in release of NO from HUVEC.

According to the investigators, "under control conditions, the maximum amount of NO available following stimulation with calcium ionophore is approximately 580 nM."

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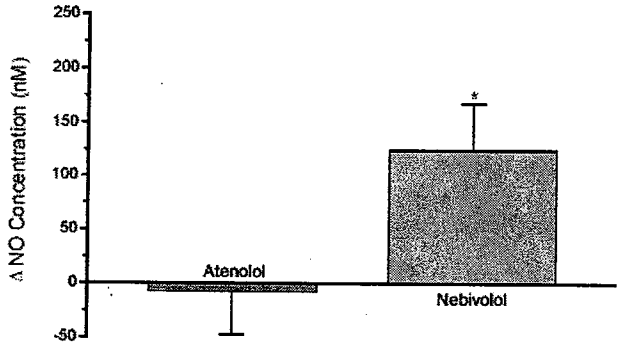
Figure 28. Peak NO Release in Endothelial Cells After Chronic Treatment with Nebivolol or Atenolol (10 µM) Followed by Stimulation with Calcium Ionophore (1 µM)



*p < 0.01 vs. control (NO release stimulated with 1 µM calcium ionophore); n = 6

(Reproduced from Sponsor, Report Number 1333_00_00, Figure 1, page 9)

In summary, nebivolol increased NO release from human endothelial cells in a concentration-dependent fashion. The investigator believes the mechanism of nitric oxide release is independent of β_1-adrenergic receptor inhibition, because atenolol at the concentration tested had no significant effect on nitric oxide concentration.

In the discussion of the findings, the report states that under normal conditions, stimulation of HUVEC preparations with 1.0 µM of acetylcholine releases nitric oxide at a concentration of 400 nM. The physiologic response is generally thought to be proportional to the concentration of nitric oxide released, and is thought to be significant at quantities greater than 100 nM.

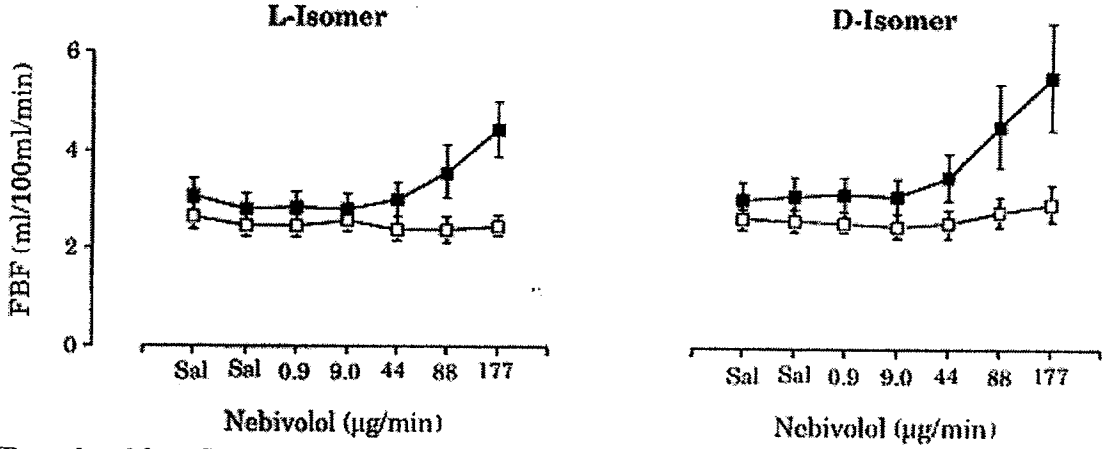
Conclusion: Peak NO release from HUVEC is a concentration-dependent phenomenon after chronic treatment with nebivolol. Although the mechanism of NO release is not known, some investigators postulate a mechanism independent of ß1-adrenergic receptor inhibition, because atenolol at the concentration tested had no significant effect on peak NO release.

11.11 16. LMD No. 106922. Study ID GBR-29. ("A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol Isomers on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-23"). (Trial Period: May 9, 1994 – May 23, 1994)

This Phase II double-blind cross-over study in 8 healthy volunteers, ages 18 to 40 years, evaluated forearm blood flow after a 6 minute intraarterial infusion of *d*- or *l*- nebivolol (0.9-177 µg/min).

Both *l*- and *d*-nebivolol significantly increased blood flow in the infused arm, compared with a saline infusion, as seen in Figure 29 below. The formulation of the individual isomers, however, contained cyclodextrin, which could have affected the results.

Figure 29. Forearm Blood Flow with Nebivolol Isomers (Mean +/- SE) (GBR-29)



(Reproduced from Sponsor, GBR-29, Figure 1, page 7)

There were no drop-outs in this study. The investigator stated there were no adverse events and no significant changes in laboratory parameters. No laboratory data was available for review.

Conclusions: Both nebivolol isomers demonstrate similar dose-dependent increases in forearm blood flow. The presence of cyclodextrin in the isomer formulations, however, may have affected these results.

11.12 19. LMD No. 107423. GBR-28. ("A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-28") (Trial Period: September 23, 1993 - November 3, 1993)

This phase II open-label crossover study in 8 healthy, non-smoking volunteers, aged 22 to 30 years, examined the effect of nebivolol on forearm blood flow. There were three study visits, separated by at least 7 days. During Visit 1, subjects received a saline infusion followed by nebivolol at 354 µg/min for 12 minutes. During Visit 2, subjects received saline followed by L-arginine at 10 mg/min for 18 minutes with nebivolol at 354 µg/min coinfused with L-arginine for the last 12 minutes and L-NMMA (4 µmol/min) coinfused with L-arginine and nebivolol for the last 6 minutes. During Visit 3, subjects received saline followed by nebivolol at 354 µg/min for 12 minutes and L-NMMA (4 µmol/min) for the final 6 minutes. Investigators measured blood flow during the last 3 minutes of each 6 minute infusion. The regimen for the Study Visits is further described in Table 183.

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Table 183. GBR-28 Drug Regimen

Treatment				
Form - intra-arterial				
Medication	Nebivolol 0.5 mg/ml	L-NMMA	L-arginine	Saline
Batch number	92F02/F?	209039 & 251060	212/62	1 ml/min
Dosage	354 µg/min	4 µmol/min	10 mg/min	
Duration	variable - as per protocol, 3 study days, 1 week apart. Visit 1 : Nebivolol for 6 minutes Visit 2 : L-arginine : min 1 - 18 co-infused with nebivolol : min 6 - 18 and L-NMMA : min 12 - 18 Visit 3 : Nebivolol : min 1 - 12 co-infused with L-NMMA : min 6 - 12			

(Reproduced from Sponsor, GBR-28, page 2)

Following Study Visit 3, subjects returned one week later for a follow-up safety appointment.

The investigator analyzed the forearm blood flow data as a percentage change from baseline using ANOVA.

Results: L-arginine did not significantly affect forearm blood flow. Following a 6 minute L-arginine infusion, the mean forearm blood flow was 3.42 ± 0.46 ml/100 ml forearm/min, compared with saline which had a mean blood flow of 3.47 ± 0.40.

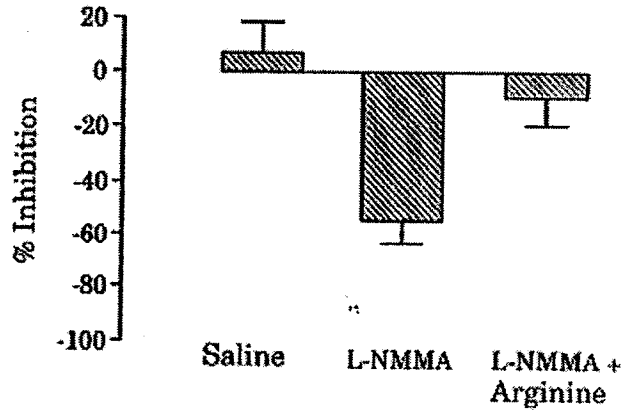
During all three study visits, nebivolol increased mean forearm blood flow following the 6 minute infusion. During Visit 1, nebivolol increased mean forearm blood flow from 3.80 ± 0.24 to 6.17 ± 0.36. During Visit 2, nebivolol increased mean forearm blood flow from 3.42 ± 0.46 (during L-arginine alone) to 6.29 ± 0.68, and During Visit 3, nebivolol increased mean forearm blood flow from 3.73 ± 0.31 to 6.27 ± 0.46. The mean forearm blood flows were not statistically significant between Visits, suggesting L-arginine did not significantly influence the vasodilator response from nebivolol. At 6 and 12 minutes of the nebivolol infusion during Visit 1, the mean blood flow was 6.17 ± 0.36 and 6.34 ± 0.42, respectively, demonstrating the lack of tachyphylaxis to the nebivolol vasodilator response.

During Visit 3, however, L-NMMA inhibited the nebivolol vasodilator response. After 6 minutes of nebivolol alone, the mean forearm blood flow was 6.27 ± 0.46 while at 12 minutes with nebivolol and L-NMMA, the mean blood flow was 4.90 ± 0.31.

During Visit 2, L-arginine almost completely counteracted the inhibitory effect of L-NMMA on nebivolol. At 6 minutes following an infusion of nebivolol with L-arginine, the mean blood flow was 6.29 ± 0.68, compared with a blood flow of 6.09 ± 0.74 at 12 minutes during the nebivolol

infusion with L-NMMA and L-arginine. The percentage inhibition of the nebivolol response at 6 and 12 minutes is summarized by the investigator in Figure 30.

Figure 30. Effect of L-Arginine and L-NMMA on Responses to Nebivolol During Visit 2 (GBR-28)



(Reproduced from Sponsor, GBR-28, Figure 1, page 11)

According to the study report, there were no drop-outs, adverse events, or significant changes in laboratory parameters or ECGs.

Conclusions: There was no evidence of tachyphylaxis following a 12 minute nebivolol infusion at 354 µg/min. L-arginine almost completely abolished the inhibitory effect of L-NMMA on the nebivolol vasodilatory response.

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11.13 20. LMD No. 107424. GBR-27. ("A Study to Compare the Effect of Nebivolol and Atenolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-27") (Trial period: August 10, 1993 – September 13, 1993)

This Phase II open label crossover study in 8 non-smoking healthy male volunteers, ages 19-28, examined the effect of nebivolol and atenolol on forearm blood flow. There were two study visits one week apart. During Visit 1, subjects received 6 minute infusions of intraarterial nebivolol in increasing doses from 18 up to 354 µg/min. During Visit 2, subjects received saline followed by a 6 minute infusion of intraarterial isoprenaline (50 ng/min) which was subsequently followed by saline for 18 minutes and a combination infusion of isoprenaline with increasing doses of atenolol from 10 to 200 µg/min. Table 184 below further describes the study regimen.

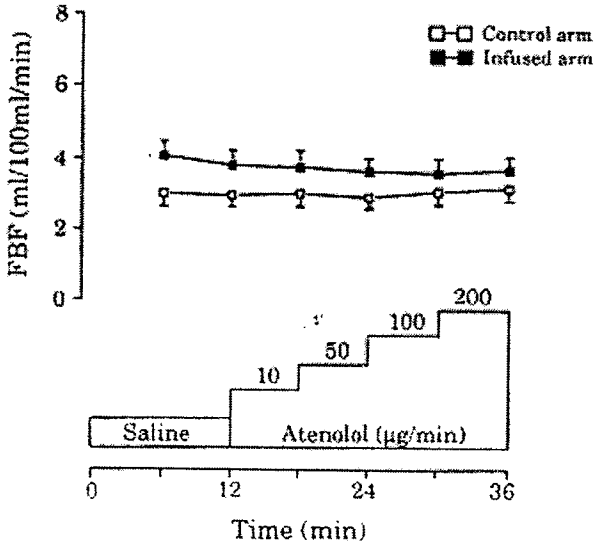
Table 184. GBR-27 Study Regimen

Treatment				
Form - intra-arterial				
Medication	Nebivolol 0.5 mg/ml	Atenolol	Isoprenaline	Saline
Batch number	92F02/F7	DS681	30250 & 30628	-
Dosage	354 µg/min	200 µg/min	50 ng/min	1 ml/min
Duration	6 minutes per dose, on 2 study days, one week apart: Day 1 - Nebivolol, increasing doses. Day 2 - isoprenaline and isoprenaline + atenolol (increasing doses)			

(Reproduced from Sponsor, GBR-27, page 1)

As seen in Figure 31 below, atenolol had no significant effect on forearm blood flow.

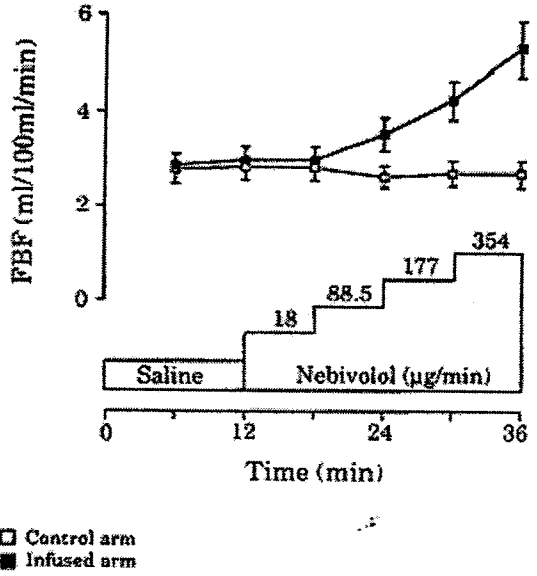
Figure 31. Effect of Atenolol on Forearm Blood Flow (Mean ± SE) (GBR-27)



(Reproduced from Sponsor, GBR-27, Figure 1, page 8)

Nebivolol dose-dependently increased forearm blood flow, as show in Figure 32 below.

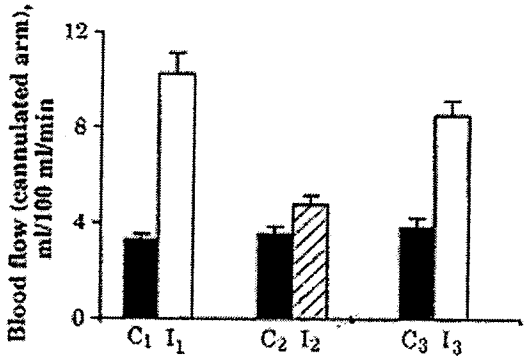
Figure 32. Effect of Nebivolol on Forearm Blood Flow (Mean ± SE) (GBR-27)



(Reproduced from Sponsor, GBR-27, Figure 3, page 10)

During Visit 2, isoprenaline infusion alone markedly increased forearm blood flow. Atenolol significantly inhibited isoprenaline induced vasodilation during the atenolol-isoprenaline coinfusion. Following atenolol and during the final isoprenaline infusion, forearm blood flow again increased, but not to the level seen with the initial isoprenaline infusion.

Figure 33. Saline Control (C) and Blood Flow During Isoprenaline (GBR-27) Before (I_1), During (I_2), and After (I_3) Atenolol



(Reproduced from Sponsor, GBR-27, Figure 2, page 9)

The percentage change in forearm blood flow, compared with saline, is shown in Table 185.

Table 185. Efficacy Results (GBR-27)

Effectiveness (n = 8)				
Venous occlusion plethysmography	Isoprenaline 50 ng/min	Isoprenaline 50 ng/min + Atenolol 200 µg/min	Atenolol 200 µg/min	Nebivolol 354 µg/min
Percentage change in forearm blood flow (drugs versus saline)	200 %	22 %	-15 %	85 %

(Reproduced from Sponsor, GBR-27, page 2)

According to the study report, there were no drop-outs, adverse events, or significant changes in laboratory or ECG parameters.

Conclusions: Nebivolol increased forearm blood flow. Atenolol, another selective ß1 adrenoceptor antagonist, had no effect on forearm blood flow and significantly inhibited isoprenaline induced vasodilation. During the final isoprenaline infusion at Visit 2, it is possible tachyphylaxis could explain the improved but diminished forearm blood flow compared with the initial isoprenaline infusion.

11.14 21. LMD No. 136347. GBR-31. ("A Study to Investigate the Vasodilator Effect of Nebivolol Racemate and Isomers on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-31. July 1997. (Trial Dates: April 26, 1995 – June 6, 1995)

Investigators submitted a Protocol with this Study Report. This Phase I single center, double blind crossover study in 8 healthy male volunteers, ages 23 to 34, examined the effect of nebivolol racemate and its isomers on forearm blood flow. Subjects received intraarterial nebivolol racemate, *l*-nebivolol, or *d*-nebivolol as 5 minute infusions during three study visits, separated by at least one week. An infusion of diluent preceeded study drug administration but failed to demonstrate any vasodilatory effect.

Investigators performed the study in accordance with the Declaration of Helsinki. The Ethics Committee approved the protocol. The study required participants to sign informed consents.

The study drug dosages are shown in Table 186.

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Table 186. Medication Regimen (GBR-31)

Treatment			
Form - dosing route	Intra-aterial infusion into the brachial artery		
Medication	L - Nebivolol [RO85548 or placebo]	D - nebivolol [RO85547 or placebo]	DL - nebivolol [RO67555 or placebo]
Batch number	94EO9/F3 - active 95B13/F4-placebo	94EO6/F3 -active 95B13/F4-placebo	94E16/F7 -active 94E18/F8-placebo
Dosage (1l/min for 5 minutes each dose)	0.91 91 44.251 88.51 1771	0.91 91 44.251 88.51 1771	1.81 181 88.51 1771 3541
Total Dosage for Study	1.6mg	1.6mg	3.35mg
Duration	30 minutes	30 minutes	30 minutes

(Reproduced from Sponsor, GBR-31, page 8)

At each study visit, investigators infused saline for 5 minutes and obtained baseline forearm blood flow measurements. Subjects then received 5 minute diluent infusions at increasing doses. Investigators measured forearm blood flow at standard intervals during the final 3 minutes of each infusion. Following the diluent infusions, subjects received nebivolol racemate and isomer infusions at increasing doses.

Table 187 shows the schedule of evaluations and procedures for GBR-31.

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Table 187. Schedule of Evaluations/Procedures (GBR-31)

Treatment			
Form - dosing route	Intra-aterial infusion into the brachial artery		
Medication	L - Nebivolol [RO85548 or placebo]	D - nebivolol [RO85547 or placebo]	DL - nebivolol [RO67555 or placebo]
Batch number	94EO9/F3 - active 95B13/F4-placebo	94EO6/F3 -active 95B13/F4-placebo	94E16/F7 -active 94E18/F8-placebo
Dosage (Il/min for 5 minutes each dose)	0.91 91 44.251 88.51 1771	0.91 91 44.251 88.51 1771	1.81 181 88.51 1771 3543
Total Dosage for Study	1.6mg	1.6mg	3.35mg
Duration	30 minutes	30 minutes	30 minutes
Disallowed medication	Any regular medication apart from paracetamol		

Assessments	Screening	Study Sessions I - III *			Final Safety Check #
		Day -1	Study Day	Day +1	
!Medical History	x				
!Clinical Assessment	x	x		x	x
!Haematology	x	x			x
!Biochemistry	x	x			x
!Heptatest (B & C)	x				
!Drug Screening	x	x			
!Urinalysis	x	x			x
!ECG	x				
!Forearm blood flow studies			x		
!Adverse event recording			x	x	x

* Separated by at least 7 days
# 7 days after third study visit

(Reproduced from Sponsor, GBR-31, page 8)

Statisticians analyzed data using ANOVA with $p<0.05$ for significance.

Efficacy results are shown in Table 188 and Table 189.

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Table 188. Summary of Absolute Blood Flow Results (GBR-31)

	Absolute Blood Flow -nebivolol ml/min/100ml	Absolute Blood Flow - control ml/min/100ml	% Change v. Diluent
L-nebivolol 177l/min	5.4	3.5	46.2
D-nebivolol 177l/min	4.7	3.4	29.9
DL-nebivolol 354l/min	5.5	3.3	63.5
	P=<0.001 in all cases		

(Reproduced from Sponsor, GBR-31, page 20)

Table 189. Efficacy Results (GBR-31)

Effectiveness	L-nebivolol 177T/min / Diluent	D-nebivolol 177T/min / Diluent	DL-nebivolol 354T/min / Diluent
Primary parameters ! Mean forearm blood flow - Diluent v.non-cannulated arm (control):ml/min/100ml	Diluent: 3.4 Control: 3.2	Diluent: 3.0 Control: 2.8	Diluent: 3.9 Control: 3.9
! Mean forearm blood flow - Nebivolol v. non-cannulated arm (control):ml/min/100ml	Nebivolol: 5.4 Control: 3.2	Nebivolol: 4.7 Control: 3.3	Nebivolol: 5.5 Control: 3.3
! % change in forearm blood flow- Nebivolol v. diluents	46.2 / 1.8 (p=<0.001)	29.9 / 0.6 (p=<0.001)	63.5 / 6.9 (p=<0.001)

(Reproduced from Sponsor, GBR-31, page 9)

Nebivolol racemate, *l*-nebivolol, and *d*-nebivolol significantly increased forearm blood flow in a dose-dependent fashion. *L*-nebivolol appeared to more potently induce vasodilation, compared with *d*-nebivolol. Although the nebivolol racemate at 177 T/min did not have as great a percent change in forearm blood flow as *l*-nebivolol, at 354T, the racemate surpassed the percent change in forearm blood flow seen with 177T *l*-nebivolol.

According to the study report, there were no drop-outs, adverse events, or significant changes in laboratory or ECG parameters. Specific laboratory and ECG results were not enclosed for review.

Conclusions: Nebivolol racemate, *l*-nebivolol, and *d*-nebivolol significantly increased mean forearm blood flow at the highest doses tested. *L*-nebivolol appears to be more potent than *d*-nebivolol in forearm vasodilatation.

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11.15 24. LMD No. 59987. Study ID: N/A. ("Invasive Haemodynamics of Nebivolol: Effects of a Single 5 mg Intravenous Injection and a 5 mg Oral Dose of Nebivolol Once Daily for 1 week on Blood Pressure, Heart Rate, Central Venous Pressure, Cardiac Output, Stroke Volume and Total Peripheral Resistance. Clinical Research Report. February 1988.") (Year of the Study: 1987)

There was no substantial protocol to review for this study.

Objectives: To determine the effect of single dose IV nebivolol 5 mg as well as oral nebivolol 5 mg daily for one week on invasive hemodynamics.

Methods: In an open-label fashion in 8 healthy volunteers, investigators administered nebivolol as a single 5 mg intravenous injection or as a 5 mg oral dose once daily for 1 week and recorded invasive hemodynamics through both radial artery and subclavian vein catheters. Investigators obtained ECGS to determine heart rate and used a 5 mg injection of indocyaninegreen into the subclavian vein to determine cardiac output. Stroke volume and total peripheral resistance were calculated values. In 5 subjects (No. 1, 2, 3, 7, and 8), investigators measured invasive haemodynamics immediately before and 0.5 hours after a single 5 mg intravenous injection of nebivolol, followed by a second session of measurements 3 hours after the last dose of a 1 week period of oral administration of nebivolol, 5 mg once daily. 3 subjects (No. 4, 5, and 6) were examined in the opposite way, which allowed for a 3 week wash-out period between the two study sessions.

Results: Table 190 shows the baseline hemodynamic results for the eight patients prior to nebivolol.

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Table 190. Individual and Mean Values of Haemodynamic Data Before Nebivolol Administration in 8 Healthy Volunteers (LMD No. 59987)

Vol. No.Init.	MAP mmHg	HR b/min	CO l/min	SV ml	TPR mmHg.min/l	CVP cm H_2O	CI ml/min/m^2	SI ml/m^2	TPRI mmHg.min/l/m^2
1.									
2.									
3.									
4.									
5.									
6.									
7.									
8.									
Mean	89	60	7.00	118	13.69	3.6	3.77	63	7.77
SD	8	8	2.01	36	4.43	2.8	.81	15	3.42
SEM	3	3	0.71	12	1.57	1.0	.29	5	1.21

(Reproduced from Sponsor, LMD No. 59987, Table 2, page 6)

Table 191 shows the hemodynamic results following IV nebivolol administration.

Table 191. Individual and Mean Values of Haemodynamic Data After Intravenous Administration of Nebivolol in 8 Healthy Volunteers (LMD No. 59987)

Vol. No.Init.	MAP mmHg	HR b/min	CO l/min	SV ml	TPR mmHg.min/l	CVP cm H_2O	CI ml/min/m^2	SI ml/m^2	TPRI mmHg.min/l/m^2
1.									
2.									
3.									
4.									
5.									
6.									
7.									
8.									
Mean	88	52	5.96	116	15.73	3.3	3.22	63	8.87
SD	8	6	1.66	36	4.04	5.0	.71	15	3.23
SEM	3	2	.59	13	1.43	1.8	.25	5	1.14
p-value*	.9454	.0078	.0156	.6914	.0078	.7422	.0156	.7422	.0078

*Wilcoxon m.p.s.r. test, 2-tailed probability versus pre-values.

(Reproduced from Sponsor, LMD No. 59987, Table 3, page 7)

Table 192 shows the hemodynamic results after oral nebivolol administration.

Table 192. Individual and Mean Values of Haemodynamic Data After Peroral Administration of Nebivolol in 8 Healthy Volunteers

Vol. No.Init.	MAP mmHg	HR b/min	CO l/min	SV ml	TPR mmHg.min/l	CVP cm H_2O	CI ml/min/m^2	SI ml/m^2	TPRI mmHg.min/l/m^2
1.									
2.									
3.									
4.									
5.									
6.									
7.									
8.									
Mean	79	53	5.67	107	14.85	3.9	3.08	58	8.31
SD	3	9	1.63	26	3.62	1.9	.72	9	2.56
SEM	1	3	.58	9	1.28	.7	.25	3	.91
p-value*	.0390	.0195	.2500	.5039	.5468	.9454	.2500	.6406	.5468

*Wilcoxon m.p.s.r. test, 2-tailed probability versus pre-values.

(Reproduced from Sponsor, LMD No. 59987, Table 4, page 8)

The overall results comparing baseline hemodynamic measurements with those obtained after both IV and PO nebivolol are shown in Figure 34 and Figure 35.

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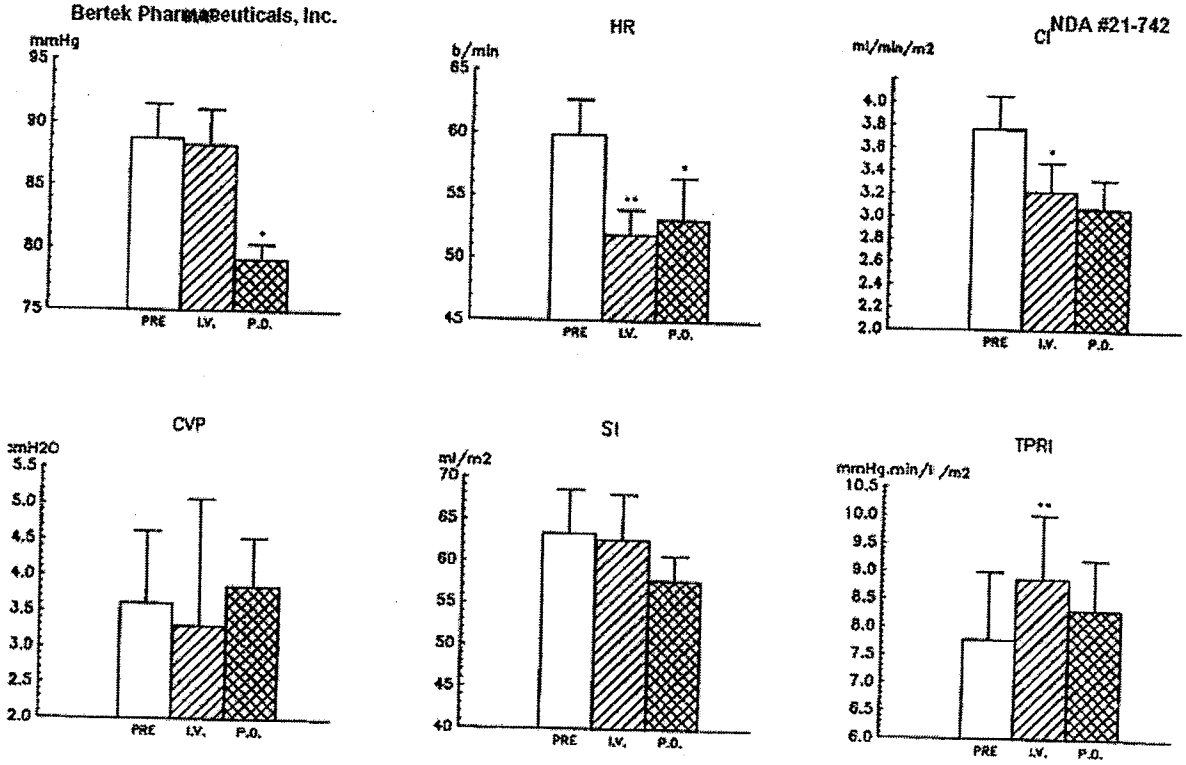
Figure 34. Mean Haemodynamic Data (+/- SEM) Before Nebivolol and After the Intravenous and Oral Application of the Drug (LMD No. 59987)



* p<0.05; ** p<0.01 by Wilcoxon m.p.s.r test, two-tailed probability versus pre.

(Reproduced from Sponsor, LMD No. 59987, Figure 1, page 9)

IV nebivolol significantly decreased heart rate and cardiac index and significantly increased TPRI. Oral nebivolol significantly decreased heart rate and MAP.

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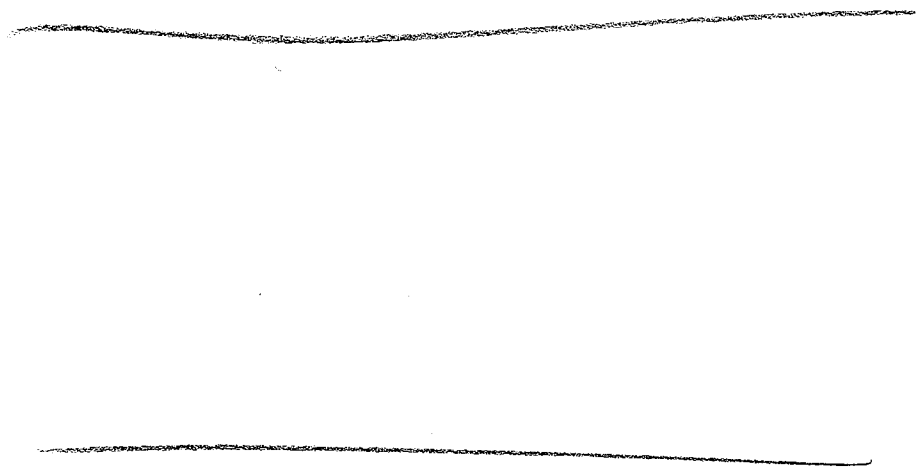
Figure 35. Individual Changes in Haemodynamics After Intravenous and Oral Application of Nebivolol (LMD No. 59987)



* p<0.05; ** p<0.01 by Wilcoxon m.p.s.r test, two-tailed probability versus pre.

(Reproduced from Sponsor, LMD No. 59987, Figure 2, page 10)

IV Nebivolol significantly decreased cardiac index and significantly increased TPRI.

Conclusions: Single dose IV nebivolol significantly decreased heart rate and cardiac index and significantly increased TPRI. One week of oral nebivolol 5 mg significantly decreased heart rate and MAP. The patient sample was small.

11.16 Line-by-Line Labeling Review

Line-by-line labeling review is pending the final Agency decision regarding approvability.

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12 REFERENCES

Bertek Pharmaceuticals Inc, Integrated Summary of Efficacy, NDA #21-742, Nebivolol, March 9, 2004, page 46.

Bristow M, University of Colorado HSC Denver, CO and ARCA Discovery, Aurora, CO, February 9, 2004, Report Number 1312_01_00, Adrenergic receptor pharmacology of nebivolol in the human heart (2004a).

Bristow M, University of Colorado HSC Denver, CO and ARCA Discovery, Aurora, CO, February 9, 2004, Report Number 1311_01_00, Adrenergic receptor pharmacology of nebivolol, its enantiomers and nine metabolites in the human heart (2004b).

Brixius K, A Bundkirchen, B Bolck, U Mehlhorn, RH Schwinger, 2001, Nebivolol, bucindolol, metoprolol and carvedilol are devoid of intrinsic sympathomimetic activity in human myocardium, Br J Pharmacol 133:1330-1338.

Hausner Elizabeth, March 25, 2002, Memo to the File, IND 33,060, Nebivolol (Correspondence Date: March 8, 2002, Submission 054, Center Receipt Date: March 11, 2002).

Hausner Elizabeth, October 17, 2002, Review and Evaluation of Toxicology Data, IND 33,060, Nebivolol hydrochloride (R67,555), Submission 059)

Hausner E, 2004, Executive Summary, Pharmacology/Toxicology Review, Cardio-Renal Division, NDA 21,742.

Janssen Statement submitted to Bertek and forwarded to FDA in e-mail dated October 14, 2004.

Lemtouni S, 2005, Executive Summary, Safety Review, Cardio-Renal Division, NDA 21,742.

Maack C, S Tyroller, P Schnabel, B Cremers, E Dabew, M Sudkamp, M Bohm, 2001, Characterization of β_1-selectivity, adrenoceptor-G_s-protein interaction and inverse agonism of nebivolol in human myocardium, Br J Pharmacol 132:1817-1826.

Mishina E, 2005, Executive Summary, Clinical Pharmacology Review, Cardio-Renal Division, NDA 21,742.

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CONSULTATION

FROM: Bruce V. Stadel, MD, MPH
Division of Metabolic & Endocrine Drug Products (DMEDP)
ODE II, CDER, FDA

THROUGH: David Orloff, MD
Director, DMEDP

TO: Daniel Shames, MD,
Director, DRUDP (HFD-580)

SUBJECT: NDA 21-742/Bertek Pharmaceuticals, Inc./Nebivolol Tablets

DATE OF REQUEST FOR CONSULTATION: 29Jan05 (informal request previously)

DATE CONSULTION COMPLETED: 02Feb05

Background

The Division of Reproductive and Urologic Drug Products (HFD-580) requested help with replies to five questions regarding possible estrogenic effects of Nebivolol, a selective beta-1 antagonist for the treatment of hypertension. For more information, see attached Request for Consultation.

Questions and Replies

Question 1 How would estrogenic effects be seen in humans, and what would be the most sensitive markers we could use to evaluate an estrogenic effect? What would be the organ systems predominantly affected, and what would be the most common malignancies seen?

The question appears to be asking for clinical signs/symptoms of estrogenicity, although laboratory tests are available, such as a competitive binding assay using mouse uterine estrogen receptors.[1]

The clinical signs and symptoms would differ for men and women.

1.1 Men

1.1.1 In men, any estrogenic effects would most likely be seen by the development of gynecomastia, which has been associated with many drugs.

The original NDA submission shows that gynecomastia was not reported in any of the 1255 men in the Sponsor's randomized, placebo controlled trials, and nebivolol was initially approved in the Netherlands in 1995 and has been approved and marketed in more that 45 countries.[2] The Safety Update through

30Jun04 shows no reports of gynecomastia.[3] Therefore, an estrogenic effect of the drug that can be detected through adverse event review is very unlikely.

In addition to gynecomastia, exogenous estrogens can cause other manifestations of hypogonadism, probably with low or normal LH. In adult men, these include erectile dysfunction, infertility, decreased beard and body hair, increased body fat, decreased size or firmness off testicles, and/or decreased muscle mass. At puberty, these also include lack of deepening of voice, impaired growth of penis and testicles, and/or excessive growth of the arms and legs in relation to the trunk. In addition, palmar erythema and spider angiomata, are sometimes seen in alcoholic liver disease, due to impaired estrogen metabolism.

1.1.2 The organs that could be affected are mainly the breast and testes.

1.1.3 For drugs that are estrogenic, cancers of the breast or testes are possible.

1.2 Women

1.2.1 Premenopausal: In premenopausal women, any estrogenic effects would most likely be seen by alterations in the menstrual cycle and/or infertility, although these effects would harder to detect that gynecomastia in men. Postmenopausal: In postmenopausal women, any estrogenic effect would most likely be seen by uterine bleeding, endometrial thickening found on ultrasound, or vaginitis. Also possible but less likely are numerous adverse events in the genitourinary system, breasts, cardiovascular system (e.g., venous thrombosis) and other sites, as listed in the Prescribing Information for estrogen drug products. The effects in postmenopausal women would be generally be easier to detect than the effects in premenopausal women, but harder to detect than gynecomastia in men.

1.2.2 The organs that could be affected are mainly the uterus and vagina.

1.2.3 For drugs that are estrogenic, the most common malignancies would be endometrial or breast cancer.

Question 2. If malignancies are seen, what would be the usual time course for development of these malignancies in humans (if known)?

2.1 For drugs that are estrogenic, a least 5 years, based on studies of the effects of estrogens in women.

Question 3 Does the Division of Reproductive and Urologic Drug Products have any historical knowledge of drug-related Leydig cell tumors in mice and whether or not they resulted in drug related human malignancies?

3.1 Yes. "Doubts have been raised about the relevance of such responses for human risk assessment..."[4] However, "Occurrence of Leydig cell adenomas in

test species is of potential concern as both a carcinogenic and reproductive effect if the mode of induction and potential exposure cannot be ruled out as relevant for humans."[4] In an Environmental Protection Agency workgroup, "androgen receptor antagonism, 5-alpha-reductase inhibition, testosterone biosynthesis inhibition, aromatase inhibition, and estrogen agonism were considered to be relevant or potentially relevant, but quantitative differences may exist across species with rodents being more sensitive."[4]

4. Could an estrogenic effect from a drug affect reproduction capabilities of either male or female human patients taking a drug chronically? Could this estrogenic effect also affect the fetus?

4.1 Yes, although this would be likely only at dose sufficient to cause generalized estrogenic effects.

5. With drug-related Leydig cell tumors in mice, is there a particular safety fold that make it acceptable for use in humans or is this information not known.

5.1 No. "A margin of exposure (MOE); the ratio of the lowest exposure associated with toxicity [in mice] to the human exposure level should be used for compounds causing Leydig cell adenoma by a hormonal mode that is relevant to humans."[4] The margin itself is a matter of judgment.

NOTE: The following modes of Leydig cell induction in animals are considered relevant to humans: androgen receptor antagonism, 5-alpha reductase inhibition, testosterone biosynthesis inhibition, aromatase inhibition, and estrogen agonism. Quantitative differences may exist across species, with rodents being more sensitive.[4] Only estrogen agonism is considered above.

References

1. Shelby MD, Newbold RR, Tully DB, et al. Assessing environmental chemicals for estrogenicity using a combination of In Vitro and In Vivo Assays. Environ Health Perspect. 1996;104:1296-1300
http://ehp.niehs.nih.gov/docs/1996/104-12/shelby.html

2. NDA 21742, Original Submission (30Apr04), Integrated Summary of Safety, Table 8.9.4.1-7

3. NDA 21742, Safety Update (12Nov04), Table 5-2.1

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4. Clegg ED, Cook JC, Chapin RE, et al. Leydig cell hyperplasia and adenoma formation: mechanisms and relevance to humans. Reprod Toxicol. 1997;11:107-21.

at Doc

Bruce V. Stadel, MD, MPH

cc: HFD-580/Mark Hirsch, MD/Harry Handelsman, MD/Division File
HFD-510/Consults

ATTACHMENT : Request for Consultation

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David Orloff
1/31/05 02:46:12 PM
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