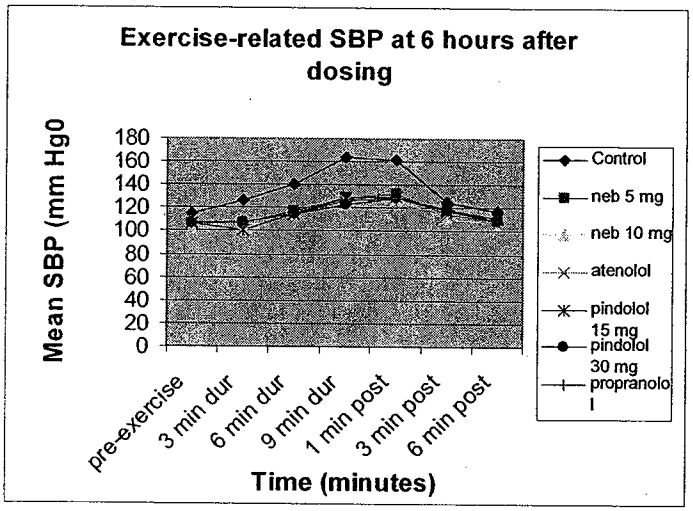
Figure 38. Mean Exercise-Related SBP on a Control Day and at 6 Hours Post-Dosing (BEL-30)



(Data from Sponsor, BEL-30, Table 1, page 9)

At 6 hours, all active drug SBPs during exercise were different from control (Wilcoxon matched-pairs signed-ranks test, 2-tailed probability $p \leq 0.05$). Pre-exercise nebivolol 5 mg and pindolol 30 mg and 6 minutes post-exercise atenolol, propranolol, and pindolol (both doses) were not significantly different from control.

In terms of heart rate, mean pre-exercise values, except for atenolol, were not significantly different from control. During exercise, all drugs were significantly different from control (Wilcoxon matched-pairs signed-ranks test, 2-tailed probability $p \leq 0.01$). At 3 minutes post-exercise, nebivolol (both doses) and pindolol 15 mg were not significantly different from control.

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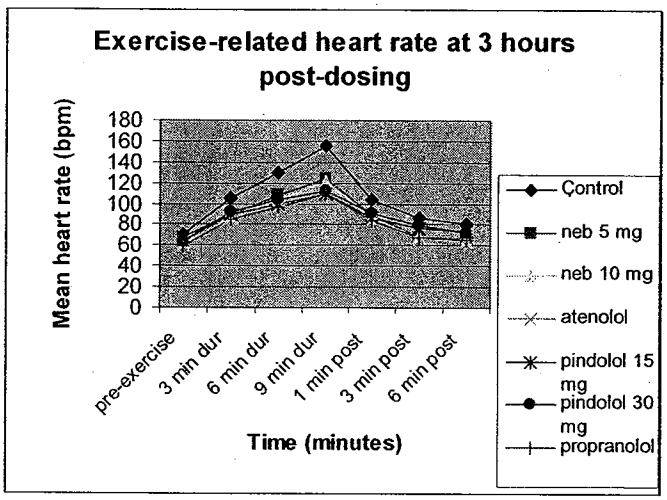
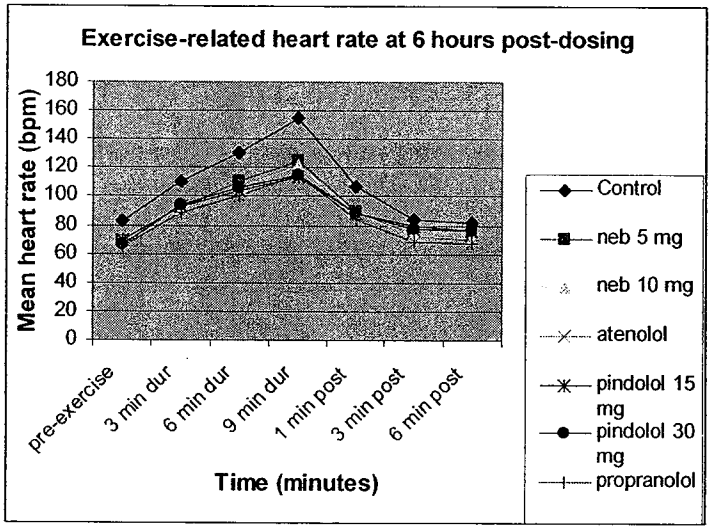
Figure 39. Mean Exercise-Related Heart Rate on a Control Day and at 3 Hours Post-Dosing (BEL-30)



(Data from Sponsor, BEL-30, Table 2, page 10)

At 3 hours post-dosing, mean heart rates of atenolol, pindolol (both doses), and propranolol at 9 minutes during exercise were significantly different from nebivolol 5 mg or 10 mg.

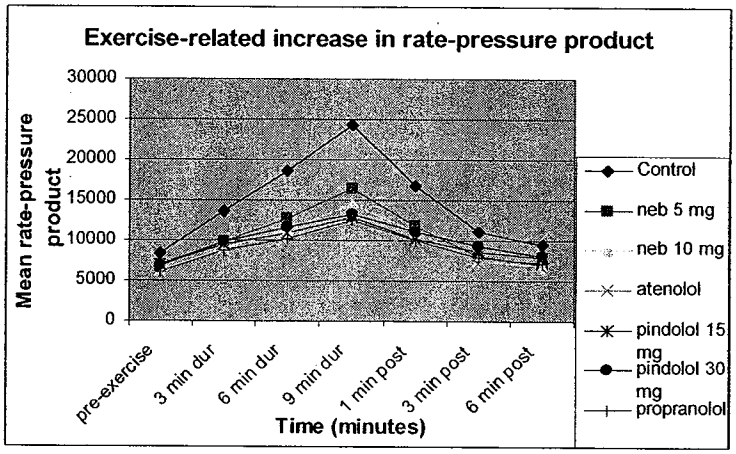
Figure 40. Mean Exercise-Related Heart Rate on a Control Day and at 6 Hours Post-Dosing (BEL-30)



(Data from Sponsor, BEL-30, Table 2, page 10)

Heart rate results at 6 hours look graphically similar to Figure 39. At 9 minutes of exercise, mean heart rates on other beta blockers, except for pindolol 30 mg and nebivolol 5 mg, were significantly lower than the mean heart rate on nebivolol 10 mg.

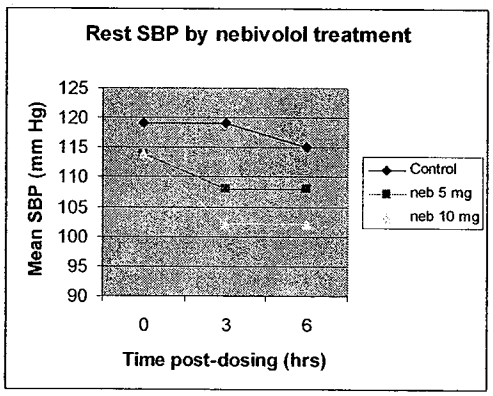
Figure 41. Rate-Pressure Product on a Control Day and at 3 Hours Post-Dosing (BEL-30)



(Data from Sponsor, BEL-30, Table 3, page 11)

At 3 hours post-dosing, all active drugs showed a significant decrease, compared to control, in rate-pressure product (RPP) regardless of timepoint. Results for pindolol 30 mg were not significantly different from nebivolol 10 mg. At 6 hours post-dosing, results looked graphically similar to Figure 41.

Figure 42. Resting SBP During a Control Day and 0, 3, and 6 Hours Post-Nebivolol Dosing (BEL-30)



(Data from Sponsor, BEL-30, Table 3, page 11)

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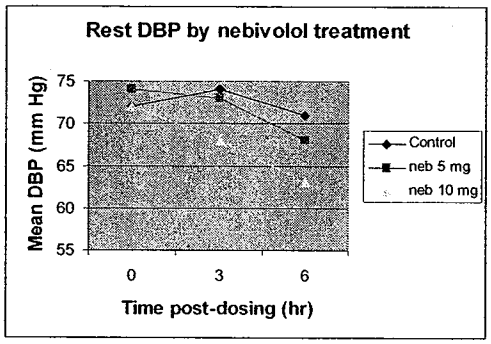
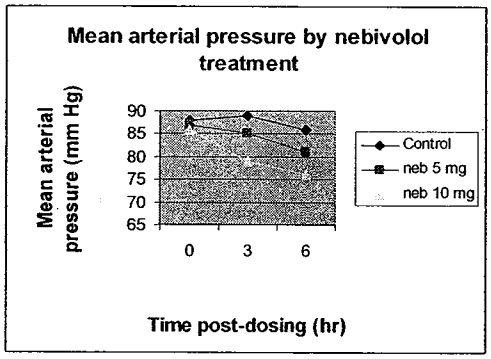
Figure 43. Resting DBP During a Control Day and 0, 3, and 6 Hours Post-Nebivolol Dosing (BEL-30)



(Data from Sponsor, BEL-30, Table 3, page 11)

Figure 44. Resting Mean Arterial Pressure During a Control Day and at 0, 3, and 6 Hours Post-Nebivolol Dosing (BEL-30)



(Data from Sponsor, BEL-30, Table 3, page 11)

Table 39. Mean (SEM) PEPc/LVETc During a Control Day and at 0, 3, and 6 Hours after Nebivolol Dosing

Drug	Time post-dosing		
	0 hours	3 hours	6 hours
Control	0.36 (0.015)	0.36 (0.018)	0.36 (0.016)
Nebivolol 5 mg	0.36 (0.008)	0.39 (0.012)	0.34 (0.009)
Nebivolol 10 mg	0.35 (0.008)	0.40 (0.014)	0.36 (0.015)

Table 40. Mean (SEM) Pre- and Post-Exercise LVET During a Control Day and at 3 and 6 Hours after Nebivolol Dosing

Time	Drug	Pre-exercise	Post-exercise	p-value*
3 hours	Control	291 (4.4)	247 (7.1)	≤ 0.01
	Nebivolol 5 mg	287 (7.3)	279 (4.8)	NS
	Nebivolol 10 mg	297 (4.4)	284 (6.3)	≤ 0.05
6 hours	Control	282 (3.9)	251 (5.3)	≤ 0.01
	Nebivolol 5 mg	292 (3.5)	276 (5.1)	≤ 0.05
	Nebivolol 10 mg	287 (3.3)	276 (5.3)	≤ 0.05

*** Wilcoxon matched-pairs signed-ranks test, 2-tailed probability vs. pre-exercise values**

Reviewer's comments:

1. This was an open-label single-dose crossover study. Because this study was not conducted in a double-blind manner, one cannot exclude the presence of bias.
2. It is not clear that all drugs were dosed at peak effect or at maximum doses; therefore, comparisons between active-treatment groups are not easily interpretable.
3. With the available data and doses studied, there appears to be a decrease in SBP, DBP, MAP with increased nebivolol dose, compared to control.
4. There appears to be a dose-related decrease in exercise-related rate-pressure product at peak exercise.
5. All active treatments, including nebivolol 5 and 10 mg, were associated with a decrease in exercise-related HR and SBP noted at peak exercise.

1.32 LMD No. 56952. Study ID: BEL-1/Part I. ("Hematological, Biochemical, and Urinary Safety During a Subacute Treatment with Nebivolol in a Double-Blind Placebo-Controlled Study. Part I, Clinical Research Report NEB-BEL-1. August 1987") (Source: Abstract and Protocol Summary (3 pages), August 1987. No protocol was submitted.) (Reviewer: Shari Targum, M.D.)

Objective: evaluate the hematologic, biochemical, and urinary safety of 2.5, 5, and 10 mg of nebivolol, compared to placebo.

Study Summary: This was a double-blind, randomized, placebo-controlled, 4-way crossover study in healthy male volunteers, with a one week washout period between each phase. Patients were given study drug once daily for 14 days. Hematology and blood chemistry, urinalysis, and adverse event assessments were collected at Days 0, 7, and 14. According to the study abstract, there were 4 volunteers for each dose.

Results: 8 males, median age 36 (range 28-44) years, median weight 80 (range 69-114) kg, were enrolled; there were no dropouts and no reported adverse events.

A review of hematology and chemistry results revealed one patient with elevated triglycerides during treatment with nebivolol 2.5 mg daily.

Reviewer comments: No obvious safety concerns were raised in this study. Triglycerides are to be further evaluated in the larger studies and in the safety review.

1.33 LMD No. 59056. Study ID: 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") (No protocol was submitted.) (Reviewer: Shari Targum, M.D.)

Objective: evaluate hemodynamic effects of nebivolol 2.5, 5 and 10 mg during subacute treatment, compared with placebo.

Inclusion criteria: Caucasian males, 18-65 years, who were extensive metabolizers of debrisoquine.

Exclusion criteria: History of cardiac arrhythmias, cardiovascular or bronchospastic disease, diabetes, thyrotoxicosis, parkinsonism, drug allergy, concomitant use of other medication.

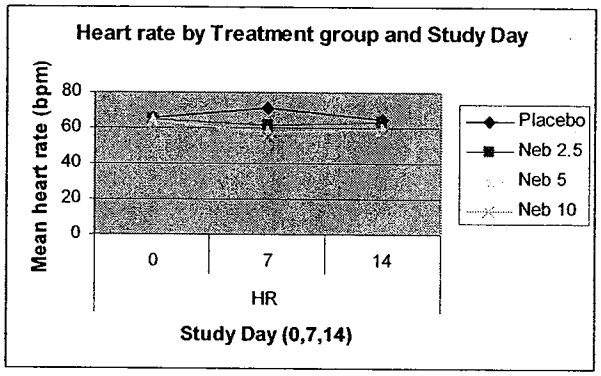
Study Summary: This was a double-blind, randomized, placebo-controlled, 4-way crossover study with a one week washout period between each phase. Healthy male volunteers were assigned to 4 treatment periods; during each study period, the subjects were given 2.5, 5 or 10 mg of a 1 mg/ml nebivolol solution or an identical placebo solution once daily in the morning. During each study phase, heart rate and BP were measured and an ECG and a venous occlusion plethysmogram were taken before dosing on a control day and on the 7^{th} and 14^{th} day of drug intake. On Days 7 and 14, volunteers underwent a treadmill exercise test 6 hours after dosing. Heart rate and SBP were measured prior to and during exercise and recovery. In addition, systolic time intervals were measured at rest (before exercise) and 30 seconds after the end of exercise.

The treadmill exercise test consisted of a 9 minute modified Bruce protocol with speed/elevation of 2.5 mph/10% (first 3 min), 3.4 mph/12% (second 3 min) and 4.2 mph/14% (last 3 min). Systolic time intervals were measured from simultaneous recordings of a peripheral ECG lead, phonocardiogram, and carotid pulse wave. At least 5 consecutive cardiac cycles were averaged for: QS2 (total electromechanical systole); LVET (left ventricular ejection time); PEP (pre-ejection period). LVET, PEP and QS2 were corrected for heart rate according to a regression formula, and the ratio of PEPc/LVETc was used as an index of left ventricular performance.

Results:
Note: Day 7 and the 7^{th} dosing day (etc.) are used interchangeably.
Eight male subjects, median age 36 (range 28-44) years, median weight 80 (range 69-114) kg and median height 179 (range 170-186) cm were entered. There were no dropouts.

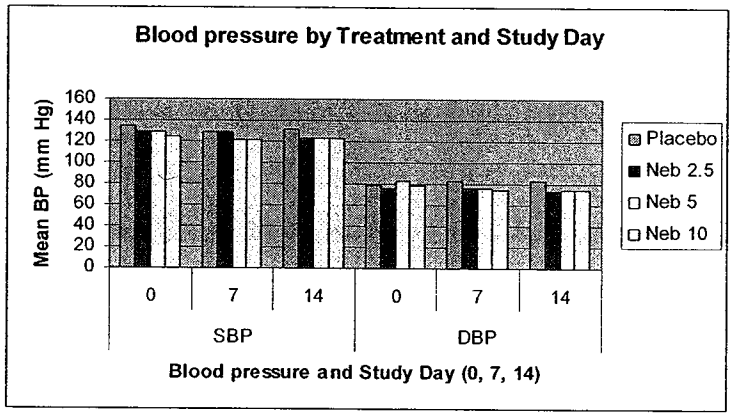
Heart rate and BP results are displayed graphically (Figure 45).

Figure 45. Heart Rate Measured Before Drug Intake on a Control Day and on the 7th and 14th Day of Dosing. (Source: Table 5, BEL-1/Part II)



Heart rates were significantly (p=0.02) lower vs. placebo (Wilcoxon matched-pairs signed-ranks test) on the 7th and 14th day of drug intake for nebivolol 5 and 10 mg.

Figure 46. Blood Pressure Results, Measured Before Drug Intake on a Control Day and on the 7th and 14th Day of Drug Intake (Source: Table 5) (BEL-1/Part II)



Day 14 results were statistically significant (p=0.03) vs. placebo (Wilcoxon matched-pairs signed-ranks test) for DBP (nebivolol 5 and 10 mg). For SBP, Day 14 results were statistically significant for nebivolol 2.5 mg dose only.

ECG: ECG measurements appear to have been taken at trough (pre-dosing) on a control day and on the 7th and 14th day of drug intake.

There were no statistically significant differences vs. placebo in PQ and QRS measurements at any time point. The QT was corrected according to Bazett and Hodges methods. In the nebivolol 10 mg group, a statistically significant increase in mean QT was seen at the 7th and 14th dosing day vs. placebo; however, the mean QT on the 14th dosing day was only 1 msec higher than on Day 0. No significant increases in QTc vs. placebo (via Bazett or Hodges) were seen in the nebivolol 10 mg group.

Plethysmography: Flow at rest, peak flow, time to peak flow and reactive hyperemia measurements revealed no statistically significant differences vs. baseline or vs. placebo.

Exercise-related hemodynamics:
Results of exercise-related heart rates appeared graphically similar between the 7th and 14th dosing day. During exercise testing on the 7th and 14th day, mean heart rates in the nebivolol 5 and 10 mg groups were significantly lower (Wilcoxon matched-pairs signed-ranks test) vs. placebo at most time points measured (including all time points measured during exercise); mean heart rates in the nebivolol 2.5 mg group were significantly lower vs. placebo at 4-9 minutes during exercise and 3, 5, and 6 minutes post-exercise.

Figure 47. Mean Heart Rate Before, During and After Exercise Testing on Day 14 (BEL-1/Part II).

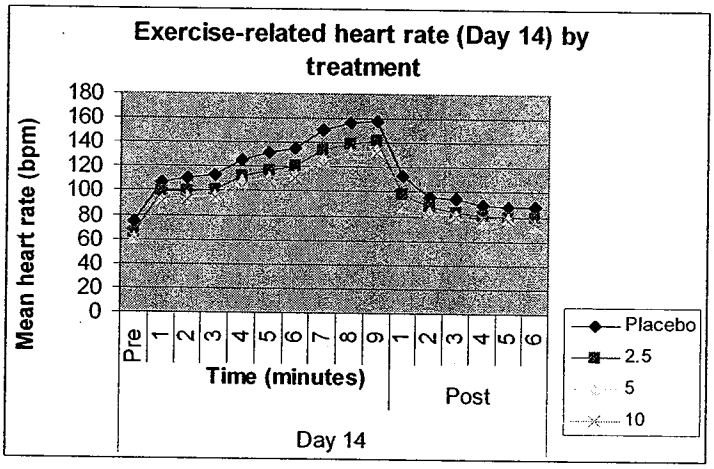
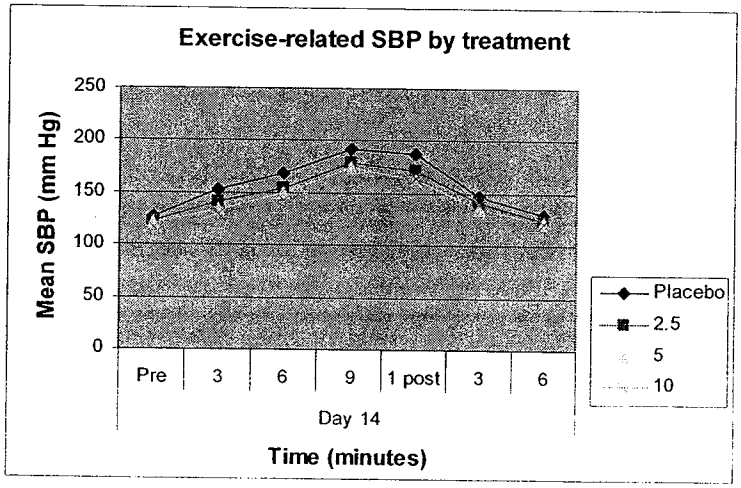
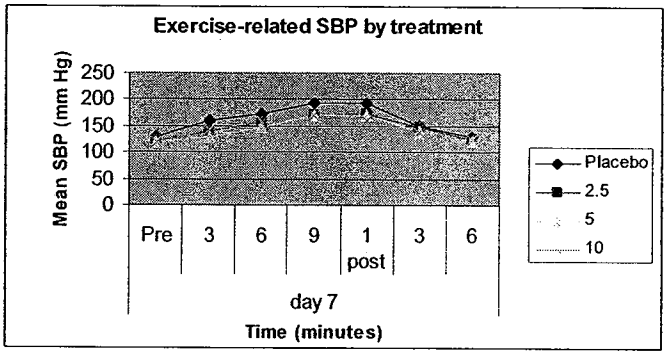


Figure 48. Mean Systolic BP Before, During, and After Exercise Testing on Day 14 (BEL-1/Part II)



Systolic BP on Day 14 was significantly lower vs. placebo during exercise in all nebivolol treatment groups.

Figure 49. Mean Systolic BP Before, During, and After Exercise Testing on Day 7 (BEL-1/Part II)



Results obtained on Day 7 showed a significantly lower SBP, compared to placebo, in all nebivolol treatment groups at 1 min post exercise.

Systolic time intervals (resting, 6 hours post-dose):
Systolic time intervals were measured on Days 7 and 14. With respect to PEPc and PEPc/LVETc ratio, no significant differences were seen at any time point (day 7 or 14) in any nebivolol group. With respect to LVETc, QS_{2c} and heart rate, results are shown in the next table:

Table 41. Mean (SEM) Resting LVETc, QS_{2c} and Heart Rate, 6 Hours After Dosing on Days 7 and 14 (BEL-1/Part II)

		Placebo	Nebivolol		
			2.5 mg	5 mg	10 mg
HR (bpm)	Day 7	68 (3.9)	64 (4.3)	62 (4.2)	56 (4.0)**
	14	71 (3.0)	66 (5.7)	61 (2.8)**	60 (4.8)*
LVETc (msec)	Day 7	287 (3.3)	292 (4.2)	296 (3.5)	298 (4.4)
	14	282 (2.8)	292 (3.4)**	296 (1.6)*	302 (3.5)**
QS_{2c} (msec)	Day 7	389 (5.7)	393 (5.9)	399 (5.4)	399 (6.3)
	14	383 (6.1)	391 (5.5)	394 (6.8)	401 (3.8)**

***p <0.05 ** p= < 0.01 p-value: 2-tailed probability vs. placebo by Wilcoxon matched-pairs signed-ranks test.**

Results of LVETc before and after exercise are presented in Table 42. In all groups, including placebo, there was a significant (p=0.008) decrease in LVETc post-exercise, compared to pre-exercise values. In the nebivolol 10 mg group, there was a significant decrease in LVETc difference, compared to placebo, on Days 7 and 14. The nebivolol 10 mg group also had the highest pre-exercise values, consistent with results in Table 41.

Table 42. Mean (SEM) LVETc (msec) Before and After Exercise, 6 hours after Dosing on Days 7 and 14.

		Pre-exercise	Post-exercise	Mean (SEM) Difference	p-value vs. placebo
Day 7	Placebo	287 (3.3)	239 (5.7)	-47.5 (5.5)	--
	Nebivolol 2.5 mg	292 (4.2)	252 (5.6)	-40 (7.0)	NS
	Nebivolol 5 mg	296 (3.5)	261 (7.0)	-35 (7.0)	0.02
	Nebivolol 10 mg	298 (4.4)	268 (6.8)	-30 (6.8)	0.04
Day 14	Placebo	282 (2.8)	233 (5.7)	-48 (6.2)	--
	Nebivolol 2.5 mg	292 (3.4)	258 (7.4)	-34 (7.0)	NS
	Nebivolol 5 mg	296 (1.6)	263 (8.0)	-32 (8.4)	NS
	Nebivolol 10 mg	303 (3.2)	280 (4.5)	-25 (4.4)	0.02

Reviewer comments:

1. This was a randomized, double-blind, placebo-controlled crossover study in 8 healthy male volunteers.
2. At the higher dose levels (nebivolol 5 and 10 mg), statistically significant decreases vs. placebo were seen with respect to resting mean heart rate, diastolic BP, exercise-related heart rate and systolic BP. On Day 14, LVETc was significantly longer than placebo in subjects receiving higher doses (5 or 10 mg) of nebivolol. Day 14 QS_{2c} was significantly longer vs. placebo in subjects receiving nebivolol 10 mg.
3. There was less decrease in mean LVETc post-exercise with increasing doses of nebivolol.
4. QTc changes were not seen in this study; however, QTc was measured at trough only.

1.34 LMD No. 59580. Study ID: 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") (No protocol was submitted) (Reviewer: Shari Targum, M.D.)

Objective: compare the acute effects of an oral intake of a solution or a tablet with an intravenous administration of this substance.

Study Summary: This was a randomized, placebo-controlled, single-dose crossover study in healthy male subjects. (**Reviewer**: the study report mentions that this study was double-blind; however, the subjects were randomized to a single administration of a placebo tablet, a 5 mg nebivolol tablet, 5 mg of a 1 mg/ml nebivolol solution and an intravenous injection of 0.5 mg of nebivolol, given over 5 minutes. Since there is no mention of a placebo solution or injection, this study could not have been completely blinded. This study is listed as "open label" in the submission study list). Subjects received study treatment in random order and with a 2-week interval between study phase. A treadmill exercise test was done at 3 and 6 hours after drug intake. Heart rate

and SBP were recorded before, during, and after exercise. ECG and rest systolic time intervals were evaluated in the morning before drug intake and at 3 and 6 hours after dosing. LVET was also measured 30 seconds after exercise testing. After intravenous nebivolol dosing, heart rate and BP were measured every 10 minutes during the first hour; in addition, ECG and systolic time intervals were measured 30 minutes and 1 hour after injection.

No primary endpoint was identified. It is not clear whether any statistics were prespecified.

Results: Ten healthy males (8 extensive and 2 poor metabolizers) participated in this study. The median age was 34.5 (range 26-43) years and median weight was 73 (range 66-92) kg. Concomitant medications were not allowed 48 hours prior to each test day.

Exercise-related heart rate (HR) effects:
Results are presented graphically in Figure 50 and Figure 51. Mean HR measured 3 hours after administration of the nebivolol 5 mg tablet was significantly less than placebo at 3-9 minutes during exercise; at 6 hours after administration of the nebivolol tablet, mean HR was significantly less than placebo at all measured time points. With regard to nebivolol 5 mg IV, mean HR was not significantly different from placebo at 3 hours post-dosing; at 6 hours, mean heart rates at some measured time points were significantly less than placebo but these findings were inconsistent. Mean HR was significantly less than placebo at 4-9 minutes during exercise 3 hours after administration of nebivolol 5 mg solution; at 6 hours post-administration of the solution, mean HR was significantly less than placebo at all timepoints during exercise, and at 4-6 minutes post-exercise.

Figure 50. Exercise-Related Heart Rates (3 Hours after Dosing) (Study ID N/A)

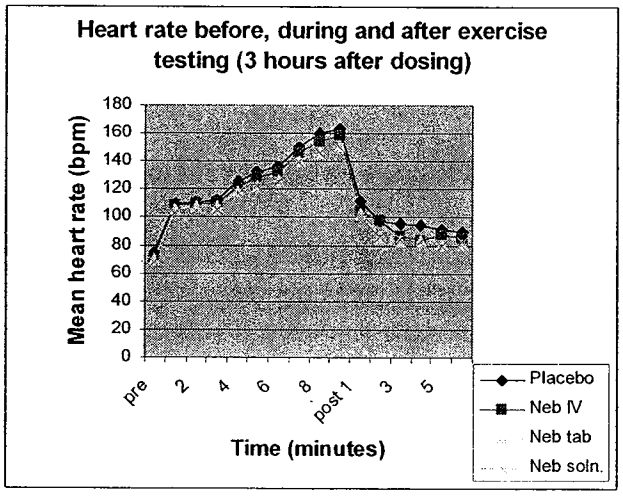


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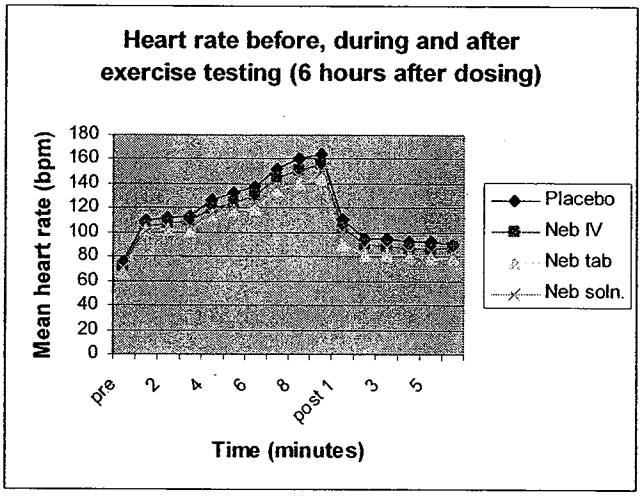
Figure 51. Exercise-Related Heart Rates (6 Hours After Dosing) (Study ID: N/A)



SBP:

Results of mean SBP measurements before, during and after exercise are presented graphically in Figure 52 and Figure 53. After dosing with nebivolol IV, SBP results at most timepoints were not significantly different from placebo. After 6 hours post-dosing with the nebivolol 5 mg tablet, mean SBP was significantly (2-tailed probability, Wilcoxon matched-pairs signed-ranks test) lower than placebo at all time points during exercise as well as pre-exercise.

Figure 52. Exercise-Related SBP (mm Hg) 3 Hours After Dosing (Study ID: N/A)

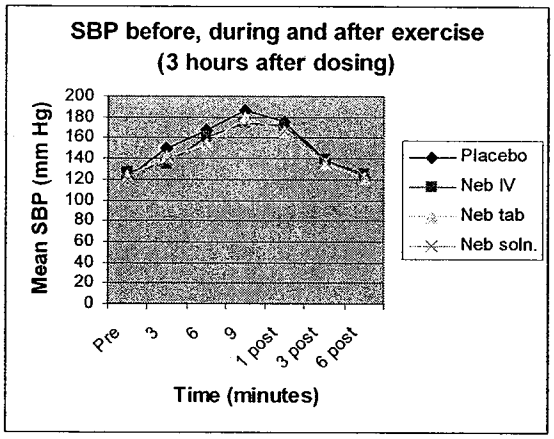


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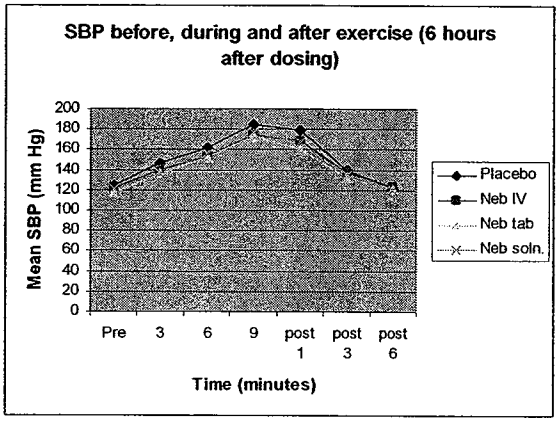
Figure 53. Exercise-Related SBP (mm Hg) 6 Hours After Dosing (Study ID: N/A)



Systolic time intervals:

HR, BP, and systolic time intervals are graphically displayed in Figure 54. According to the sponsor's analyses (Wilcoxon matched-pairs signed-ranks test 2-tailed probability vs. 0 hour values), statistically significant decreases ($p \leq 0.05$) were noted for the decreases in DBP and SBP (20 minutes-1 hour) and increase in QS2c (30 min-1 hour). A statistically significant ($p \leq 0.05$) decrease in HR was seen only at 20 minutes; in addition, a significant decrease in LVETc ($p \leq 0.05$) was seen only at 6 hours (360 minutes).

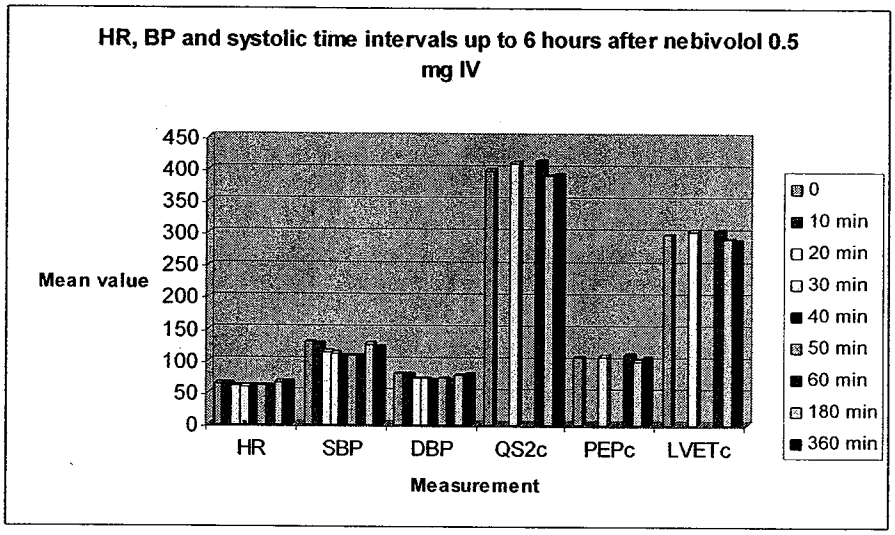
In addition, an analysis of LVET pre and post exercise (performed 3 and 6 hours after dosing) showed significantly smaller decreases in the change in LVET after administration of nebivolol 5 mg tablet, compared with placebo. There were no significant changes in LVET change after administration of nebivolol IV.

Table 43. Change in LVETc Post-Pre Exercise, 3 and 6 Hours After Dosing

	3 hours		6 hours	
	Mean (SEM)	**P**	**Mean (SEM)**	**P**
Placebo	-51 (4.4)	--	-46 (5.4)	--
Nebivolol IV	-52 (4.9)	NS	-43 (5.4)	NS
Nebivolol tablet	-34 (5.3)	0.04	-27 (4.3)	0.01
Nebivolol solution	-39 (7.0)	NS	-27 (6.6)	0.008

P-value obtained from Wilcoxon matched-pairs signed ranks test, 2-tailed probability vs. placebo

Figure 54. Mean HR (bpm), BP (mm Hg), and Systolic Time Intervals (msec) Before and Up to 6 Hours After IV Administration of Nebivolol 0.5 mg



PEPc/LVETc: The PEPc/LVETc ratio, measured at 0, 3, and 6 hours after dosing, showed no significant differences between nebivolol and placebo (the only statistically significant finding was a significant decrease from baseline at 3 hours in subjects receiving the nebivolol solution; however, this 3 hour measurement was not different from placebo).

ECG Intervals: ECG intervals (PQ, QRS, QT, QTc, QTm) were measured before and at 3 and 6 hours after dosing (for the IV formulation only, ECGs were additionally measured at 30 minutes and 1 hour). There was a borderline significant increase in the PQ interval at 3 hours for the nebivolol solution (173 msec vs. 162 msec for placebo, Wilcoxon matched-pairs signed ranks test, 2-tailed probability p=0.05). QT measurement decreased from 378 msec at baseline to 355 at 6 hours post-dosing for those on placebo (p=0.04). Otherwise, no findings of note are seen by this reviewer.

Reviewer Comments:

1. This was an open-label single-dose crossover study in healthy male volunteers.
2. Since no protocol was submitted, it is unclear what analyses were prespecified.

1.35 LMD No. 59899. Study ID: 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") (No protocol was submitted.) (Reviewer: Shari Targum, M.D.)

Objective: Investigate acute hemodynamic effects of various doses of nebivolol in comparison with placebo at rest and during exercise.

Study Summary: This was a double-blind, placebo-controlled single-dose crossover study in healthy volunteers. Subjects were randomized (according to a list that was not submitted) to 5 consecutive study phases separated by a one week interval. During each study phase, subjects received 1, 2.5, 5 or 10 mg of a nebivolol solution (1 mg/ml) or matched placebo at a fixed hour. HR, BP, and ECG were taken prior to dosing. At six hours post-dosing subjects performed a treadmill exercise test where HR and SBP were measured. Systolic time intervals were measured at rest before exercise and 30 seconds after the end of exercise.

Exercise testing consisted of a 9 minute modified Bruce protocol (3 minutes each at 2.5 mph/10% grade, 3.4 mph/12% grade, 4.2 mph/14% grade).

Systolic time intervals included QS2, LVET, PEP with corrections for heart rate according to a resting supine regression equation. PEPc/LVETc was used as an index of LV performance. The difference between LVETc before and 30 seconds after exercise was expressed as Δ LVETc; a post-exercise regression equation was used to correct for HR.

Statistical analyses were done using the Wilcoxon matched-pairs signed-ranks test, two-tailed probability. No primary endpoint was identified.

Results: Eight healthy subjects (6 males, 2 females) entered the study with no dropouts. Results of exercise-related HR and SBP changes are presented in the following figures.

Figure 55. Mean Exercise-Induced Increase in HR and SBP 6 Hours Post-Dosing

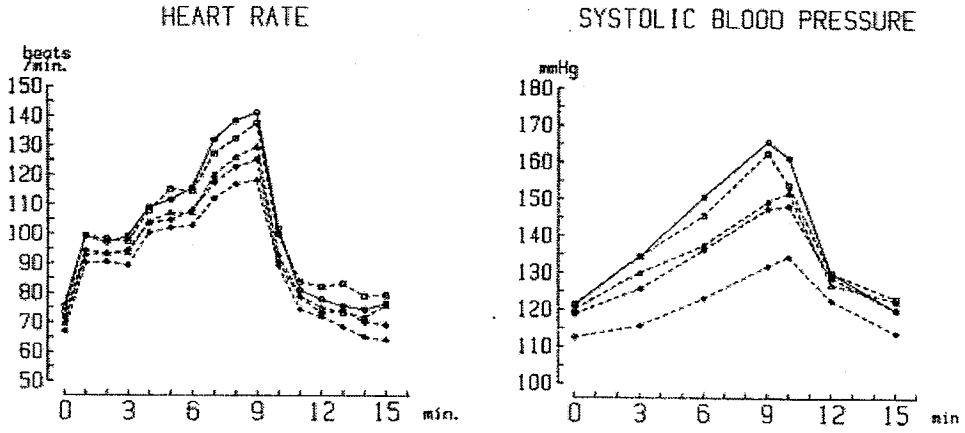
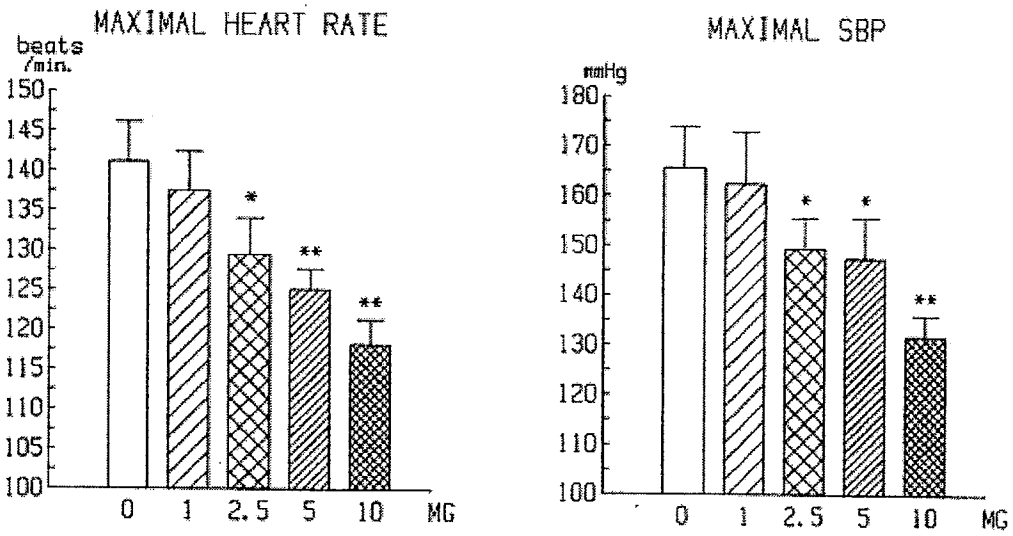


Figure 1 : Mean values of the exercise-induced increase of heart rate and systolic blood pressure, 6 hours after oral administration of placebo (●—), 1 mg (○—), 2.5 mg (△—), 5 mg (▲—) and 10 mg (○—) of nebivolol in 8 volunteers. 11

(Reproduced from Sponsor, BEL-35, Figure 1, page 11)

Figure 56. Mean HR and SBP at Maximal Exercise (9 minutes) Measured 6 Hours Post Dosing



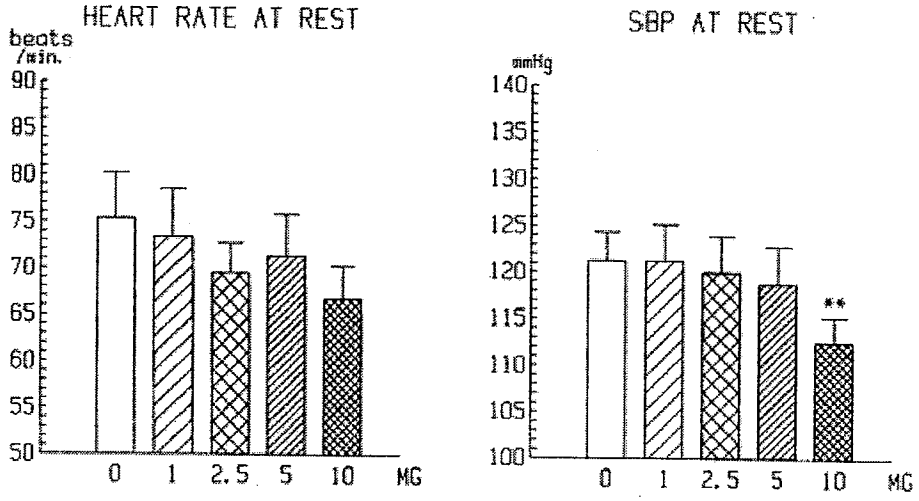
*p≤0.05; **p≤0.01 by Wilcoxon matched-pairs signed-ranks test, 2-tailed probability versus placebo.
Figure 2 : Mean heart rate and systolic blood pressure at maximal exercise, 6 hours after oral administration of placebo, 1 mg, 2.5 mg, 5 mg and 10 mg of nebivolol in 8 volunteers.

(Reproduced from Sponsor, BEL-35, Figure 2, page 12)

As seen above, there is a decrease in HR and SBP at maximal exercise in subjects receiving nebivolol 2.5 – 10 mg.

Resting HR and SBP are presented in Figure 57. Since these measurements were done prior to dosing, and this was a single-dose study, it is unclear why SBP in the nebivolol 10 mg group would be significantly less than placebo, unless this was a random finding or related to some carryover effect.

Figure 57. Mean Resting HR and SBP (Pre-Dose)



**p<0.01 by Wilcoxon matched-pairs signed-ranks test, 2-tailed probability versus placebo.
Figure 3 : Mean rest values of heart rate and systolic blood pressure, (SBP) just before oral administration of placebo, 1 mg, 2.5 mg, 5 mg and 10 mg of nebivolol in 8 volunteers.

(Reproduced from Sponsor, BEL-35, Figure 3, page 13)

Systolic time intervals: There were no significant differences vs. placebo in QS2, PEPc or LVETc for systolic time intervals at rest, 6 hours after administration of nebivolol. Only those receiving nebivolol 10 mg showed a significant decrease in resting HR (mean 58 $\pm$ 2.9, p = 0.05) compared with placebo (mean 66 $\pm$ 4.4). For the parameter PEPc/LVETc, there was a significant difference vs. placebo (mean 0.36 $\pm$ 0.014) in subjects receiving nebivolol 1 mg (mean 0.34 $\pm$ 0.015) and nebivolol 10 mg (mean 0.32 $\pm$ 0.011). With regard to exercise-related Δ LVETc, the decrease was significantly lower vs. placebo (mean -36.4 $\pm$ 4.6) in the group receiving nebivolol 5 mg (mean -18.8 $\pm$ 5.2) and 10 mg (mean -13.3 $\pm$ 3.5).

Reviewer Comments:

1. This was a single-dose, double-blind, placebo-controlled crossover study. No protocol was submitted; thus it cannot be verified which analyses were pre-specified.
2. At maximal exercise, significant decreases in HR and SBP, compared with placebo, were seen in subjects receiving nebivolol 2.5 - 10 mg.
3. There was a significant decrease in PEPc/LVETc in subjects receiving nebivolol 10 mg.
4. The decrease in exercise-related LVETc was significantly lower, compared to placebo, in subjects receiving nebivolol 5 and 10 mg.
5. No safety issues were identified.

1.36 LMD No. 59922. Study ID: BEL-38. ("Acute Hemodynamic Effects of 2 Enantiomers of Nebivolol (R 67138 and R 67145) in Mean at Rest and During Exercise. Clinical Research Report NEB-BEL-38. March 1988") (No protocol was submitted.) (Study Period: March – May, 1987) (Reviewer: Shari Targum, M.D.)

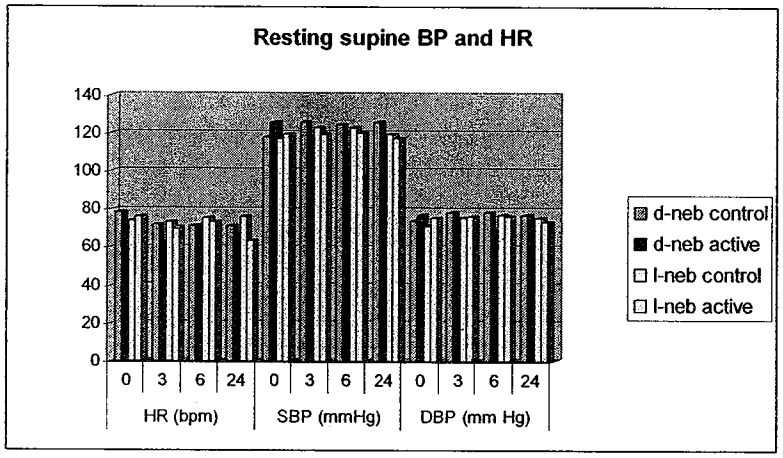
Objective: investigate effects of a single oral intake of 2 enantiomers of nebivolol on systemic and cardiac hemodynamics at rest and during exercise.

Study Summary: This was an open-label, single-site, single dose study in healthy subjects with 2 phases (2 study days, a control day and an experimental day, per phase) 1 week apart. Subjects received either *d*-nebivolol 5 mg or *l*-nebivolol 10 mg. Assessments were measured at 0, 3, 6 and 24 hours post-dosing, and included HR, BP, and systolic time intervals. A 9 minute treadmill test (see description BEL-35) was performed at 6 hours post-dosing or at 6 hours on the control day.

The statistical analysis was done via Wilcoxon matched-pairs signed-rank test. No primary endpoint was specified.

Results: Seven subjects (5 males and 2 females), median age 33 (range 26-50) years entered the study. There were no reported adverse events or dropouts.

Figure 58. Resting Supine BP and HR (BEL-38)



According to the sponsor, resting HR and BP significantly decreased after intake of *d*-nebivolol but not after *l*-nebivolol.

Resting PEPc/LVETc is shown in Figure 59. According to the sponsor, PEPc/LVETc significantly (difference from control day value) decreased after intake of *l*-nebivolol. This is graphically apparent only at the 24 hour post-dosing time point.

Exercise-related changes in HR, SBP and LVETc shortening are shown graphically in Figure 60. According to the sponsor, the significant LVETc shortening with exercise was unaffected by *l*-nebivolol and less pronounced after intake of *d*-nebivolol. Exercise-related increases in HR and SBP were inhibited after *d*-nebivolol but not *l*-nebivolol.

Figure 59. Resting PEPc/LVETc

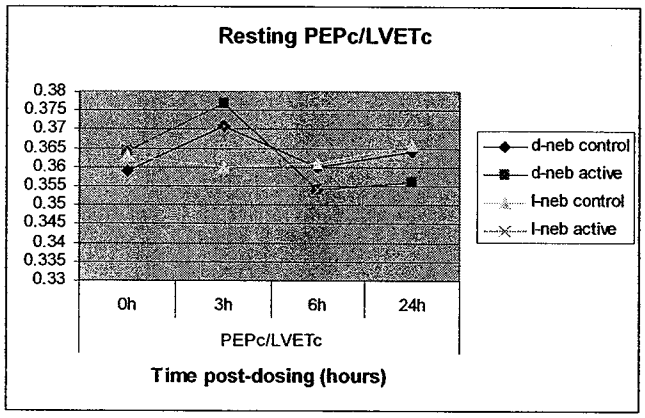
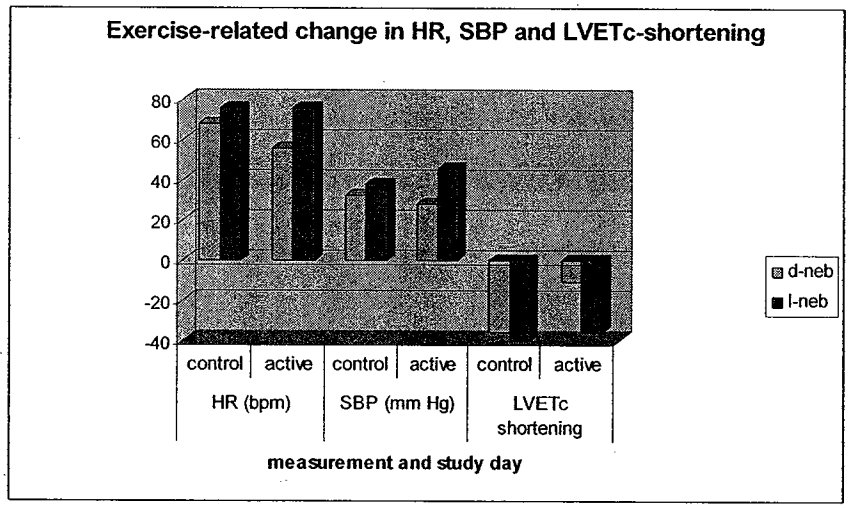


Figure 60. Exercise-Related Change in HR, SBP, and LVETc-Shortening



Reviewer Comments:

1. This was a small, open-label study comparing different doses of *d*- and *l*-nebivolol. No protocol was submitted and the analyses compared active treatment with control. No statistical analysis compared *d*- and *l*-nebivolol.
2. According to the sponsor, resting HR and BP, as well as HR and SBP increases at maximal exercise, were reduced after intake of a single dose of *d*-nebivolol; resting PEPc/LVETc decreased and exercise-related LVETc shortening was less pronounced after intake of *l*-nebivolol.
3. Nebivolol appears to have been well tolerated in this small single-dose study.

1.37 LMD No. 59970. Study ID: 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") (No protocol was submitted.) (Reviewer: Shari Targum, M.D.)

Objective: investigate subacute hemodynamic effects of the racemic mixture *dl*-nebivolol in comparison with its 2 enantiomers: *d*- and *l*-nebivolol.

Study Summary: This was a double-blind, multiple-dose, crossover study with 3 treatment periods separated by 1 week. Healthy subjects received either *d*-nebivolol 5 mg, *l*-nebivolol 5 mg, or *dl*-nebivolol 10 mg daily for 1 week; each treatment period included a control day. HR, SBP and systolic time intervals at rest were measured prior to dosing on Days 1, 2, 3, 4, and 7 of treatment and on Day 1, 2, and 4 after treatment discontinuation. The same measurements were taken 6 hours after drug intake, except for Day 2 and 3 of dosing, and at the same times during control days. Treadmill exercise testing was done 6 hours post-dosing on Days 1, 4, and 7 of the treatment week, Day 1, 2, and 4 after treatment discontinuation, and at the same time on the control days.

Systolic time intervals were measured from simultaneous recordings of a peripheral ECG lead, phonocardiogram and carotid pulse wave. At least 5 consecutive cardiac cycles were averaged for the following parameters: QS2 (total electromechanical systole); LVET (left ventricle ejection time); PEP (pre-ejection period). LVET, PEP and QS2 were corrected for HR according to a resting supine regression equation. PEPc/LVETc was used as an index of LV performance. The difference between LVETc before and 30 seconds after exercise was expressed as a post-pre-exercise value.

Exercise testing was done with a modified Bruce protocol as noted in BEL-35. Systolic time intervals were performed as noted in BEL-35. Statistical evaluation was calculated using the Wilcoxon matched-pairs signed-ranks test, two-tailed probability.

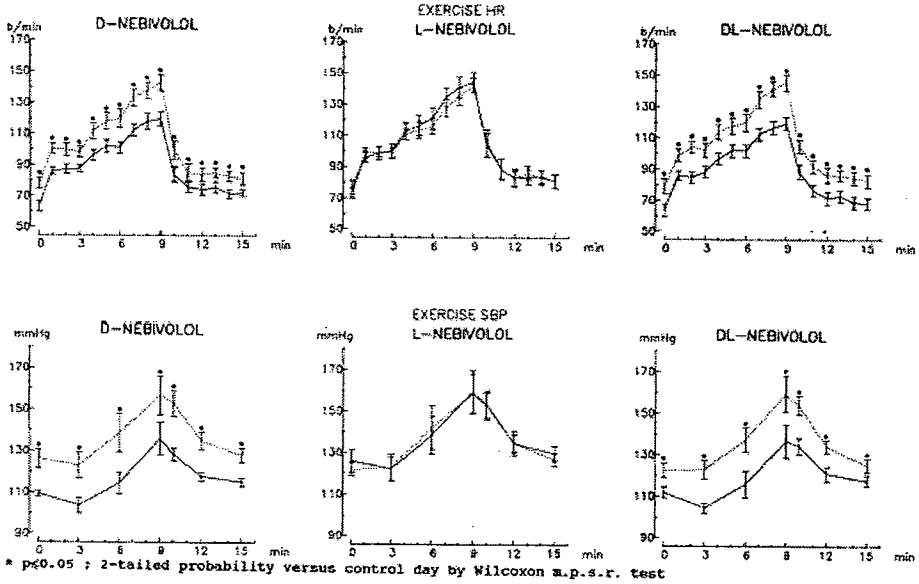
Results: Five males and 2 females, median age 33 (range 26-50) years, entered the study. Results of HR, SBP, PEPc/LVETc and Δ LVET with exercise are shown graphically in Figures 1 and 2. Exercise-associated SBP and HR increases were reduced after *d*-nebivolol or *dl*-nebivolol but not after *l*-nebivolol. Resting PEPc/LVETc decreased transiently during treatment with *l*-nebivolol, was unchanged with *d*-nebivolol, and was more persistently decreased during *dl*-nebivolol treatment. LVET shortening with exercise was unaffected by *l*-nebivolol but was less pronounced after *d*-nebivolol and *dl*-nebivolol.

Reviewer Comments:

1. Exercise-associated increases in HR and SBP were reduced after intake of *d*-nebivolol but not *l*-nebivolol.

2. LVET shortening with exercise was less pronounced after intake of *d*-nebivolol but not *l*-nebivolol.
3. Resting PEPc/LVETc was transiently decreased during treatment with *l*-nebivolol, not affected by *d*-nebivolol, and decreased more persistently during treatment with *dl*-nebivolol.

Figure 61. Heart Rate (Upper Panel) and SBP (Lower Panel) Before, During, and After Exercise Testing on a Control day (.....) and On Day 7 (_____) of a Subacute Treatment with *d*-Nebivolol 5 mg Daily, *l*-Nebivolol 5 mg Daily, and *dl*-Nebivolol 10 mg Daily in 7 Healthy Volunteers (BEL-36)



(Reproduced from Sponsor, BEL-36, Figure 1, page 14)

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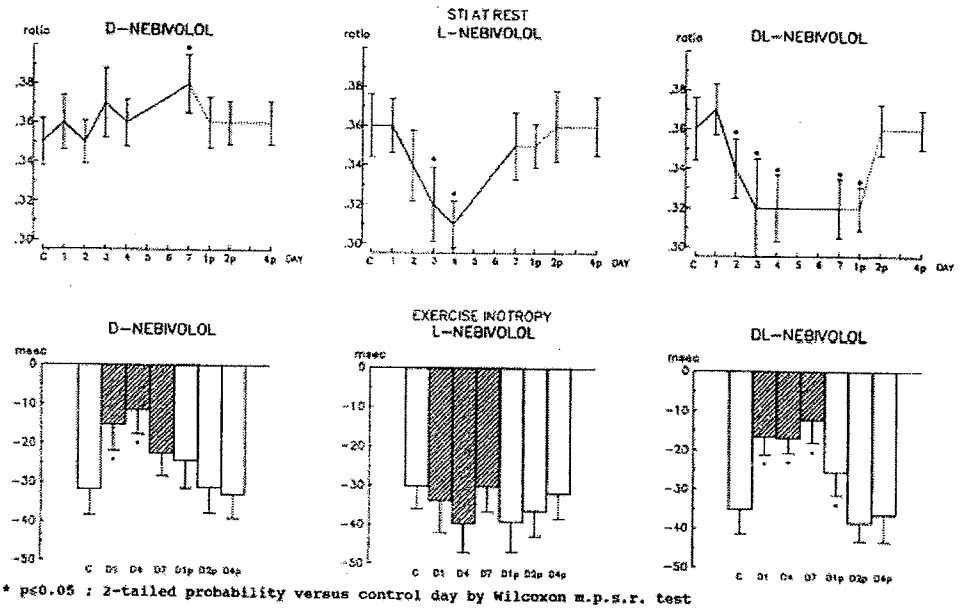
Figure 62. Mean Values (±SE) of $PEP_c/LVET_c$ Ratio (Upper Panel) and $\Delta LVET_c$ Post-Pre Exercise Testing (Lower Panel) on a Control Day (C) and Regularly During and After a 7-Day Treatment with *d*-Nebivolol 5 mg/day, *l*-Nebivolol 5 mg/day, and *dl*-Nebivolol 10 mg/day in 7 Healthy Volunteers (BEL-36)



* p≤0.05 ; 2-tailed probability versus control day by Wilcoxon m.p.s.r. test

(Reproduced from Sponsor, BEL-36, Figure 2, page 15)

1.38 LMD No. 64858. Study ID: 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") (Source: Study Report, undated. No protocol was submitted. According to the report, the study started October 1, 1989 and ended (implausibly) on February 28, 1989) (Reviewer: Shari Targum, M.D.)

Objective: determine the lowest acute dose of nebivolol that produces the maximum beta-blockade.

Study Summary: This was an open-label study in healthy male volunteers. One week prior to drug administration, subjects underwent maximal cycle ergometer testing, initially at 120 watts, with a 15 watt increase every minute until exhaustion. Expired air was analyzed for oxygen and carbon dioxide content (to obtain VO_2 max). Five days after the initial VO_2 max test, each subject performed a submaximal cycle ergometer test for 15 minutes at 75% VO_2 max; resting HR/BP were measured 15 minutes before exercise. Oxygen consumption (VO2) and respiratory quotient (Rq) were obtained during each minute of exercise. This submaximal test served at the control. Each subject then performed 4 similar submaximal tests, at least 48 hours apart (to allow for washout). Each test was performed 3 hours after single-dose administration of nebivolol 1 mg, 2.5 mg, 5 mg and 10 mg solution. Blood pressure was measured every two minutes at

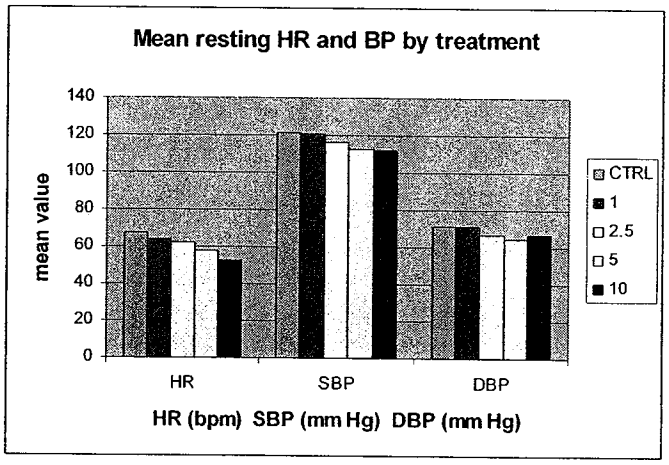
exercise; results were calculated from minute 6-15 during exercise. Plasma nebivolol levels were collected before and 3 hours after dosing.

No primary endpoint was specified in the study report. Statistical analysis was performed via ANOVA and paired t-test, corrected for analysis of multiple comparisons (Bonferroni correction). Statistical significance was established at the 0.05 confidence level.

Results: Eleven healthy subjects (20-30 years old) were enrolled and completed the study. No adverse events were reported.

Resting BP/HR responses: Results are shown graphically in Figure 63.

Figure 63. Mean Resting Heart Rate (HR) and Blood Pressure (BP) by Treatment (CTRL = Control; 1, 2.5, 5, and 10 Refer to mg Nebivolol Dose Groups) (RSA-1)



According to the sponsor, the decrease in DBP was not statistically significant. The decrease in SBP was statistically significant only at the 10 mg dose. Heart rate decreases were statistically significant at the 5 and 10 mg doses.

Exercise-related parameters:
Respiratory quotient was 0.96-0.97 across treatment groups with no significant difference noted. VO2 and work done was not significantly different across groups.

The study report listed a single mean exercise SBP, DBP, and HR value per treatment group.

Table 44. BP and HR During Submaximal Steady-State Exercise

	Control	1 mg	2.5 mg	5 mg	10 mg
Mean HR (bpm)	166	159*	153*	143*	132*
Mean SBP (mm Hg)	179	178	173	167*	162*
Mean DBP (mm Hg)	62	61	61	59	58

* $p < 0.05$, n=11

Serum levels: no nebivolol levels were analyzed in this study report.

Reviewer Comments:

1. This was an open-label study with no placebo control group; placebo effects or bias cannot be excluded.
2. Resting HR was significantly decreased after nebivolol 5 and 10 mg; resting SBP was significantly decreased after nebivolol 10 mg.
3. Exercise-related HR was significantly decreased (vs. control) after 1 mg of nebivolol and continued to decrease after nebivolol 10 mg; exercise-related SBP was significantly decreased after nebivolol 5 and 10 mg.
4. No protocol was submitted and it cannot be verified which analyses were pre-specified.
5. Nebivolol, at these exposures, appeared to be well tolerated.

1.39 LMD No. 65577. Study ID 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") (September 8, 1987 – April 27, 1988) (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the effect of isometric handgrip on blood pressure and heart rate in 14 healthy adult male subjects, 25 to 51 years of age, following two weeks of therapy with either nebivolol 5 mg po qd or atenolol 100 mg po qd.

Methods: A 3 minute isometric handgrip (IHG) test was performed at baseline and after two weeks of therapy with either nebivolol or atenolol.

Results: The effect of isometric handgrip on diastolic and systolic blood pressure was not significantly affected by nebivolol or atenolol. The effect of isometric handgrip on heart rate was significantly reduced by atenolol (Table 45, Figure 64, and Figure 65), but not nebivolol.

Table 45. Mean Values (±SEM) of Blood Pressure and Heart Rate During Handgrip Power Test Before and After a 2-Week Treatment with Nebivolol or Atenolol in 14 Volunteers (BEL-9)

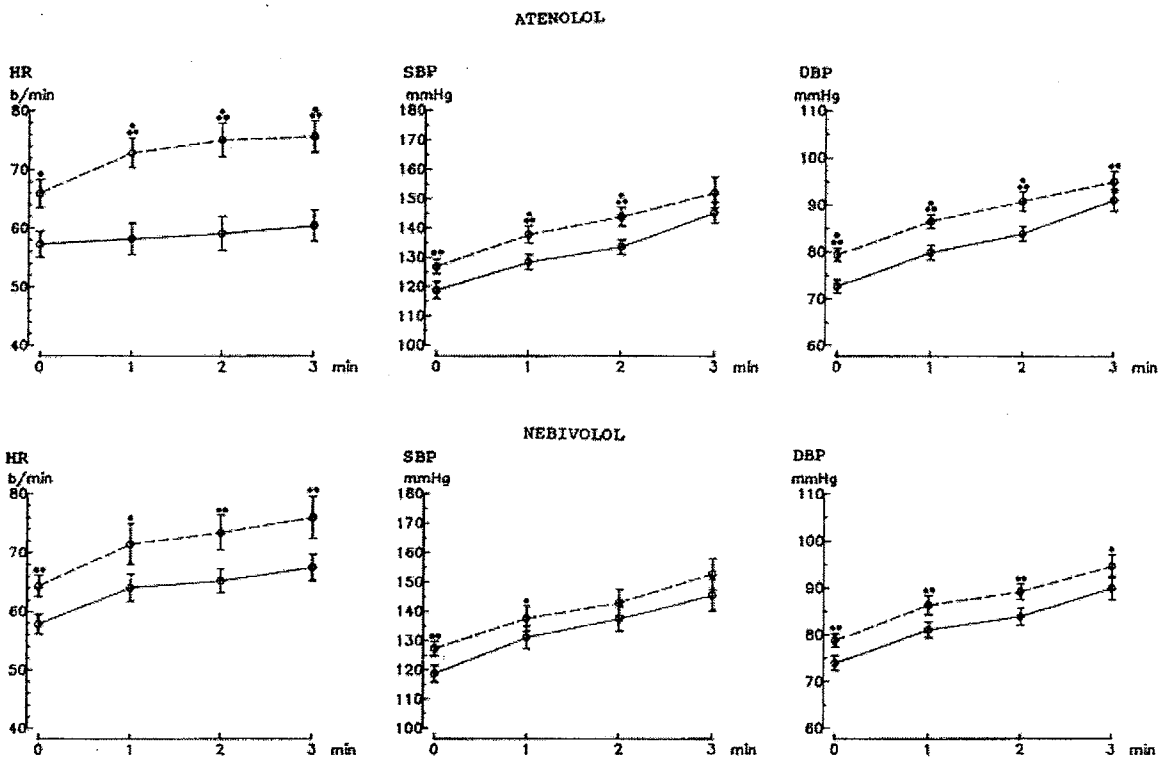
		Nebivolol 5 mg/day for 2 weeks				Atenolol 100 mg/day for 2 weeks			
		0 min	1 min	2 min	3 min	0 min	1 min	2 min	3 min
SBP (mmHg)	pre	127±2.6	138±4.3	143±4.5	153±5.3	127±2.5	138±3.0	144±3.3	152±5.3
	post	119±2.9	131±3.9	137±4.2	146±5.4	119±3.0	128±2.7	134±2.5	145±3.6
	p1	0.002	0.01	n.s.	n.s.	0.006	0.0002	0.0002	n.s.
	p2	---	n.s.	n.s.	n.s.	---	n.s.	n.s.	n.s.
DBP (mmHg)	pre	79±1.4	86±2.1	89±1.7	95±2.4	79±1.4	87±1.5	91±2.1	95±2.2
	post	74±1.6	81±1.7	84±1.9	90±2.5	73±1.4	80±1.6	84±1.6	91±2.4
	p1	0.005	0.005	0.003	0.04	0.0002	0.0002	0.0008	0.004
	p2	---	n.s.	n.s.	n.s.	---	n.s.	n.s.	n.s.
HR (b/min)	pre	64±1.8	71±3.5	73±3.0	76±3.6	66±2.4	73±2.5	75±2.9	76±2.7
	post	58±1.7	64±2.3	65±2.0	67±2.3	57±2.2	58±2.7	59±2.9	60±2.7
	p1	0.002	0.01	0.005	0.008	0.03	0.0006	0.0006	0.0008
	p2	---	n.s.	n.s.	n.s.	---	0.04	0.05	n.s.

p1 = Wilcoxon m.p.s.r. test versus pre

p2 = Mann-Whitney U-test on differences with 0 min values before treatment versus same differences after treatment

(Reproduced from Sponsor, BEL-9, Table 2, page 6)

Figure 64. HandgripTest Before (---) and After (___) a 14-Day Treatment with Atenolol or Nebivolol in 14 Volunteers (BEL-9)



*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 Wilcoxon matched-pairs signed-ranks test, 2-tailed probability.

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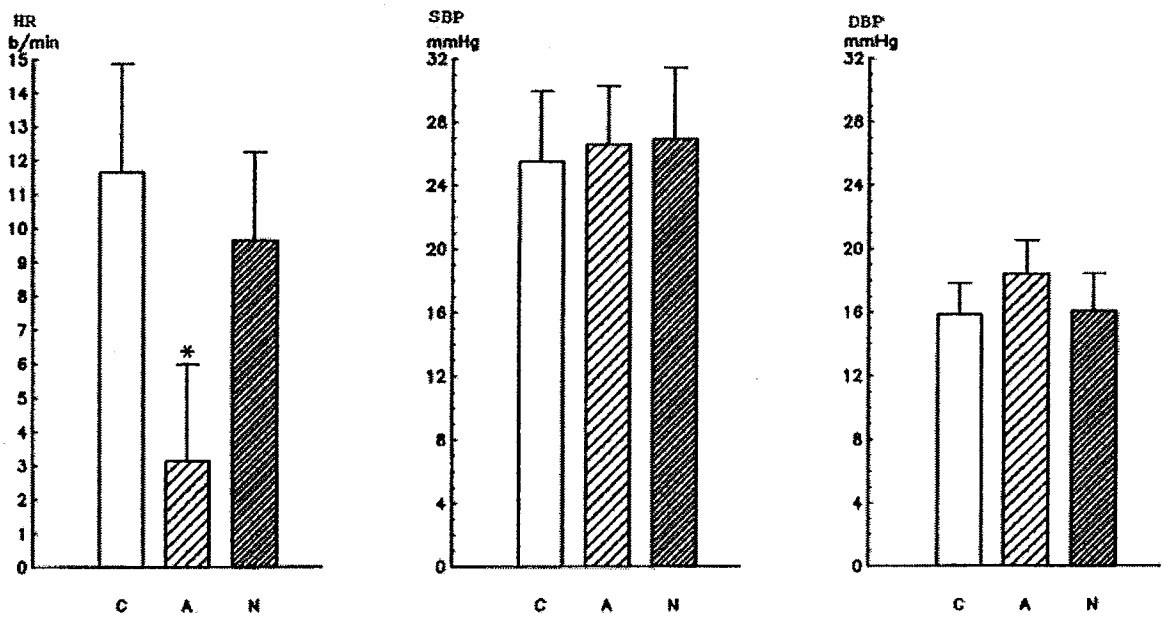
Figure 65. Increase of Heart Rate and Blood Pressure During a HandgripTest on a Control Day (C) and After a 14-Day Treatment with Atenolol 100 mg O.D. (A) or Nebivolol 5 mg O.D. (N). (BEL-9)



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LMD No. 69017. Study ID BEL-9. ("Non-Invasive Cardiac Haemodynamics of Nebivolol in Man (Acta Antwerpiensa; 6(2): 2-21, 1989")

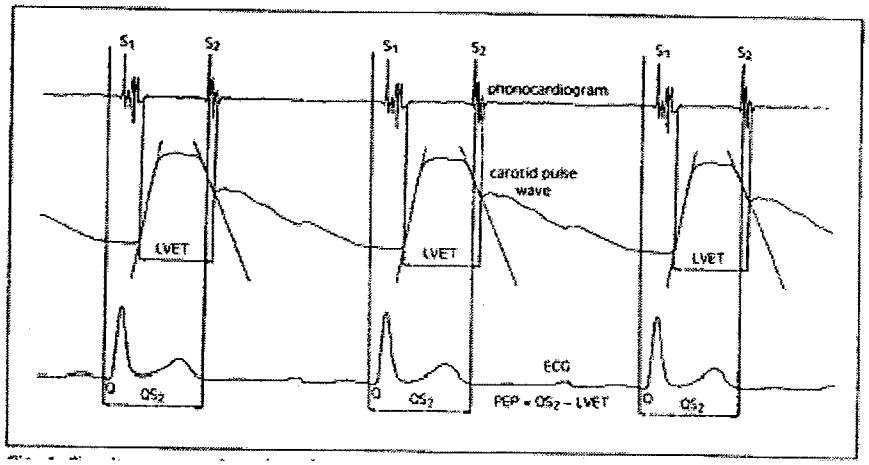
This journal article discussed the three systolic time intervals (STI): pre-ejection period (PEP), left ventricular ejection time (LVET), and total electromechanical systole. The authors discussed their use of these tests in different populations: patients with hypertension, myocardial infarction, and congestive heart failure. Equilibrium radionuclide angiocardiography (ERNA) was also used to evaluate patients. The authors stated QS2c is a sensitive index of inotropy. If QS2c shortens, it is consistent with a positive inotropic effect, and if QS2c lengthens, it is consistent with a negative inotropic effect. PEPc = isometric contraction time. If PEPc shortens, it implies an increase in preload and an improvement in left ventricular compliance. LVETc = isotonic contraction time and is afterload dependent. A lengthening of LVETc is indicative of afterload reduction, and a shortening is indicative of an increase in afterload. The ratio of PEPc to LVETc (PEPc/LVETc) is considered an indirect and accurate measure of left ventricular performance.

Table 46. Correction to Heart Rate of 72 for PEP, LVET, and QS2 for a Group of Normal Subjects and Different Groups of Patients with Cardiovascular Diseases, According to Our Resting Supine Regression Equations

	n	PEP_c	$LVET_c$	QS_{2c}
Normal subjects	219	0.4187(72-HR) + PEP	-1.2396(72-HR) + LVET	-1.7112(72-HR) + QS_2
Ischemic heart disease	104	0.4918(72-HR) + PEP	-1.4856(72-HR) + LVET	-1.9762(72-HR) + QS_2
Hypertension	182	0.3432(72-HR) + PEP	-1.7828(72-HR) + LVET	-2.1155(72-HR) + QS_2
Acute myocardial infarction	210	0.5825(72-HR) + PEP	-1.7860(72-HR) + LVET	-1.6062(72-HR) + QS_2
Acute heart failure	32	0.1632(72-HR) + PEP	-1.0750(72-HR) + LVET	-1.2382(72-HR) + QS_2

(Reproduced from Sponsor, Table 1, page 3)

Figure 66. Simultaneous Registration of Phonocardiogram, Carotid Pulse Wave, and Electrocardiogram



(Reproduced from Sponsor, Figure 1, page 3)

After performing a variety of studies in healthy volunteers, as well as patients with clinical conditions of hypertension, congestive heart failure, or myocardial infarction, the investigators compared the effect of different doses of nebivolol to atenolol, pindolol, and propranolol. The investigators concluded nebivolol improved left ventricular performance at rest and offset the negative influence usually seen with beta blockers on exercise inotropy. The exact mechanism of these effects, however, is unknown.

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Table 47. Mean Values of the Ratio PEPc/LVETc on a Control Day and After an Acute Oral Administration of Different ß-Adrenoceptor Antagonists in 8 Volunteers

	0 hr	3 hr	6 hr	24 hr
Control	0.36	0.36	0.36	0.36
Propranolol 80 mg	0.35	0.41* ↗	0.36	0.35
Atenolol 100 mg	0.35	0.42** ↗	0.34	0.36
Pindolol 15 mg	0.36	0.37	0.31** ↘	0.35
Pindolol 30 mg	0.36	0.38	0.32* ↘	—
Nebivolol 5 mg	0.36	0.39	0.34** ↘	0.34** ↘
Nebivolol 10 mg	0.36	0.40** ↗	0.36	0.34** ↘

* $p \leq 0.05$; ** $p \leq 0.01$ Wilcoxon matched-pairs signed-ranks test, 2-tailed probability

(Reproduced from Sponsor, Table 2, page 5)

Table 48. Mean Values ±SE of the Pre-Post Exercise LVETc (msec) on a Control Day and 3 Hours After an Acute Oral Administration of Different ß-Adrenoceptor Antagonists

Control	propranolol 80 mg	atenolol 100 mg	pindolol 15 mg	pindolol 30 mg	nebivolol 5 mg	nebivolol 10 mg
+53 ± 7.4	+0.4 ± 6.2	-4.5 ± 3.5	-3.0 ± 3.6	-2.0 ± 4.9	+15 ± 7.8	+18 ± 6.0

(Reproduced from Sponsor, Table 3, page 5)

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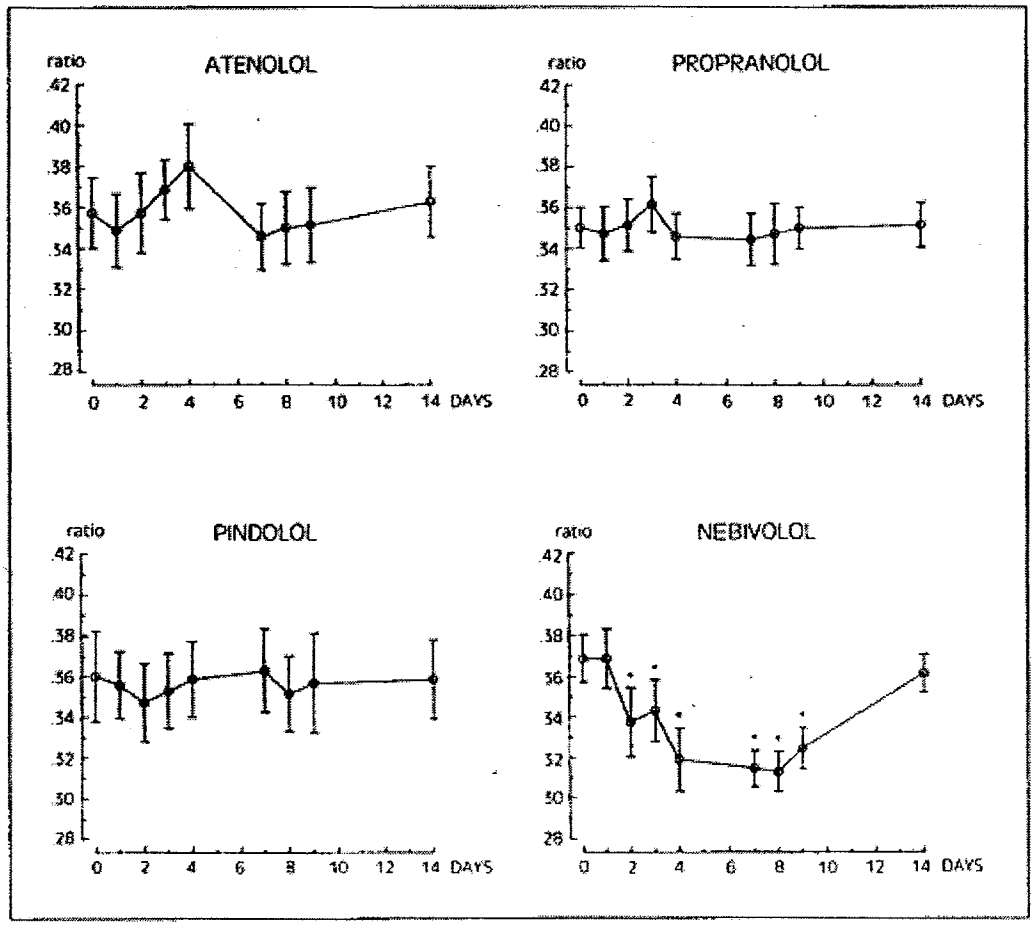
Figure 67. Mean Values ±SE of the Ratio PEPc/LVETc During a 7-Day Treatment and After Discontinuation of Treatment with Atenolol 100 mg O.D., Propranolol 160 mg O.D., Pindolol 5 mg T.I.D. and Nebivolol 5 mg O.D. in 7 Volunteers



* p ≤ 0.05 Wilcoxon matched-pairs signed ranks test, 2-tailed probability

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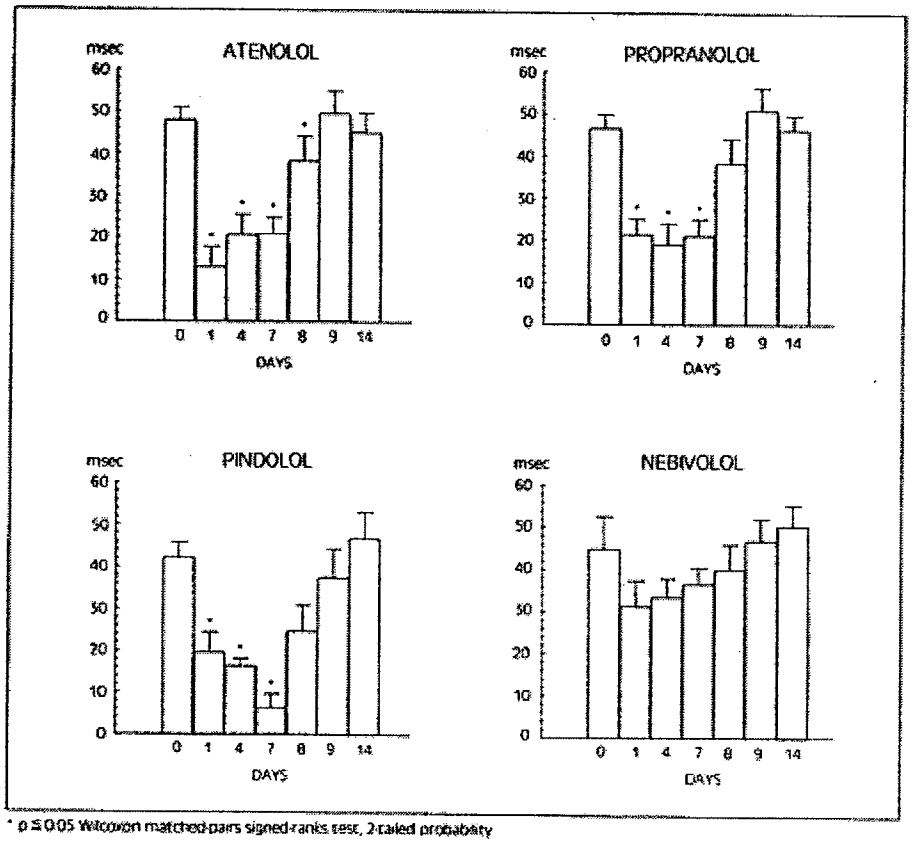
Figure 68. Mean Values ±SE of the ΔLVETc Pre-Post Exercise During a 7-Day Treatment and After Discontinuation of Treatment with Atenolol 100 mg O.D., Propranolol 160 mg O.D., Pindolol 5 mg T.I.D. and Nebivolol 5 mg O.D. in 7 Volunteers



* p ≤ 0.05 Wilcoxon matched-pairs signed-ranks test, 2-tailed probabaty

Fig. 3: Mean values ± SE of the Δ $LVET_c$ pre-post exercise during a 7-day treatment and after discontinuation of treatment with atenolol 100 mg o.d., propranolol 160 mg o.d., pindolol 5 mg t.i.d. and nebivolol 5 mg o.d. in 7 volunteers.

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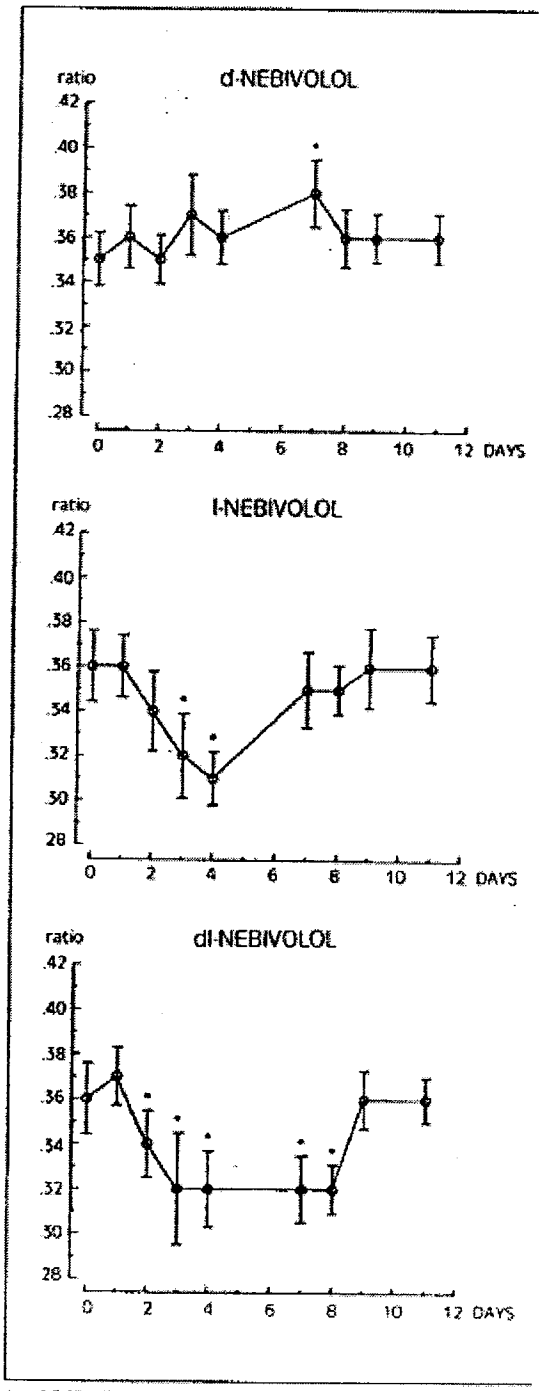
Figure 69. Mean Values ±SE of the Ratio PEPc/LVETc During a 7-Day Treatment and After Discontinuation of Treatment with *d*-Nebivolol 5 mg O.D., *l*-Nebivolol 5 mg O.D. and *dl*-Nebivolol 10 mg O.D. in 7 Volunteers



* p ≤ 0.05 Wilcoxon matched pairs signed-ranks test, 2 tailed probability

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Figure 70. Mean Values ±SE of the ΔLVETc Pre-Post Exercise During a 7-Day Treatment and After Discontinuation of Treatment with *d*-Nebivolol 5 mg O.D., *l*-Nebivolol 5 mg O.D., and *dl*-Nebivolol 10 mg O.D. in 7 Volunteers

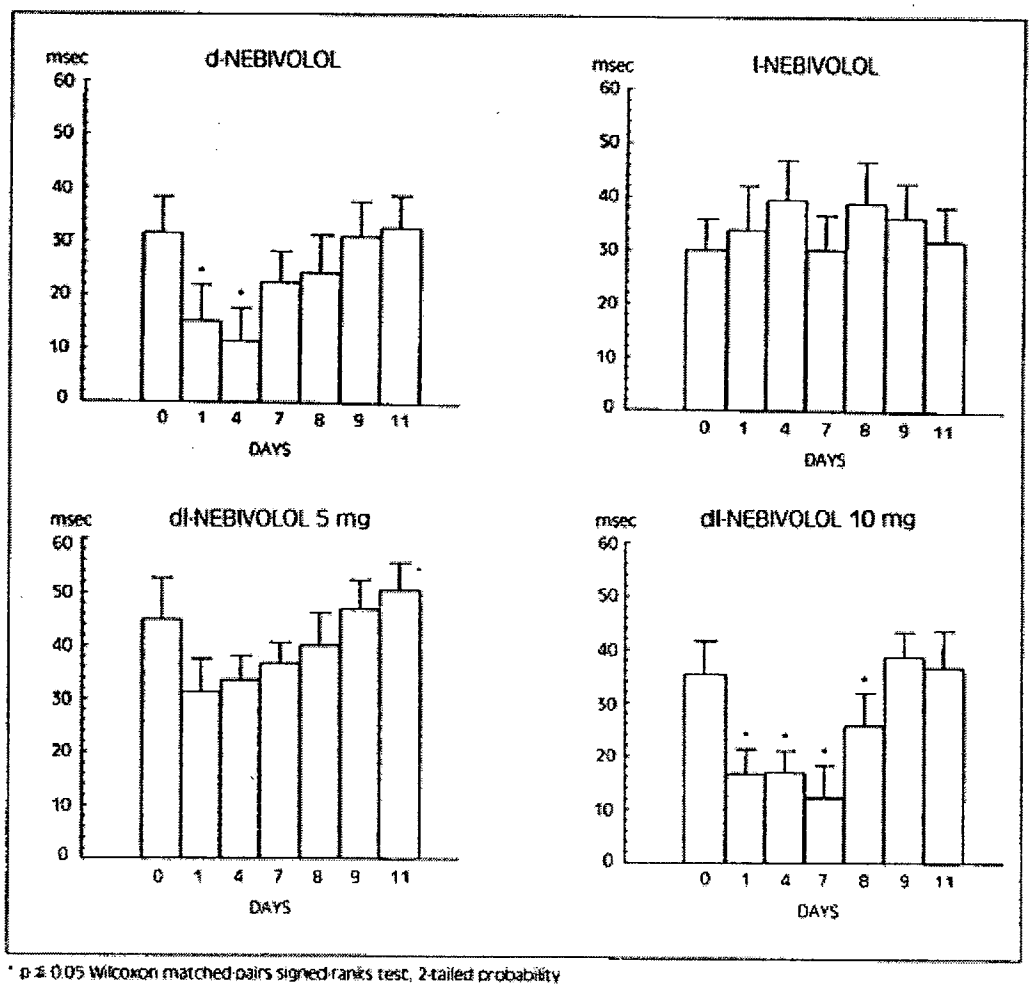

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Table 49. Correlations Between Changes of STI and ERNA During Treatment with Atenolol 100 mg O.D. and Nebivolol 5 mg O.D. in 14 Healthy Volunteers

Correlation	r	p
Δ Stroke volume - Δ $PEP_c/LVET_c$	-.4842	0.009
Δ Stroke volume - Δ PEP_c	-.5864	0.001
Δ Cardiac output - Δ $PEP_c/LVET_c$	-.6727	0.0001
Δ Cardiac output - Δ PEP_c	-.7146	0.00001

(Reproduced from Sponsor, Table 4, page 12)

Table 50. Mean Values SE of All Parameters of Blood pressure, Heart Rate, STI, and ERNA Before and After a 14-Day Treatment with Atenolol 100 mg O.D. and Nebivolol 5 mg O.D. in 14 Volunteers

	Atenolol			Nebivolol			
	Pre	Post	p1	Pre	Post	p1	p2
SBP (mmHg)	127 ± 2.5	119 ± 3.0	0.006	126 ± 2.7	119 ± 2.9	0.002	n.s.
DBP (mmHg)	79 ± 1.4	73 ± 1.4	0.0002	79 ± 1.4	74 ± 1.6	0.005	n.s.
MAP (mmHg)	95 ± 1.7	88 ± 1.9	0.0006	94 ± 1.8	88 ± 2.0	0.003	n.s.
HR (b/min)	63 ± 2.6	51 ± 2.2	0.0002	61 ± 2.6	55 ± 1.5	0.003	0.02
QS_{2c} (msec)	396 ± 3.9	409 ± 5.2	0.005	396 ± 4.6	390 ± 4.4	n.s.	0.01
PEP_c (msec)	105 ± 2.5	107 ± 2.2	n.s.	106 ± 2.3	90 ± 2.8	0.0004	0.0006
$LVET_c$ (msec)	291 ± 3.3	303 ± 4.1	0.008	291 ± 3.1	300 ± 4.4	0.009	n.s.
$PEP_c/LVET_c$	0.36 ± 0.010	0.35 ± 0.007	n.s.	0.36 ± 0.007	0.30 ± 0.011	0.0002	0.0006
EF (%)	72 ± 1.6	69 ± 1.5	0.003	72 ± 1.4	77 ± 1.5	0.001	0.0004
EDV (ml)	136 ± 6.7	142 ± 4.4	n.s.	134 ± 6.1	156 ± 5.8	0.001	0.004
ESV (ml)	38 ± 3.1	44 ± 2.8	0.01	38 ± 2.4	37 ± 3.2	n.s.	0.04
SV (ml)	97 ± 4.9	98 ± 2.8	n.s.	97 ± 4.8	119 ± 3.7	0.0004	0.0002
CO (l/min)	6.05 ± 0.28	4.97 ± 0.23	0.0006	5.86 ± 0.28	6.50 ± 0.26	0.008	0.0002
PVR (mmHg.min/l)	16.2 ± 0.76	18.1 ± 0.79	0.01	16.6 ± 0.79	14.0 ± 0.76	0.0008	0.0002
PFR (EDV/ml)	3.11 ± 0.11	2.78 ± 0.11	0.005	3.08 ± 0.108	3.02 ± 0.09	n.s.	0.003
PFR (ml/sec)	419 ± 24	389 ± 19	n.s.	416 ± 23	462 ± 22	0.003	0.0002

p1 Wilcoxon matched-pairs signed-ranks test, 2-tailed probability on post-values versus pre-values

p2 Wilcoxon matched-pairs signed-ranks test, 2-tailed probability on differences post-pre nebivolol versus differences post-pre atenolol

(Reproduced from Sponsor, Table 5, page 12)

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1.40 LMD No. 106561. Study ID NED-11. ("Pharmacological Properties of Nebivolol in Man") (Eur J. Clin Pharmacol (1997) 51: 379-384) (Reviewer: Karen A. Hicks, M.D.)

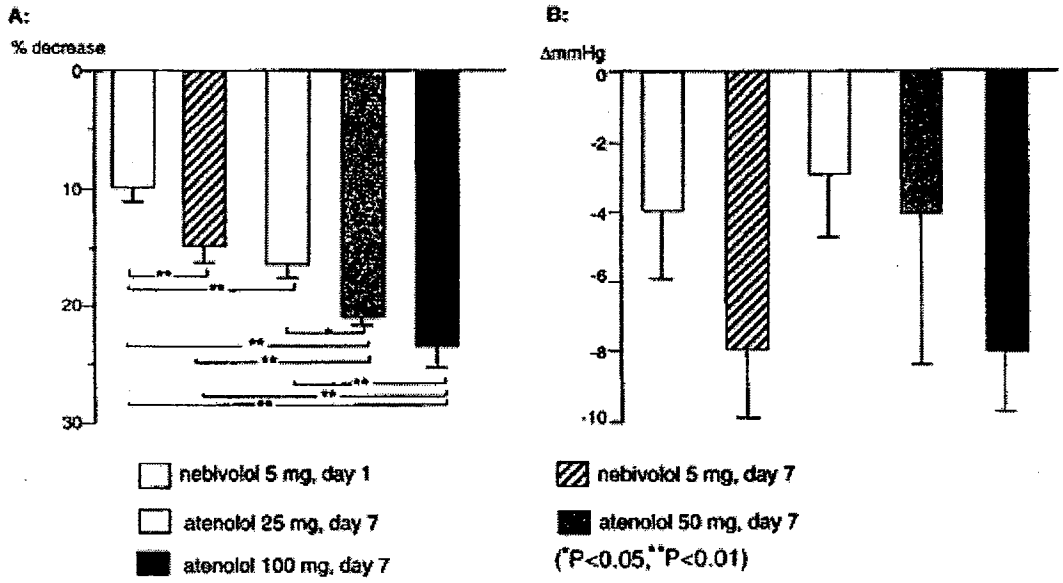
Objectives: To determine

1. the beta-1 blocking potency of nebivolol
2. the beta-1 adrenoceptor selectivity of nebivolol in man after repeated dosing (7 days) and following a single oral dose, compared with 7 days of atenolol therapy.
3. whether or not nebivolol has any alpha blockade activity

Methods: Investigators randomized 12 healthy subjects in an open, randomized, two-way crossover study. In Session 1, patients were randomized to nebivolol 5 mg daily x 8 days. In Session 2, patients were given escalating doses of atenolol 25 mg, 50 mg, and 100 mg daily x 7 days each, with a 3 day washout period between different atenolol doses. There was a two-week wash-out period between Session 1 and Session 2. Investigators obtained measurements on Days 1 and 7. To assess beta-one potency, the percentage decrease in exercise induced tachycardia was determined on study drug. To assess beta-one selectivity, the heart rate response to isoprenaline was evaluated. An exercise test was performed 30 minutes after the last isoprenaline dose. To assess alpha one blockade, the phenylephrine dose response test was used.

Results: Twelve subjects were randomized, and eleven subjects completed the study. One female subject discontinued the study due to hematuria. Change in exercise induced tachycardia (EIT) was decreased 10% after a single oral dose of nebivolol and 15% after one week of nebivolol therapy. After one week of treatment, there was no difference in EIT after nebivolol (15% reduction) versus after atenolol (16% reduction) therapy. This study found nebivolol had no additional alpha one blocking ability.

Figure 71. A: Percentage Decrease in Exercise-Induced Tachycardia (n = 11) B: Mean Reduction in Mean Arterial Pressure at Rest (n = 11) (NED-11)



(Reproduced from Sponsor, NED-11, Figure 2, page 3)

Figure 72. Isoprenaline Induced Tachycardia: CD_{20} Ratio (n = 11) (NED-11)

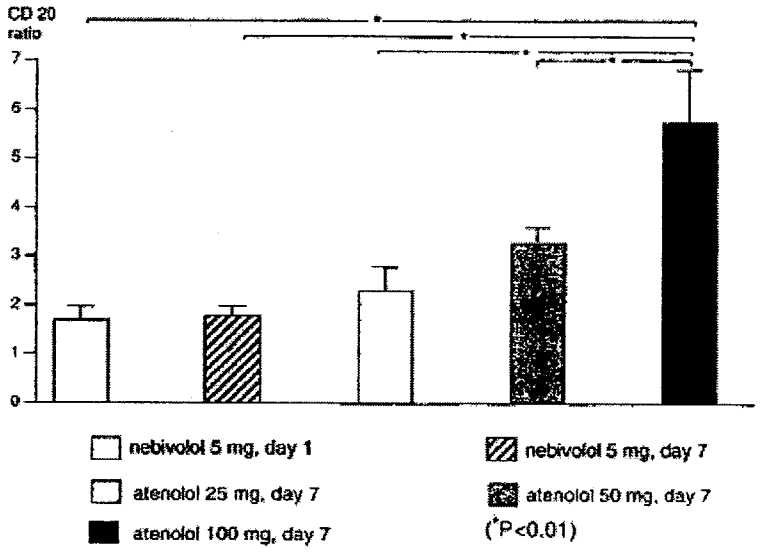


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Figure 73. Phenylephrine Dose-Response Test (n = 9) (NED-11)

	Pre-drug Day 0	Nebivolol, 5 mg Day 8	
PS_{25} ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.78 (0.09)	0.86 (0.15)	NS
PD_{15} ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.82 (0.10)	0.96 (0.12)	NS
PM_{20} ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.81 (0.08)	0.83 (0.10)	NS

NS no statistical difference, PS_{25} dose of phenylephrine increasing systolic blood pressure with 25 mmHg, PD_{15} dose of phenylephrine increasing diastolic blood pressure with 15 mmHg, PM_{20} dose of phenylephrine increasing mean arterial pressure with 20 mmHg

(Reproduced from Sponsor, NED-11, Table 2, page 4)

1.41 LMD No. 65660. Study ID 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") (Reviewer: Karen A. Hicks, M.D.)

Objectives: To determine the effects of the acute oral intake of *d,l*-nebivolol 5 mg, *d*-nebivolol 2.5 mg, and *l*-nebivolol 2.5 mg on heart rate, blood pressure, and systolic time intervals at rest and during exercise in 10 healthy volunteers.

Methods: Ten healthy volunteers (5 males, 5 females) between 28 and 51 years of age received in random sequence a dose of *d*-nebivolol 2.5 mg, *l*-nebivolol 2.5 mg, or *d,l*-nebivolol 5 mg, separated one week apart. Subjects underwent a complete evaluation 6 hours after single oral intake. Heart rate was recorded before and every minute during exercise, as well as up to 6 minutes of recovery. Systolic blood pressure was recorded before, every 3 minutes during exercise, at the end of exercise, and at 1, 3, and 6 minutes of recovery. ECG and systolic time intervals at rest were obtained in the morning prior to drug intake. Subjects exercised 9 minutes using a Modified Bruce Protocol.

Results: Increases in heart rate and systolic blood pressure during exercise after intake of *d*-nebivolol (2.5 mg) or *d,l* nebivolol (5 mg) were equally and significantly reduced. *l*-Nebivolol did not affect increases of heart rate and systolic blood pressure during exercise. Only *d,l* nebivolol significantly reduced the shortening of LVETc after exercise.

Table 51. Baseline Characteristics (BEL-15)

Baseline characteristics - subject disposition	
Number of volunteers entered (M/F)	10 (5/5)
Age: median (min-max), yrs	34 (28-51)
Premature discontinuation:	0

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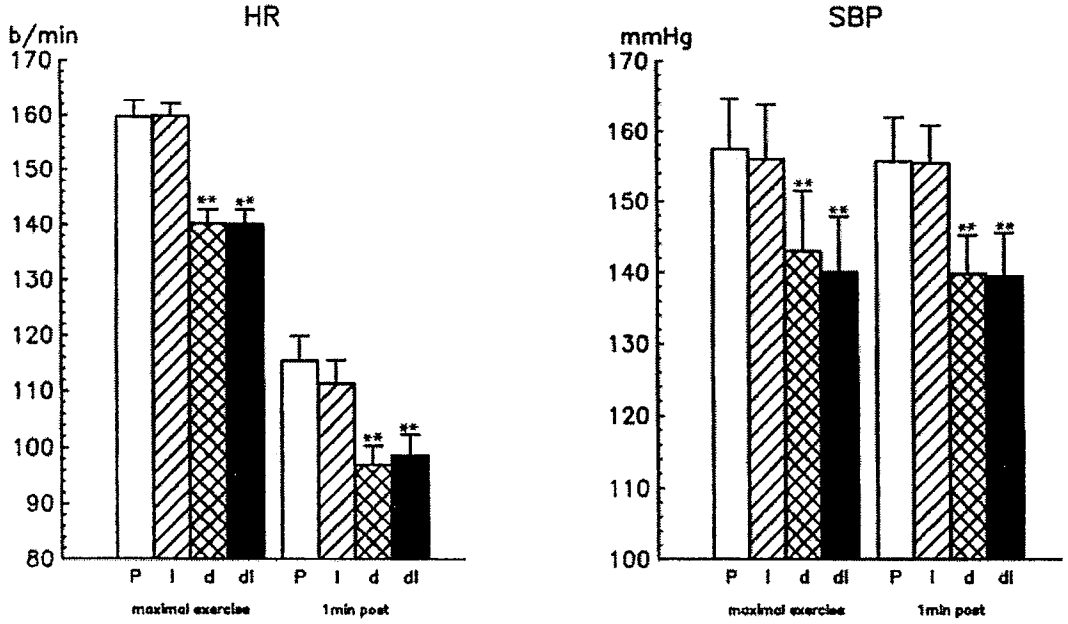
Table 52. Efficacy Results (BEL-15)

Results Treadmill test values (6 h)		Placebo	d-nebivolol	l-nebivolol	dl-nebivolol
HR, b/min	pre/9min ex	74/160	69/140**	76/160	69/140**
SBP, mm/Hg	pre/9min ex	118/158	110/143**	116/156	109/140**
LVETc, msec	post-pre ex	-41	-32	-40	-25*
Rest values (6h)					
HR, ms		70	64*	70	62**
PQ, ms		151	151	146	152
QRS, ms		92	91	91	94
QT, ms		383	394	381	395*
QTc, ms		411	404	408	399**
QTm, ms		401	401	397	395
QS2c, ms		402	406	397	401
PEPc, ms		108	108	107	107
LVETc, ms		293	298	291	295
PEPc/LVETc		0.37	0.36	0.37	0.36
QT/QS2		0.95	0.94	0.95	0.94

*Asterisks refer to differences with placebo; levels of significance: * $p \leq 0.05$; ** $p \leq 0.01$*

(Reproduced from Sponsor, BEL-15, page 2)

Figure 74. Heart Rate and Systolic Blood Pressure at Maximal Exercise and 1 Min After the End of Exercise After a Single Oral Intake of 2.5 mg of *d*-Nebivolol, 2.5 mg of *l*-Nebivolol , and 5 mg of *dl*-Nebivolol in a Double-Blind Placebo-Controlled Study in 10 Healthy Volunteers (BEL-15)



(Reproduced from Sponsor, BEL-15, Figure 2, page 9)

Figure 75. Mean Rest Values of Systolic Time Intervals After a Single Oral Intake of 2.5 mg of *d*-Nebivolol (d), 2.5 mg of *l*-Nebivolol (l), and 5 mg of *dl*-Nebivolol (dl) in a Double-Blind Placebo (P)-Controlled Study in 10 Healthy Volunteers (BEL-15)

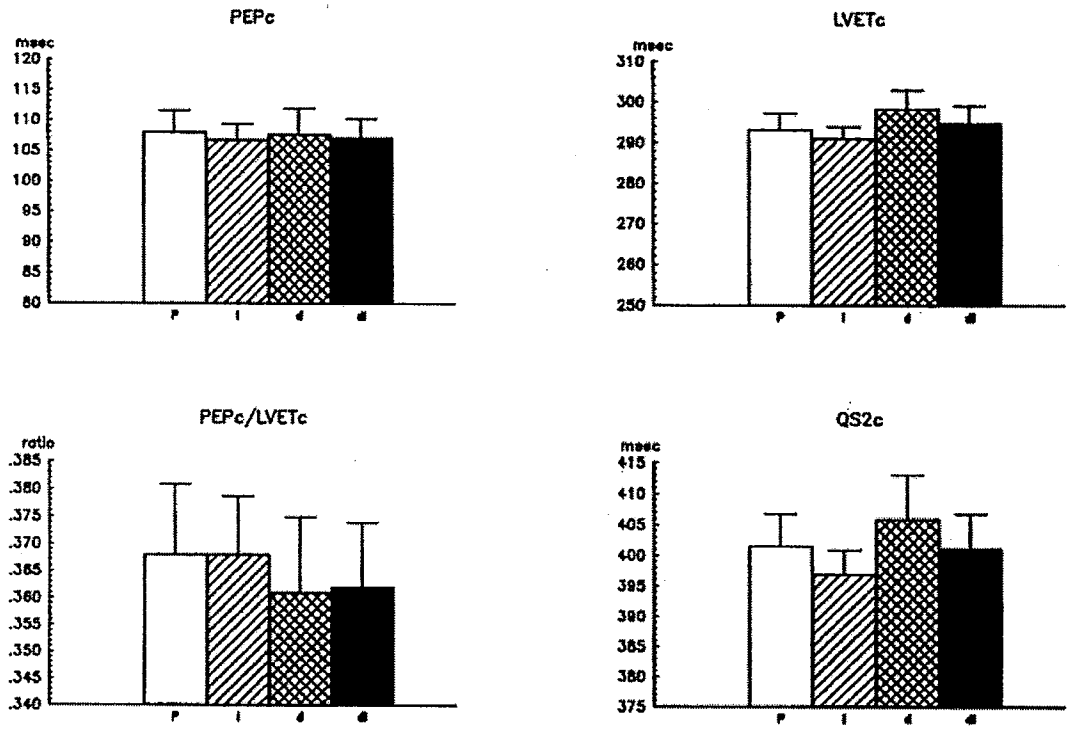


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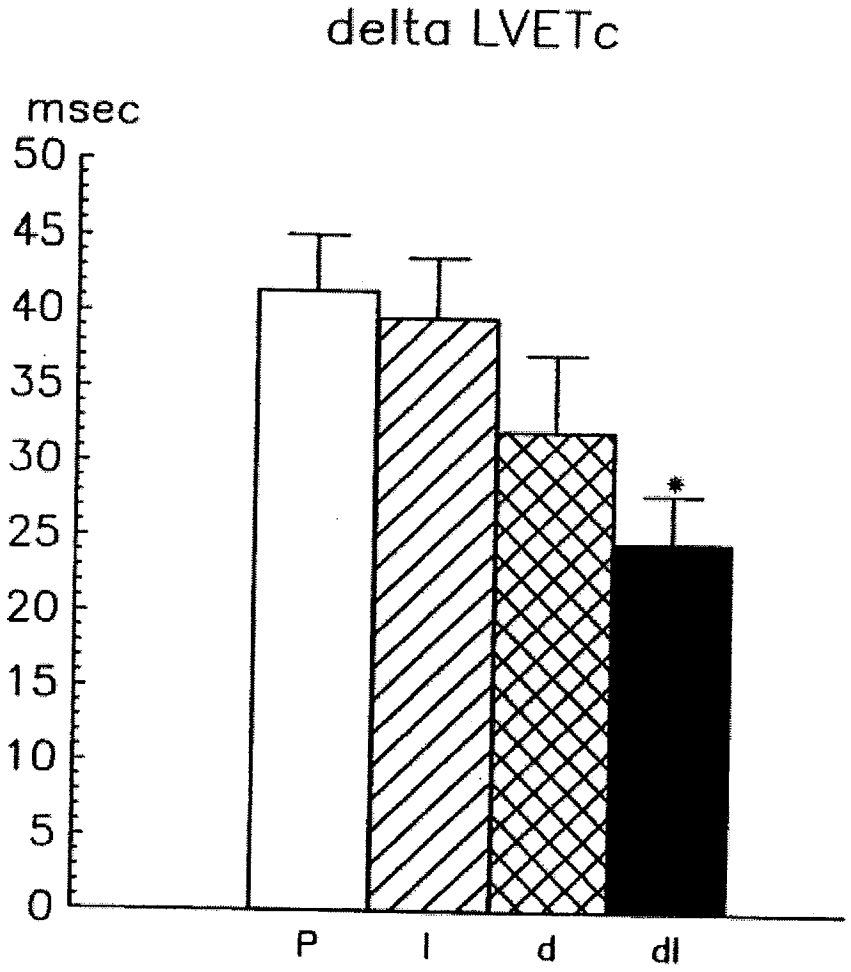
Figure 76. Shortening of LVETc After Exercise, After a Single Oral Intake of 2.5 mg of *d*-Nebivolol (d), 2.5 mg of *l*-Nebivolol (l), and 5 mg of *dl*-Nebivolol (dl) in a Double-Blind Placebo (P)-Controlled Study in 10 Healthy Volunteers (BEL-15)



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1.42 LMD No. 68099. Study ID: 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") (Source: study report. No protocol was submitted) (Reviewer: Shari Targum, M.D.)

Objective: determine the lowest dose of nebivolol that will produce the maximum beta blockade after 3 weeks administration.

Study Summary: This was a double-blind, placebo-controlled, parallel-group study. Healthy males were given nebivolol 1, 2.5, 5, or 10 mg or matching placebo once daily for 3 weeks. Every 4th day, HR and BP would be measured 3 hours after drug ingestion.

Subjects completed a submaximal cycle[2] test at baseline and after 3 weeks of treatment (3 hours after the last ingestion of drug); exercise measurements included HR, BP, maximal oxygen consumption, and rate of perceived exertion. Laboratory testing was performed pre-treatment and after 3 weeks of treatment.

Analysis: ANOVA and paired t-test, corrected for analysis of multiple comparisons (Bonferroni correction) were used to analyze the significance of differences between experimental variables. No primary endpoint was identified.

Results: Fifty males, median age 23 (range 21-41) years, average VO_2 max 50.3 ml O_2/kg/min, were recruited for this study. No adverse events were reported. One subject was unable to complete the full 15 minute exercise test after 3 weeks of the 10 mg dose. He stopped the study due to exhaustion in the 13th minute (Borg rating 10); data for this subject was collected from minute 6 to 12 and not to minute 16.

Resting HR/BP:
According to the sponsor, drug effects on resting HR and BP are shown below:

Table 53. Effects on Resting Heart Rate and Blood Pressure (RSA-5)

Mean (SD)	Heart rate (bpm)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Placebo: pre-drug	59.4 (7.29)	126.3 (9.82)	79.2 (5.43)
post-drug	58.3 (5.78)	121.9 (7.88)	78.5 (5.8)
Neb 1 mg: pre-drug	57.7 (4.76)	117.8 (8.65)	79 (3.02)
post-drug	53.4 (6.69)	113.9 (9.92)	75.1 (5.59)
Neb 2.5 mg: pre-drug	60.4 (5.85)	121.7 (6.9)	81.4 (3.6)
post-drug	54.1 (9.14)	114.9 (8.5)	75.6 (5.42)
Neb 5 mg: pre-drug	62.3 (5.4)	122.6 (8.18)	79 (8.9)
post-drug	53.8 (6.36)	114.1 (11.1)	73.9 (8.1)
Neb 10: pre-drug	58.4 (6.52)	121 (5.35)	77.8 (3.79)
post-drug	48.6 (6.04)*	107.1 (9.91)*	69.96 (6.4)*

*** = p <0.01. Post-drug = average of 5 visits on drug. The analysis does not clarify whether the statistical difference includes a comparison vs. placebo. Raw data were not submitted.**

According to the sponsor's analysis, changes from baseline in resting HR and BP were statistically significant only in subjects receiving nebivolol 10 mg daily. It should also be noted that subjects in the placebo, 1, and 10 mg nebivolol groups had mean HR below 60 prior to drug intake.

[2] **First, a progressive maximum cycle ergometer test was performed. Subjects began pedaling at a work load of 120 watts; the work load was increased 15 watts every minute until exhaustion. Expired air was analyzed for oxygen and carbon dioxide content. Three days after the initial maximum oxygen consumption test (VO2max), each subject performed a submaximal steady state cycle ergometer test for 15 minutes at a workload corresponding to the workload achieved at 75% of their VO2max. This submaximal test was repeated on Day 20; results were calculated from minute 6-16 during exercise.**

Figure 77. Nebivolol Dose Response: Heart Rate Over 3 Week Period

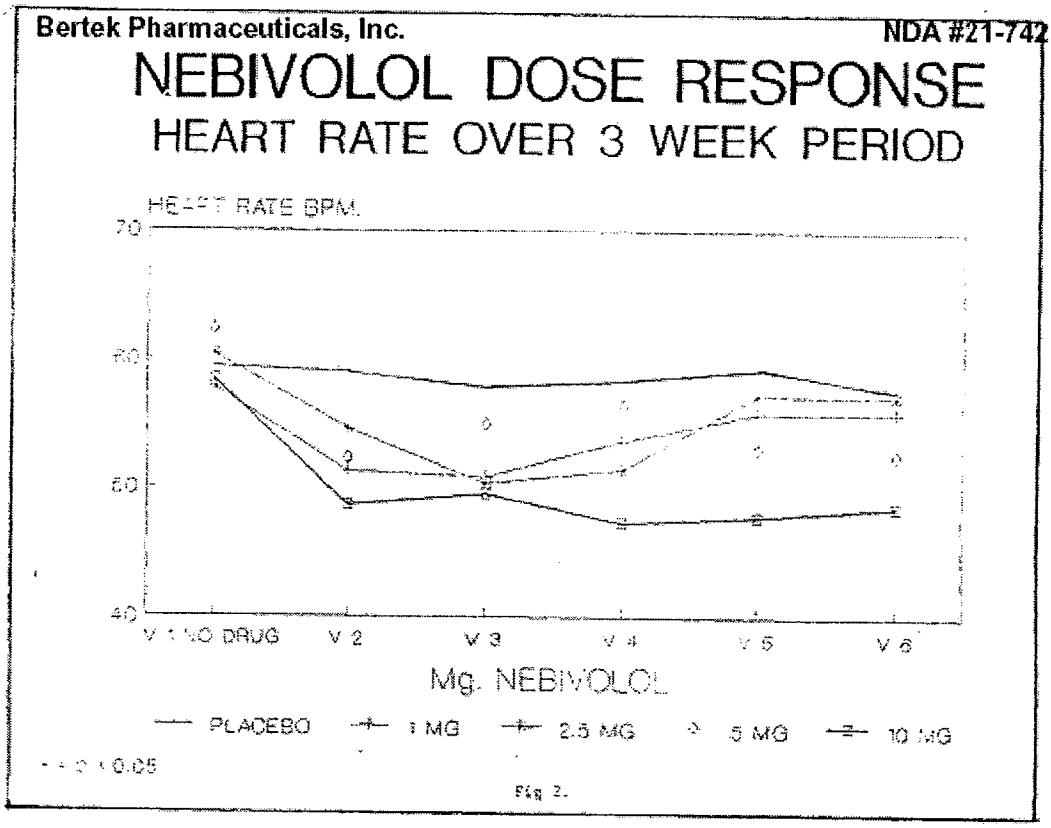

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Figure 78. Nebivolol Dose Response: Systolic BP Over 3 Week Period

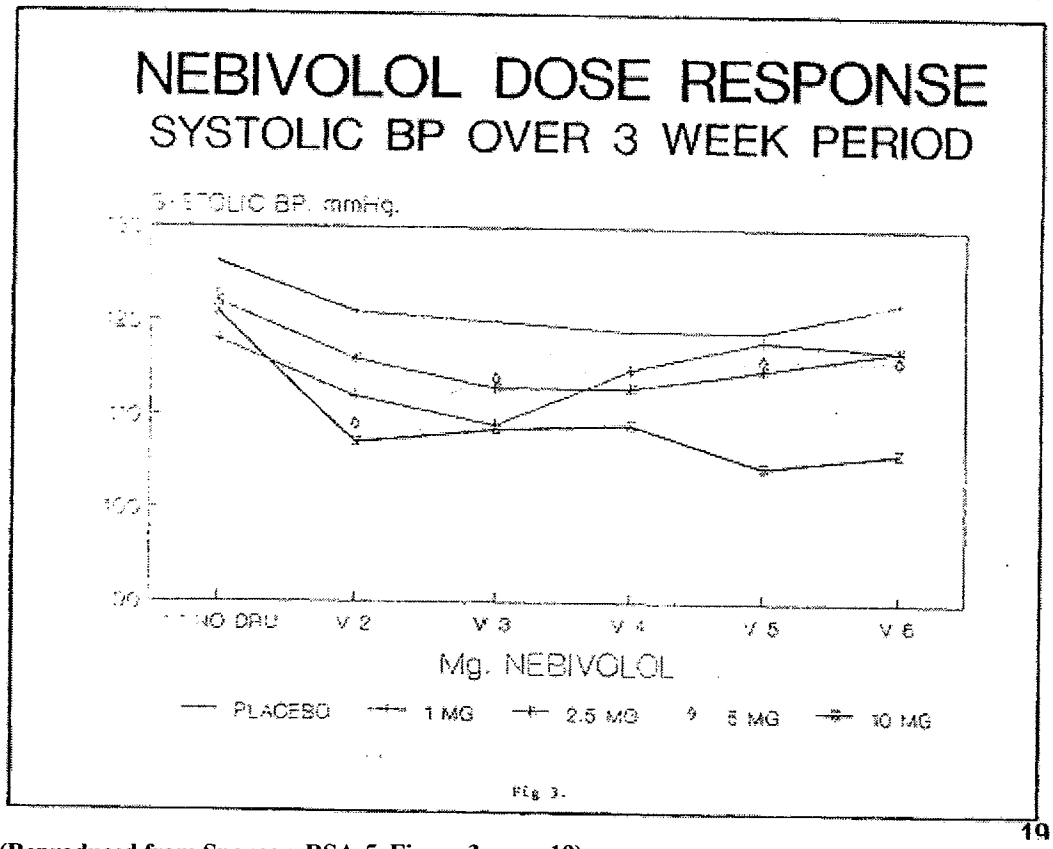

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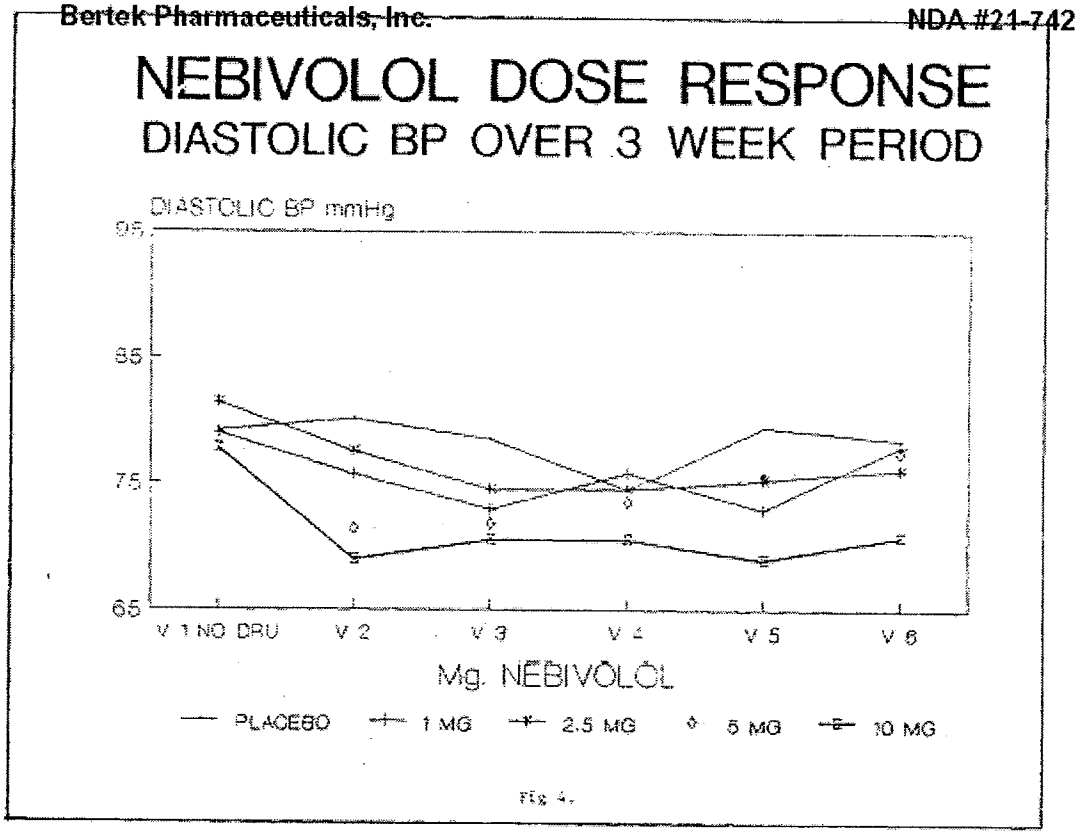
Figure 79. Nevibolol Dose Response: Diastolic BP Over 3 Week Period (RSA-5)



(Reproduced from Sponsor, RSA-5, Figure 4, page 20)

Exercise measurements:

Heart rate and BP measurements during exercise are depicted below; raw data were not submitted. According to the sponsor, SBP was significantly reduced only at the 10 mg nebivolol dose.

Table 54. Effects on HR/BP during exercise

Mean (SD)	Heart rate (bpm)	SBP (mm Hg)	DBP (mm Hg)
Placebo: pre-drug	171.7 (13.6)	190.7 (17.7)	59.5 (8)
post-drug	166.6 (13.4)	193.6 (16.8)	54.6 (4.4)
Neb 1 mg: pre-drug	165.5 (15)	185.7 (17.7)	63.6 (10.9)
post-drug	151.1 (21.65)*	177.3 (17.5)	62.1 (8.5)
Neb 2.5 mg: pre-drug	174.3 (13.2)	182.1 (25.5)	57.9 (9.71)
post-drug	153.6 (12.4)*	175.6 (28.4)	58.4 (7.9)
Neb 5 mg: pre-drug	172.5 (12.4)	184.7 (18.3)	58.2 (4.39)
post-drug	148.6 (15.1)*	175.7 (21)	54.8 (3.7)
Neb 10: pre-drug	164.8 (10.1)	185 (22.8)	62.1 (7)
post-drug	133.3 (13.7)*	168.4 (24)*	55.1 (4.2)

***= statistically significant ($p < 0.05$). The analysis does not clarify whether the statistically significant result includes the difference vs. placebo.**

According to the sponsor, there were no significant changes in ventilation or oxygen consumption. Respiratory quotient and perceived exertion "tended to increase" with the 10 mg dose but did not reach statistical significance.

No pharmacokinetic data were submitted in the study report.

Reviewer Comments:

1. This was a double-blind, placebo-controlled, parallel-group, multiple-dose study in healthy male subjects; several dose groups had a mean resting bradycardia at baseline.
2. According to the sponsor, only nebivolol 10 mg daily significantly decreased HR and BP.
3. As presented by the sponsor, a decrease in exercise-related HR increase was seen in subjects taking nebivolol 1 mg daily or more; a decrease in exercise-related SBP rise was seen only in subjects taking nebivolol 10 mg daily.
4. No significant changes were seen in perceived exertion, oxygen consumption, respiratory quotient, or ventilation.
5. No protocol or raw data were submitted; therefore, pre-specified analyses or results cannot be verified by this reviewer.

1.43 LMD No. 88216. Study ID SWE-1. ("Nebivolol—Blockade of Exercise Induced Tachycardia. Clinical Research Report NEB-SWE-1. March 1991") (Trial Period: August 7, 1988 – November 1, 1988) (Reviewer: Karen A. Hicks, M.D.)

Objectives: To evaluate beta-one blocking potency as compared to atenolol in healthy volunteers. To evaluate whether or not the ancillary properties of nebivolol reduce the subjective symptoms of exhaustion due to exercise as compared to atenolol.

Methods: This was a randomized, single blind, double dummy, four way crossover study in healthy volunteers. Ten healthy volunteers, ages 20-40, were randomized to placebo, nebivolol solution 2.5 mg, nebivolol solution 5 mg, and tenormin 50 mg. Vital signs were assessed by bicycle ergometry.

Results: Nebivolol 2.5 and 5.0 mg once daily for four days reduced exercise induced heart rate 24 hours after the last dose in a similar way to atenolol 50 mg. The perception of leg fatigue, general fatigue, and dyspnea during exercise was similar for nebivolol 2.5 mg, nebivolol 5 mg, and atenolol 50 mg.

Table 55. Main Features of the Trial Sample (SWE-1)

Baseline comparability - patient disposition (mean (SD)	n = 10
Number of patients entered (M/F)	10/0
Age: median (min-max), yrs	31.5 (2.5)
Weight (kg)	79.2 (13.3)
Length (cm)	183 (7.3)

(Reproduced from Sponsor, SWE-1, page 3)

Table 56. Efficacy Results (SWE-1)

Effectiveness (n = number of patients with data)	placebo	nebivolol 2.5 mg	nebivolol 5.0 mg	atenolol 50 mg
Primary parameters				
• Exercise test				
- Exercise time (min) mean (SEM)	19.9 (0.89)	19.7 (0.87)	19.6 (0.79)	19.3 (0.65)
- HR (b/m) at HCW mean (SEM	177 (2.9)	160 (4.2)**	166 (4.0)***	166 (4.1)*
- SBP (mmHg) at HCW mean (SEM)	189 (5.8)	178 (4.5)*	187 (7.2)	179 (5.8)*
- leg fatigue rating at HCW, median (range)	7.5 (5-10)	8 (5-10)	9 (5-10)**	8.5 (5-10)**
- general fatigue rating at HCW, median (range)	7 (5-9)	7 (4-9)	8 (4-9)	7.5 (4-9)
- dyspnoea rating at HCW, median (range)	7 (3-9)	6.5 (4-9)	7.5 (3-10)	7.5 (4-10)
Secondary parameters				
• Resting haemodynamics mean (SEM)				
- Supine HR	63.2 (2.46)	*58.5 (2.65)	58.1 (2.78)	*57.4 (2.57)
- Sitting HR	77.6 (3.29)	*69.2 (2.83)	69.2 (3.02)	69.0 (4.71)
- Supine SBP	117.0 (2.49)	115.5 (1.89)	116.5 (2.79)	112.5 (2.50)
- Sitting SBP	121.5 (3.88)	*113.9 (3.51)	118.5 (2.89)	*111.7(3.00)
- Supine DBP	72.5 (3.18)	70.0 (2.11)	72.0 (2.49)	68.0 (3.43)
- Sitting DBP	75.0 (2.11)	72.5 (2.83)	74.5 (3.4)	*71.1 (2.74)

Asterisks refer to differences with placebo
Levels of significance: * $p \leq 0.05$; **$p \leq 0.01$, ***$p \leq 0.001$
HCW = highest capacity workload.

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Figure 79. Heart Rate During Exercise (SWE-1)

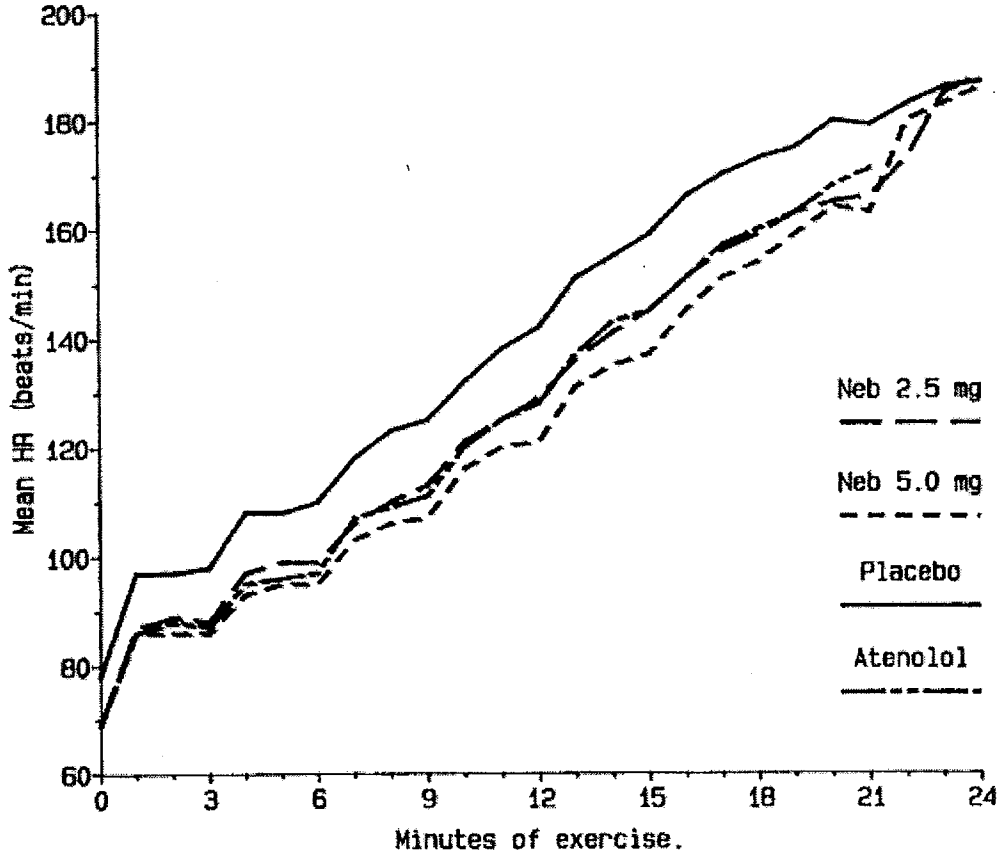

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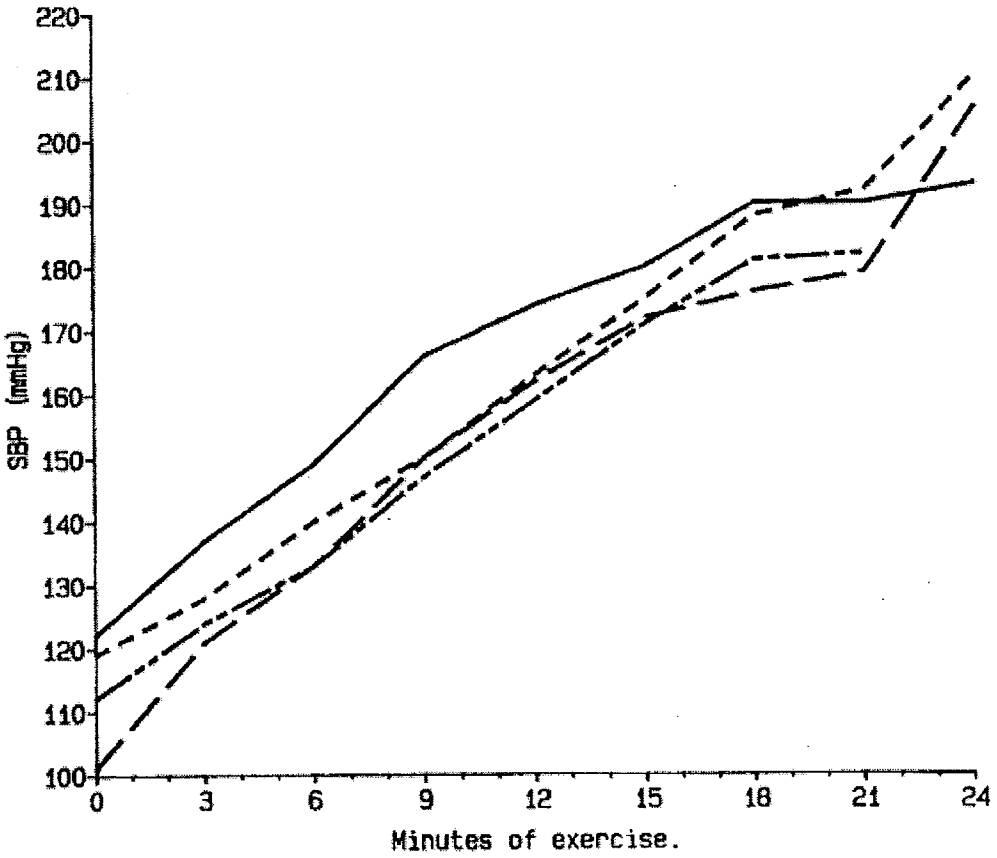
Figure 80. Systolic Blood Pressure During Exercise (SWE-1)



(Reproduced form Sponsor, SWE-1, Figure 2, page 20)

Table 57. Haemodynamic Variables at the Highest Comparable Workload (Mean and SEM) (N.B. The Highest Comparable Workload was Different for heart Rate (HR) as Compared to Systolic Blood Pressure (SBP) and Rate Pressure Product (RPP). (SWE-1)

	HR beats/min		SBP mmHg		RPP mmHg x beats/min	
Placebo	177	(2.9)	189	(5.8)	33190	(1410)
nebivolol 2.5 mg	166**	(4.0)	178*	(4.5)	29310**	(1236)
nebivolol 5.0 mg	160***,+	(4.2)	187	(7.2)	29540**	(1641)
atenolol	166*	(4.1)	179*	(5.8)	29380**	(1457)

*, **, *** = Statistically significantly different from the placebo value (Student's t-test for related samples). $p<0.05$, $p<0.01$, and $p<0.001$ respectively.

+ = Statistically significantly different from the nebivolol 2.5 mg value, $p<0.05$

(Reproduced from Sponsor, SWE-1, Table 4a, page 25)

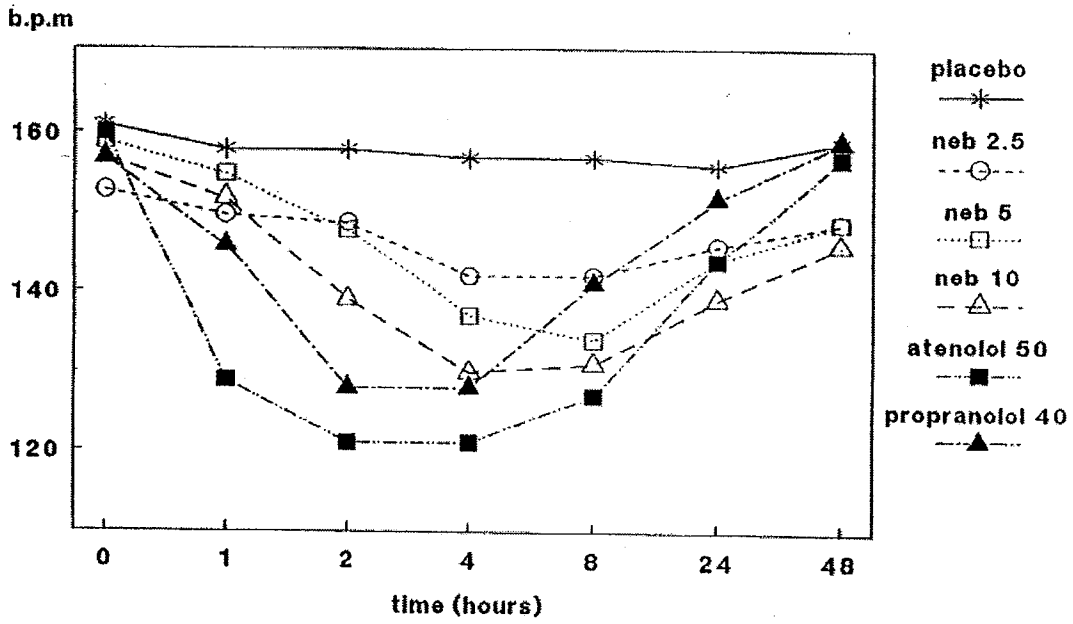
1.44 LMD No. 88260. GBR-19. ("The Effect of Nebivolol on Heart Rate, Blood Pressure, and Cardiac Output at Rest and During Exercise in Healthy Volunteers. February 1991") (Trial Period: April 1, 1988 – February 28, 1989) (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the effect of single doses of nebivolol oral solution 2.5, 5, and 10 mg, compared with placebo, atenolol 50 mg, and propranolol 40 mg on cardiac index, blood pressure, and heart rate.

Methods: This was a randomized, double dummy, six period crossover study in healthy male volunteers, ages 18 to 45. Subjects were randomized to placebo, nebivolol 2.5, 5, and 10 mg, atenolol 50 mg, and propranolol 40 mg during 6 sessions, separated by at least one week. Placebo, propranolol, and atenolol were administered in tablet form. Nebivolol was administered as an oral solution. Thirteen subjects were initially enrolled, but one patient was withdrawn at the first study session.

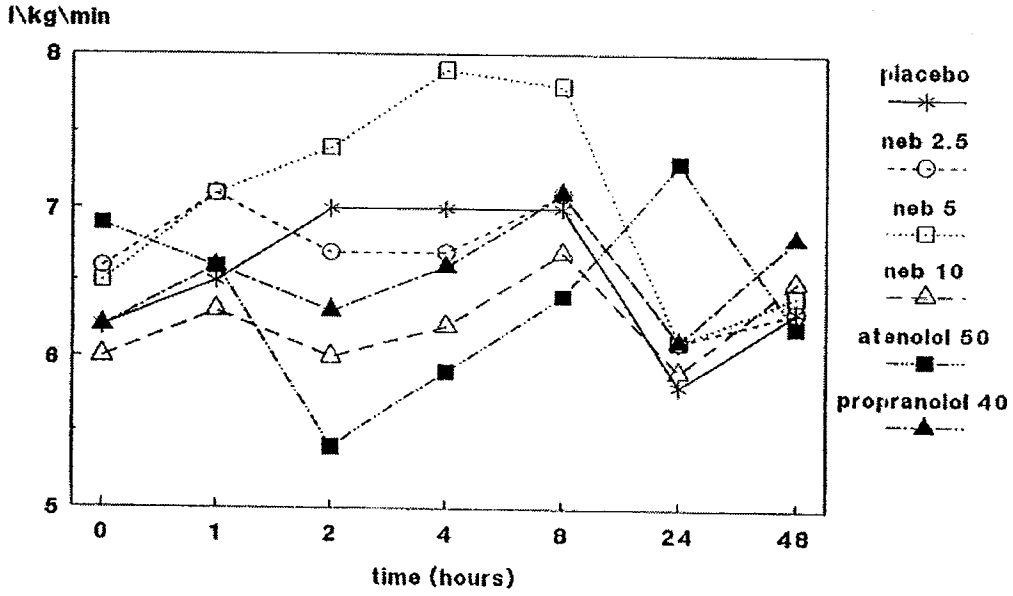
Results: All treatment groups reduced supine and standing heart rate 8 hours post-dose. The magnitude of heart rate reduction was greatest in the standing position. The maximum % inhibition of exercise heart rate was 9.6% for nebivolol solution 2.5 mg, 14.5% for nebivolol solution 5 mg, 17.4% for nebivolol solution 10 mg, 18.9% for propranolol 40 mg, and 24.2% for atenolol 50 mg. Atenolol significantly reduced exercise cardiac index, compared with placebo at 2 hours post dose, and this was significantly different from nebivolol 5 mg and propranolol 40 mg at this time. There were inconsistent effects of study treatments on resting blood pressure, cardiac output, and systolic time intervals. Nebivolol had a dose-dependent reduction in exercise heart rate, which became evident at 2 hours post dose. Nebivolol 10 mg resulted in slightly more diarrhea than the other treatment groups.

Figure 81. Exercise Heart Rate (GBR-19)



(Reproduced from Sponsor, GBR-19, Figure 2, page 9)

Figure 82. Exercise Cardiac Index (GBR-19)



* atenolol significantly different from placebo nebivolol 5mg and propranolol

(Reproduced from Sponsor, GBR-19, Figure 3, page 10)

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1.45 LMD. No. 106914. Study ID BEL-26. ("Cardiovascular and Metabolic Effect of *d*-, *l*-, and *dl*-Nebivolol. Synoptic Clinical Research Report NEB-BEL-26. September 1994") (No Protocol was submitted.) (Trial Period: March until October, 1990) (Reviewer: Shari Targum, M.D.)

Objective: To evaluate cardiovascular and metabolic effects of *d*-, *l*- and *d,l*-nebivolol during exercise testing.

Methods: This was a single-site, randomized, double-blind, placebo-controlled, crossover study with 5 treatment periods and 10 day washout periods in-between treatments. Healthy male nonsmokers, aged 25-40 years, were given either *d*-nebivolol 2.5 mg, *l*-nebivolol 2.5 mg, *d,l*-nebivolol 2.5 mg, *d,l*-nebivolol 5 mg, or matching placebo once daily for a 4 day treatment period. On the 4th day of treatment, subjects underwent a submaximal exercise test where blood pressure (BP), heart rate (HR), metabolic/hormonal variables, oxygen consumption, CO_2 production, respiratory quotient, and exercise time were measured.

Results: Fifteen males, median age 28.8 (range 25-40) years were enrolled. There were no reported adverse events and no dropouts.

No raw data was submitted. According to the sponsor, *d,l*- nebivolol (2.5 and 5 mg) and *d*-nebivolol 2.5 mg "significantly and similarly reduced exercise induced tachycardia." *l*-Nebivolol "did not influence the exercise induced tachycardia." None of the treatment groups "influenced exercise time" (no data submitted); there were said to be no differences between the groups in oxygen consumption, CO_2 production, respiratory quotient, or metabolic/hormonal variables.

Reviewer Comment:
No protocol or data were submitted. The data and basis for the sponsor's conclusions cannot be analyzed by this reviewer.

1.46 LMD No. 106917. Study ID 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") (Trial Period: March 1990 – January 1991) (Reviewer: Karen A. Hicks, M.D.)

Objective: To assess the metabolic effect of nebivolol and atenolol during dynamic exercise.

Methods: No study protocol was available for review. Sixteen healthy non-smoking volunteers between the ages of 20 and 25 years enrolled in this double-blind, crossover study. The duration of the study was 56 days. Subjects received 14 days of placebo, followed by 14 days of daily treatment with either nebivolol 5 mg or atenolol 50 mg. Subjects subsequently underwent a 14-day washout followed by 14 days of the

alternative therapy. A submaximal exercise test was performed on days 14, 28, and 56. Blood pressure, heart rate, laboratory parameters, oxygen consumption (VO_2), CO_2 production (VCO_2), respiratory quotient (RQ), and exercise time (Tmax) were determined. Results were analyzed using ANOVA and ANCOVA.

Results: A total of 16 males, median age 22 years, participated in and completed the study. There were no premature discontinuations. No raw data was available for review. According to the sponsor, nebivolol 5 mg did not affect exercise time during submaximal endurance exercise testing in healthy volunteers, compared with atenolol. Additionally, the sponsor stated the metabolic changes during prolonged exercise were similar for nebivolol, atenolol, and placebo. According to the study report, there were no major adverse events in any of the treatment groups.

Table 58. Efficacy and Safety Results (BEL-25 (a))

Therapeutic results (n = number of subjects with efficacy data)	**(n = 16)**
1) HR, SBP during exercise :	Nebivolol and atenolol significantly and similarly reduced HR and SBP during exercise as compared to placebo.
2) Exercise time :	Reduced during treatment with atenolol, not reduced with nebivolol as compared to placebo. There was no statistical significant difference between nebivolol and atenolol.
3) VO_2, VCO_2, RQ :	No differences between the groups.
4) Metabolic and hormonal variables :	There were no relevant differences between the treatment groups.

Safety (n = number of subjects with data)	n = 16
Adverse events (AE)	there were no major adverse events in any of the treatment groups

Conclusions
The results of the present trial demonstrate that:
- Nebivolol 5 mg does not affect exercise time during submaximal endurance exercise testing in healthy volunteers, this in contrast to atenolol.
- The metabolic changes during prolonged exercise are similar for nebivolol, atenolol and placebo.

(Reproduced from Sponsor, BEL-25(a), page 2)

Reviewer Comment: No protocol and no raw data were available for review. I cannot draw definitive conclusions from the information provided.

1.47 LMD. No. 106918. Study ID 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") (Trial Period: March 1990 – January 1991) (Reviewer: Karen A. Hicks, M.D.)

Objective: To assess the metabolic effects during submaximal, endurance, exercise testing.

Methods: There was no protocol available for review. This was a double-blind, crossover study in male non-smokers between the ages of 30 and 55 years who had borderline hypertension (SBP > 140 and < or = 160 mm Hg and/or abnormally quick rise of BP during exercise (Heck criteria)). The study duration was 56 days. Subjects received 14 days of placebo followed by 14 days of daily nebivolol 5 mg or atenolol 50 mg. Subjects then underwent a 14 day wash-out followed by 14 days of the alternative treatment. Subjects underwent submaximal exercise tests on days 14, 28, and 56. Blood pressure, heart rate, laboratory parameters, oxygen consumption (VO_2), CO2 production (VCO_2), respiratory quotient (RQ), and exercise time were evaluated. Results were analyzed using ANOVA and ANCOVA.

Results: A total of 16 men, median age 43.7 years, participated in and completed the study. There were no premature discontinuations. No raw data was provided for analysis. According to the sponsor, nebivolol 5 mg and atenolol 50 mg did not affect exercise time during submaximal endurance testing in patients with borderline hypertension. The sponsor also stated metabolic changes during prolonged exercise were similar for nebivolol, atenolol, and placebo. According to the study report, there were no major adverse events in any of the treatment groups.

Reviewer Comment: No protocol and no raw data were available for review. I cannot draw definitive conclusions from the information provided.

1.48 LMD. No. 108077. Study ID 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") (Trial Period: September 1988 – December 1989) (Reviewer: Karen A. Hicks, M.D.)

Objectives:

1. "To explore if nebivolol interfered less with energy supply during submaximal exercise than an approximately equipotent dose of atenolol.
2. To evaluate any effects on renal function: after a first dose of the drugs and placebo, effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured."

Methods: This was a double-blind, randomized, cross-over, placebo-controlled trial in healthy male volunteers, ages 20 to 25. The total study duration was 18 days. Patients underwent two four-day periods of daily single doses of placebo, nebivolol 2.5 mg, nebivolol 5 mg, or atenolol 50 mg orally, with a ten-day washout between each study period. Renal blood flow was measured on day 1 during both periods. A submaximal stress test and laboratory evaluation was performed on day 4 during both periods. Investigators analyzed results using MANOVA and Student t- test.

Results: 18 male subjects, ages 20 to 25, were enrolled in this study. There were no discontinuations. Six subjects each were enrolled in nebivolol 2.5 mg, nebivolol 5 mg, and atenolol 50 mg treatment groups. There were no significant adverse events. The study results were as follows:

Table 59. Study Results (BEL-16)

	mean decrease compared with placebo		
HR during exercise, bpm	18.6***	26.2***	21.6***
SBP during exercise,mmHg	NS	19.9**	9.6**
renal bloodflow	NS	NS	NS
ERPF	NS	NS	NS
GFR	NS	NS	NS
	Levels of significance: **p ≤ 0.01, *** p ≤ 0.001		
Secondary parameters	compared to placebo		
plasma glucose	increased at rest and during exercise after nebivolol 2.5 mg increased at rest, unchanged during exercise after nebivolol 5 mg unchanged at rest, decreased during exercise after atenolol 50 mg		
lactic acid	higher after atenolol 50 mg lower after nebivolol 2.5 and 5 mg		
plasma free fatty acid	atenolol 50 but not nebivolol (2.5 and 5 mg) impaired the normal exercise - induced increase		

(Reproduced from Sponsor, BEL-16, page 2)

The investigators concluded nebivolol did not have a significant effect on renal blood flow, ERPF, or GFR after a single dose of study drug. The investigators stated there was a statistically significant degree of beta-blockade for nebivolol and atenolol, when compared with placebo. Although the investigators did not provide evidence of this finding, they stated "with nebivolol, effective beta-blockade [did] not interfere with normal energy supply during exercise. After atenolol, but not after nebivolol, lipolysis in adipose tissue and thus availability of free fatty acids (FFA) as an energy source for working muscles [was] diminished."

Reviewer Comment: No protocol was submitted and limited data was provided. The data and basis for the sponsor's conclusions cannot be analyzed by this reviewer.

1.49 LMD No. 92970. Study ID 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") (Trial Period: November 22, 1989 – June 3, 1991) (Reviewer: Karen A. Hicks, M.D.)

Objective: The primary objective was to compare the effect of nebivolol on exercise endurance (tiredness and time of exercise) with that of atenolol and placebo. The secondary objective was to compare the antihypertensive effect of nebivolol with that of atenolol and placebo.

Methods: This was a phase II placebo-controlled, double-blind crossover study. A total of 48 male and female patients, ages 20 to 70, with uncomplicated hypertension were enrolled, and 47 patients were randomized to one of three double-blind treatment sequences following a four-week single blind placebo run-in period. Uncomplicated hypertension was defined as a diastolic blood pressure $\geq$ 95 mm Hg and $\leq$ 115 mm Hg and systolic blood pressure $\geq$ 160 mm Hg and $\leq$ 220 mm Hg. There was a three-week wash-out period between each double-blind treatment period. Patients received nebivolol 5 mg, atenolol 50 mg, or placebo. Although nebivolol was never administered following atenolol, in two out of three sequences, atenolol was administered following nebivolol. As such, a complete analysis of carry-over effects could not be performed. Efficacy assessments included bicycle exercise tests, blood pressure, symptom assessments, and Questionnaire Visual Analogue Scale. Safety assessments included body weight, adverse event monitoring, ECG, physical examination, and laboratory evaluation. The investigators used the intent-to-treat population for evaluation as well as an analysis of variance, Cochran Q-test, and McNemar test for statistical analysis.

Results: A total of 47 patients (30 men and 17 women), with a median age of 51.0, received double-blind treatment. Compliance was greater than 80% in all treatment groups.

Four out of the 47 patients dropped out of the trial. Two of these patients dropped out at the end of the wash-out period, one patient dropped out before nebivolol initiation, and one patient dropped out before atenolol and placebo treatment. In the nebivolol and atenolol treatment groups, 44% and 38% of patients, respectively, experienced adverse events. Headache, dyspepsia, and fatigue were the most common adverse events in the nebivolol treatment group.

Table 60. Safety Results (INT-2)

Safety	nebivolol 5 mg	atenolol 50 mg	placebo
Body weight	Virtually no changes		
Heart rate, bpm mean supine standing	66.0*** 70.1***	61.0*** 65.7***	78.1 85.9
Adverse events (AE) during treatment only : discrete AE or AE classes in ≥ 5 % of patients with any treatment			
- musculo-skeletal system disorders	3	1	3
- central/peripheral nervous system disorders	7	8	12
(headache/paraesthesia/vertigo)	(6/1/1)	(4/1/2)	(6/3/5)
- psychiatric disorders	2	3	2
(insomnia)	(1)	(3)	(2)
- gastro-intestinal system disorders	3		1
- respiratory system disorders	1	3	2
- general disorders	6	8	7
(fatigue)	(4)	(7)	(5)
Total No. of patients assessed	45	45	46
No. (%) of patients with one or more AE	20 (44.4%)	17 (37.8%)	17 (37.0%)
No. (%) of drop-outs because of AE	1 (2%) in wash-out period after placebo 2 (4%) in atenolol period 1 (2%) in wash-out period after nebivolol		
Electrocardiogram : normal at baseline, abnormal at end point	3	3	1
Physical examination : general condition : % of patients with a rating "good" at end point last double-blind treatment period	93	100	93
Laboratory parameters	No clinically important changes		

(Reproduced from Sponsor, INT-2, page 10)

A responder experienced a decrease in supine diastolic blood pressure to below 90 mm Hg (normalized responder) or a decrease in diastolic blood pressure versus baseline of at least 10 mm Hg, absolute DBP values being still above 90 mm Hg (non-normalized responder).

Table 61. Response Rate (INT-2)

Group	N	No. of responders at end point		% response	Comparison of treatment effects: p-values		
					Overall comparison between 3 treatments (Cochran Q-test)	Two-by-two comparison between treatments (Mc Nemar test)	
		Normalized (supine DBP ≤ 90 mmHg)	Non-normalized (shift *vs* baseline ≥ 10 mmHg)			*vs* placebo	*vs* atenolol
nebivolol	45	22	4	58		< 0.001	0.095
atenolol	44	31	3	77	< 0.001	< 0.001	-
placebo	46	9	1	22		-	

(Reproduced from Sponsor, INT-2, Display 14, page 45)

In the nebivolol, atenolol, and placebo treatment groups, the exercise-induced increase in heart rate was 49.9 beats per minute (bpm), 45.4 bpm, and 57.7 bpm, respectively, which was statistically significant between nebivolol and atenolol ($p = 0.032$) and between nebivolol and atenolol treatment groups and placebo ($p < 0.001$).

The exercise-induced increase in systolic blood pressure was 44.7 mm Hg, 33.1 mm Hg, and 48.5 mm Hg for the nebivolol, atenolol, and placebo treatment groups, respectively. Atenolol significantly reduced the exercise-induced increase in systolic blood pressure compared with nebivolol ($p = 0.004$) and placebo ($p < 0.001$). Nebivolol was not statistically significantly different than placebo ($p = 0.087$) in this parameter.

Nebivolol, atenolol, and placebo decreased supine diastolic blood pressure from 99.7 mm Hg to 92.5 mm Hg, to 88.3 mm Hg, and to 97.9 mm Hg, respectively. Nebivolol was significantly different from atenolol ($p = 0.003$) in this parameter. Additionally, both nebivolol and atenolol were significantly different than placebo ($p < 0.001$) in reducing supine diastolic blood pressure. There were similar findings for standing diastolic blood pressure as well as supine and standing systolic blood pressure and mean arterial pressure.

Symptom changes and Quality of Life scores were not substantially different between treatment groups.

Nebivolol and atenolol significantly decreased supine and standing heart rate, compared to placebo ($p < 0.001$). At the endpoint, atenolol had significantly lower supine and standing heart rates (61.0 and 65.7 bpm, respectively), compared with nebivolol (66.0 bpm and 71.0 bpm, respectively) ($p \leq 0.001$).

Table 62. Clinical Findings/Efficacy Results (INT-2)

Clinical findings	Run-in	Double-blind treatment		
(n = number of patients with efficacy data at end point)	all patients (n = 47)	nebivolol 5 mg (n = 45)	atenolol 50 mg (n = 44)	placebo (n = 46)
• Primary efficacy parameters				
- bicycle exercise test : mean at start of exercise/at target work load (mean change)				
. heart rate, bpm		69.6***/ 119.5*** (49.9)***	66.1***/ 111.5*** (45.4)***	64.4/142.1 (57.7)
. systolic blood pressure, mmHg		141.6***/ 186.3** (44.7)◊	137.6***/ 170.9*** (33.1)***	156.1/204.6 (48.5)
- diastolic blood pressure, mmHg : mean at end point				
supine	99.7	92.5***	88.3***	97.9
• Other blood pressure parameters, mmHg : mean at end point				
- diastolic blood pressure				
standing	102.6	93.8***	90.8***	100.3
- systolic blood pressure				
supine	160.9	148.5***	142.8***	158.2
standing	160.1	142.6***	137.1***	152.3
- mean arterial pressure				
supine	120.3	111.3***	106.5***	118.0
standing	121.8	110.1***	106.3***	117.6
• Response at end point, % (supine DBP decreased to ≤ 90 mmHg or by ≥ 10 mmHg)		58***	77***	22
• Symptom assessments mean total score of all symptoms at end point		46.6	48.1	48.7

Asterisks refer to differences with placebo. Significant differences between nebivolol and atenolol for bicycle exercise test : shift in heart rate from target work load to start of exercise ($p = 0.032$) and shift in systolic blood pressure from target work load to start of exercise ($p = 0.004$), diastolic blood pressure (supine : $p = 0.003$; standing : $p = 0.021$), systolic blood pressure (supine : $p = 0.016$; standing : $p = 0.013$) mean arterial pressure (supine : $p = 0.002$; standing : $p = 0.006$), heart rate (supine : $p < 0.001$; standing : $p = 0.001$), and response ($p = 0.095$).
Levels of significance: ◊ $p \leq 0.1$; * $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$

(Reproduced from Sponsor, INT-2, page 9)

According to the investigators, nebivolol had less beta blockade effect than atenolol, and nebivolol and atenolol both significantly reduced blood pressure, compared with placebo. Both nebivolol and atenolol appeared to be tolerable. (The study was performed initially because nebivolol was thought to decrease total peripheral vascular resistance and

possibly have a less negative inotropic effect than other beta blockers at a similar degree of beta blockade, as determined by systolic flow intervals.)

Conclusions: Nebivolol (5 mg daily) resulted in less beta blockade than atenolol. Both nebivolol and atenolol significantly reduced blood pressure, compared with placebo. The tolerability of nebivolol and atenolol appeared to be comparable.

1.50 LMD No. 107426. Study ID GBR-4. ("A Comparison of the Haemodynamics of Nebivolol and Atenolol in Hypertensive Patients. Clinical Research Report NEB-GBR-4. December 1993") (Trial Period: November 1989 – November 1991) (Reviewer: Karen A. Hicks, M.D.)

Objective: To compare the hemodynamic effects of nebivolol 5 mg and atenolol 50 mg at rest and during exercise.

Methods: This was a randomized, double-blind, phase II, cross-over study to compare the hemodynamic effects of oral nebivolol 5 mg and atenolol 50 mg. Hypertensive patients, ages 35 to 65, entered a 4-week run-in period (Phase A), followed by a 4 week period of once daily oral therapy (Phase B) with either nebivolol 5 mg or atenolol 50 mg. Following a four-week wash-out period (Phase C), patients crossed over to the alternative treatment for an additional four weeks (Phase D) of once daily therapy. The total study duration was 16 weeks, and there were 6 clinic visits during the course of the study. Blood pressure, heart rate, and cardiac output were measured at rest and during or immediately following a 70% submaximal exercise test. The primary efficacy endpoint was the change in exercise heart rate from baseline.

Results: Although 12 patients entered the study, only 10 received active treatment. One patient was discontinued due to significant hypertension, and the other patient was discontinued due to an intercurrent illness. Five patients experienced adverse events through the course of the study.

Table 63. Adverse Events (GBR-4)

Patient No	Event (Preferred term)	Severity	Relationship to Study Drug	Study Treatment
3	Infection, skin	Mild	None	Atenolol
7	Slowing down	NK	NK	Atenolol
	Ankle/finger swelling	Mild	NK	Atenolol
10	Lethargy	Moderate	Possible	Atenolol
	Insomnia	Moderate	Possible	Atenolol
	Paraesthesia	Mild	None	All*
	Palpitations	Moderate	None	Placebo
11	Bladder papilloma	NK	None	Atenolol
12	Dizziness	Severe	Possible	Atenolol
	Slurred speech	Severe	Possible	Atenolol
	Headache	Mild	Possible	Nebivolol
	Allergy	Mild	Possible	Nebivolol
	Palpitations	Mild	Possible	Nebivolol
	Dizziness	Moderate	Possible	Placebo
	Slurred speech	Moderate	Possible	Placebo

NK = Not Known
*All = Adverse event was present in all three phases (placebo, Atenolol & Nebivolol) of the study.

(Reproduced from Sponsor, GBR-4, Table 7, page 27)

Table 64. Safety Results (GBR-4)

Safety	Nebivolol	Atenolol	Placebo
• Adverse events (AE), n: Infection, skin		1	
Slowing down		1	
Ankle/finger swelling		1	
Lethargy		1	
Insomnia		1	
Paraesthesia	1	1	1
Palpitations	1		1
Bladder papilloma		1	
Dizziness		1	1
Slurred speech		1	1
Headache	1		
Allergy	1		
No. of patients with one or more AEs	2	5	2
• Clinical laboratory tests	There were no clinically significant changes with either drug		

(Reproduced from Sponsor, GBR-4, page 4)

Both nebivolol and atenolol decreased exercise heart rate and resting blood pressure and heart rate. There were no statistically significant differences in resting and exercise hemodynamics between nebivolol and atenolol.

Table 65. Efficacy Results (GBR-4)

Effectiveness (means) (n = number of patients with effectiveness data)	Nebivolol (n = 10)	Atenolol (n = 10)
Exercise Blood Pressure: Systolic/Diastolic, mmHg	159.1/100.4	152.9/99.9
- during exercise, mean difference from baseline: Heart rate, bpm	-18.1	-22.1
Cardiac output	-0.6	0.4
- at rest, mean difference from baseline: systolic blood pressure, mmHg	-9.3	-10.6
diastolic blood pressure, mmHg	-6.8	-7.8
Heart rate, bpm	-14.6	-5.4
Body weight, kg	0.4	-0.6

(Reproduced from Sponsor, GBR-4, page 3)

1.51 LMD No. 59898. Study ID N/A. ("Haemodynamic Effects of Subacute Treatment with Nebivolol: A Comparison Between Poor and Normal Metabolizers. February 1988") (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the hemodynamic effects of nebivolol 5 mg and 10 mg in poor and extensive metabolizers, compared with control.

Methods: Fourteen normal (13 male, 1 female) and 7 poor (5 male, 2 female) metabolizers participated in this study. The median age of the extensive metabolizer group was 32.5 years, with a range between 25 and 49 years. The median age of the poor metabolizer group was 28 years, with a range between 27 and 35. Six normal metabolizers received nebivolol 5 mg daily for 7 days, and 8 normal metabolizers received nebivolol 5 mg daily for 14 days. Four poor metabolizers received nebivolol 5 mg daily for 7 days, and 3 poor metabolizers received this dosage for 14 days. Three poor metabolizers received nebivolol 10 mg daily, with 2 subjects receiving 7 days and 1 subject receiving 14 days of therapy. Nine minute modified Bruce treadmill tests were performed 6 hours after dosing on Day 7 or Day 14, as well as at baseline. Blood pressure and heart rate were monitored at rest and during exercise.

Investigators measured systolic time intervals using a peripheral lead of the ECG, phonocardiogram, and carotid pulse wave.

Investigators used the Wilcoxon matched-pairs signed-ranks test and two-tailed probability for statistical analysis.

Results: Fourteen normal and 7 poor metabolizers received oral nebivolol 5 or 10 mg daily for 1 or 2 weeks. Subjects performed a treadmill exercise test at baseline and 6

hours following the intake of the final dose of study drug. Nebivolol significantly inhibited exercise-induced increases in heart rate and systolic blood pressure, but this inhibition was comparable between the extensive and poor metabolizers.

Table 66. Mean Heart Rate and Systolic Blood Pressure Before, During, and After Exercise Testing on a Control Day and Day 7 or 14 of a Subacute Treatment Period with Nebivolol 5 or 10 mg/day in 14 Normal and 7 Poor Metabolizers

		Normal metabolizers (n=14)			Poor metabolizers (n=7		
		Control	Nebivolol		Control	Nebivolol	
		Mean±SEM	Mean±SEM	p*	Mean±SEM	Mean±SEM	p
Heart rate (b/min)	Pre exercise	74±2.1	64±2.6	0.0006	83±3.4	62±2.9	0.02
	3' during ex.	106±2.4	92±2.6	0.0002	109±2.2	94±3.0	0.02
	6'	128±3.9	108±3.3	0.0002	137±2.9	115±3.7	0.02
	9'	154±4.8	129±3.6	0.0002	162±2.1	136±4.4	0.02
	1' post ex.	114±4.7	92±4.6	0.0002	116±3.1	99±3.2	0.02
	3'	90±4.0	78±3.5	0.0007	97±3.0	85±4.3	n.s.
	6'	86±3.1	74±3.2	0.002	93±3.1	78±4.1	0.02
Systolic blood pressure (mmHg)	Pre exercise	117±2.6	108±2.8	0.004	114±1.8	111±3.3	n.s.
	3' during ex.	130±5.0	110±3.4	0.0002	129±4.7	115±5.1	0.03
	6'	148±5.0	122±4.3	0.0002	144±3.9	129±7.1	n.s.
	9'	169±4.9	141±5.1	0.0002	166±3.7	149±7.0	0.04
	1' post ex.	164±5.9	140±5.1	0.0002	168±5.7	148±6.9	0.02
	3'	133±2.6	119±3.0	0.0002	134±4.6	122±2.0	0.03
	6'	119±2.0	109±2.6	0.005	118±2.6	113±2.6	n.s.

* 2-tailed probability by Wilcoxon matched-pairs signed-ranks test versu control values (n.s. = not significant).

(Reproduced from Sponsor, Table 1, page 5)

There was no significant difference in resting or post exercise systolic time intervals in extensive or poor metabolizers.

After exercise, left ventricular ejection time, also known as $LVET_c$, decreased in both the placebo (control) and nebivolol treatment groups, but nebivolol significantly decreased the shortening of the $LVET_c$ in both poor and extensive metabolizers, as seen in Figure 83.

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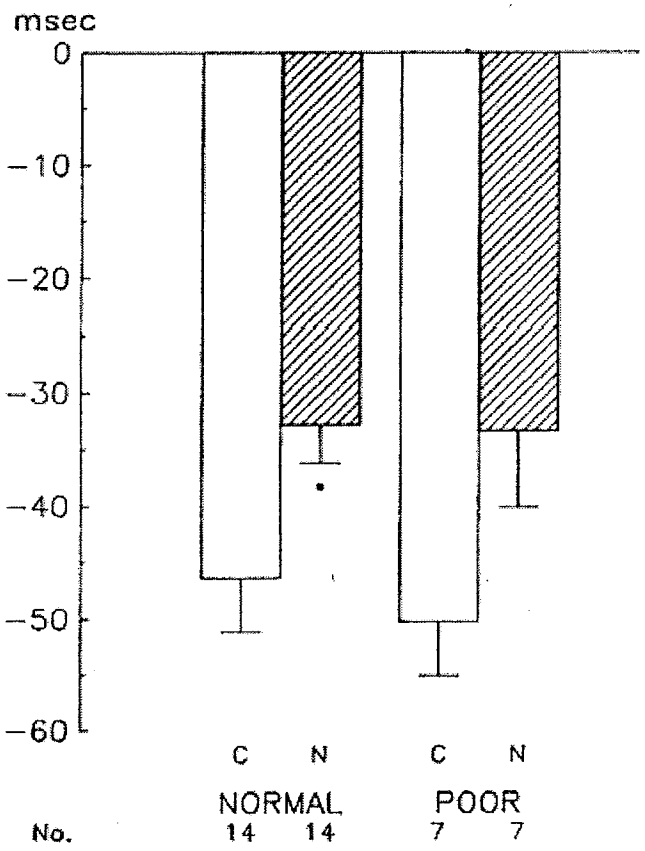
Figure 83. Mean Values of $LVET_c$ Post-Pre Exercise on a Control Day (C) and on Day 7 or 14 of a Subacute Treatment Period with Nebivolol 5 or 10 mg/day (N) in 14 Normal and 7 Poor Metabolizers



*p≤0.05 2-tailed probability versus control day by Wilcoxon matched-pairs signed-ranks test

(Reproduced from Sponsor, Figure 3, page 8)

The ratio of the preejection period/left ventricular ejection time, also known as $PEP_c/LVET_c$, measured systolic performance and decreased significantly in both poor and extensive metabolizers.

Conclusions: Nebivolol inhibited the increase in heart rate and systolic blood pressure during treadmill exercise testing in both poor and extensive metabolizers. There were no significant differences in systolic time intervals between poor and normal metabolizers at rest or after exercise.

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1.52 LMD No. 62826. Study ID 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") (Report Date August 1988) (Trial Period: November 18, 1987 to February 11, 1998) (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the hemodynamic effects of nebivolol at rest and post exercise in poor and extensive metabolizers.

Methods: Twelve healthy male subjects, ages 18 to 65 years of age (median age 34.5 years), participated in this trial. Of these twelve subjects, 6 subjects were poor metabolizers and 6 subjects were extensive metabolizers. For 8 consecutive days and at the same time each day, all study subjects received nebivolol 5 mg suspension. Investigators measured systolic time intervals at rest, blood pressure, and heart rate on a control day and on days 1, 2, 3, 5, and 8 of nebivolol therapy as well as on days 1, 2, 3, 4, 7, and 10 after discontinuation of nebivolol. Investigators performed 9 minute modified Bruce exercise tests and obtained the above measurements 6 hours after study drug administration on a control day and on days 1, 3, 5, and 8 during nebivolol therapy. Exercise tests and the measurements were also performed on days 1, 2, 4, 7, and 10 after nebivolol was discontinued.

Results: One minute after completion of exercise, nebivolol significantly decreased increases in heart rate and systolic blood pressure in both poor and extensive metabolizers. The heart rate effect carried over from day 1 of therapy in the normal metabolizers until two days post discontinuation of nebivolol in the poor metabolizers. There was no carry over effect in blood pressure reduction.

Table 67. Exercise-Induced Increase of Heart Rate Before, During, and After Discontinuation of An 8-Day Treatment with Nebivolol in 6 Poor and 6 Normal Metabolizers (BEL-4/Part I)

	Pre exercise	During exercise			Post exercise		
		3 min	6 min	9 min	1 min	3 min	6 min
	Mean±SEM p	Mean±SEM p	Mean±SEM p	Mean±SEM p	Mean±SEM p	Mean±SEM p	Mean±SEM p
Normal metabolizers							
Day 0	67±4.6 --	107±3.4 --	125±4.6 --	149±7.1 --	94±5.2 --	78±3.9 --	80±4.5 --
1	53±2.2 0.03	87±2.0 0.03	102±2.7 0.03	124±4.1 0.03	79±4.2 0.03	65±3.0 n.s.	62±2.6 0.03
3	55±2.6 0.03	88±1.6 0.03	104±2.3 0.03	121±2.5 0.03	75±2.3 0.03	65±3.1 0.03	65±2.9 0.03
5	56±2.7 n.s.	89±0.8 0.03	104±1.3 0.03	123±3.7 0.03	76±3.6 0.03	67±1.9 n.s.	66±2.0 0.03
8	54±3.1 0.03	87±1.0 0.03	102±1.4 0.03	122±3.1 0.03	76±2.7 0.03	67±3.7 n.s.	66±2.1 0.03
Day 1 post	62±2.5 n.s.	93±2.2 n.s.	109±3.4 0.03	130±4.3 0.03	76±3.2 0.03	70±3.1 n.s.	68±3.0 0.03
2	61±3.7 n.s.	92±3.1 0.03	110±2.9 n.s.	133±4.0 0.03	83±3.2 n.s.	69±4.6 n.s.	69±5.7 0.03
4	65±5.2 n.s.	98±3.0 0.03	115±4.2 n.s.	138±4.6 n.s.	87±6.8 n.s.	76±6.1 n.s.	73±5.9 0.03
7	64±2.5 n.s.	95±4.4 0.03	112±4.2 0.03	135±5.7 n.s.	84±4.4 n.s.	71±5.5 n.s.	74±4.3 0.03
10	62±4.9 n.s.	94±3.3 n.s.	113±3.3 n.s.	136±6.4 0.03	86±5.5 n.s.	77±6.2 n.s.	76±6.6 n.s.
Poor metabolizers							
Day 0	62±2.2 --	103±4.5 --	121±5.5 --	143±8.4 --	89±7.2 --	77±6.8 --	79±6.2 --
1	54±2.1 n.s.	92±3.8 n.s.	104±3.0 0.03	123±5.7 0.03	79±5.0 0.03	72±4.9 n.s.	70±4.8 n.s.
3	64±3.4 n.s.	92±4.1 0.03	106±4.5 0.03	121±6.8 0.03	77±6.4 0.03	67±5.5 n.s.	66±5.3 0.03
5	60±3.9 n.s.	89±3.9 0.03	106±3.9 0.03	122±4.5 0.03	79±5.3 0.03	68±5.0 n.s.	66±4.7 0.03
8	60±3.8 n.s.	88±4.1 0.03	104±4.1 0.03	120±5.9 0.03	76±5.4 0.03	65±4.4 n.s.	63±3.8 0.03
Day 1 post	60±5.2 n.s.	92±5.3 0.03	111±7.1 n.s.	127±8.5 n.s.	78±8.7 n.s.	67±7.0 0.03	69±5.4 0.03
2	62±2.0 n.s.	93±4.6 0.03	109±5.0 n.s.	128±6.6 0.03	77±6.8 0.03	67±5.0 n.s.	67±5.9 0.03
4	65±3.2 n.s.	97±3.4 n.s.	114±6.6 n.s.	137±6.5 n.s.	88±7.1 n.s.	73±6.1 n.s.	75±3.6 n.s.
7	70±4.0 n.s.	97±3.2 n.s.	116±5.4 n.s.	137±6.6 n.s.	86±7.4 n.s.	75±5.0 n.s.	71±5.5 n.s.
10	69±4.4 n.s.	99±4.5 n.s.	117±5.7 n.s.	139±7.4 n.s.	91±6.2 n.s.	80±6.5 n.s.	75±5.4 n.s.
Total group							
Day 0	65±2.5 --	105±2.7 --	123±3.4 --	146±5.3 --	92±4.3 --	77±3.7 --	79±3.6 --
1	53±1.5 0.001	89±2.2 0.001	103±1.9 0.0004	123±3.4 0.0004	79±3.1 0.0004	69±2.9 0.02	66±2.9 0.001
3	59±2.5 n.s.	90±2.2 0.0004	105±2.4 0.0004	121±3.5 0.0004	76±3.3 0.0004	66±3.0 0.001	65±2.9 0.0004
5	58±2.4 0.04	89±1.9 0.0004	105±2.0 0.0004	122±2.8 0.0004	78±3.1 0.0004	68±2.6 0.002	66±2.5 0.0004
8	57±2.5 0.01	87±2.0 0.0004	103±2.1 0.0004	121±3.2 0.0004	76±2.9 0.0004	66±2.8 0.01	65±2.1 0.0004
Day 1 post	61±2.8 n.s.	92±2.7 0.001	110±3.8 0.001	128±4.6 0.001	77±4.4 0.003	69±3.7 0.01	68±3.0 0.0004
2	61±2.0 n.s.	93±2.6 0.0004	109±2.8 0.002	131±3.8 0.0004	80±3.7 0.001	68±3.3 0.006	68±3.9 0.0004
4	65±2.9 n.s.	97±2.2 0.004	114±3.7 0.03	137±3.8 n.s.	88±4.7 n.s.	74±4.1 n.s.	74±3.3 0.03
7	67±2.4 n.s.	96±2.6 0.002	114±3.3 0.007	136±4.2 0.005	85±4.1 0.05	73±3.6 n.s.	72±3.3 0.01
10	66±3.3 n.s.	97±2.7 0.02	115±3.2 0.01	137±4.7 0.02	89±4.0 n.s.	79±4.3 n.s.	76±4.1 n.s.

p-value : Wilcoxon m.p.s.r. test, 2-tailed probability versus Day 0-values.

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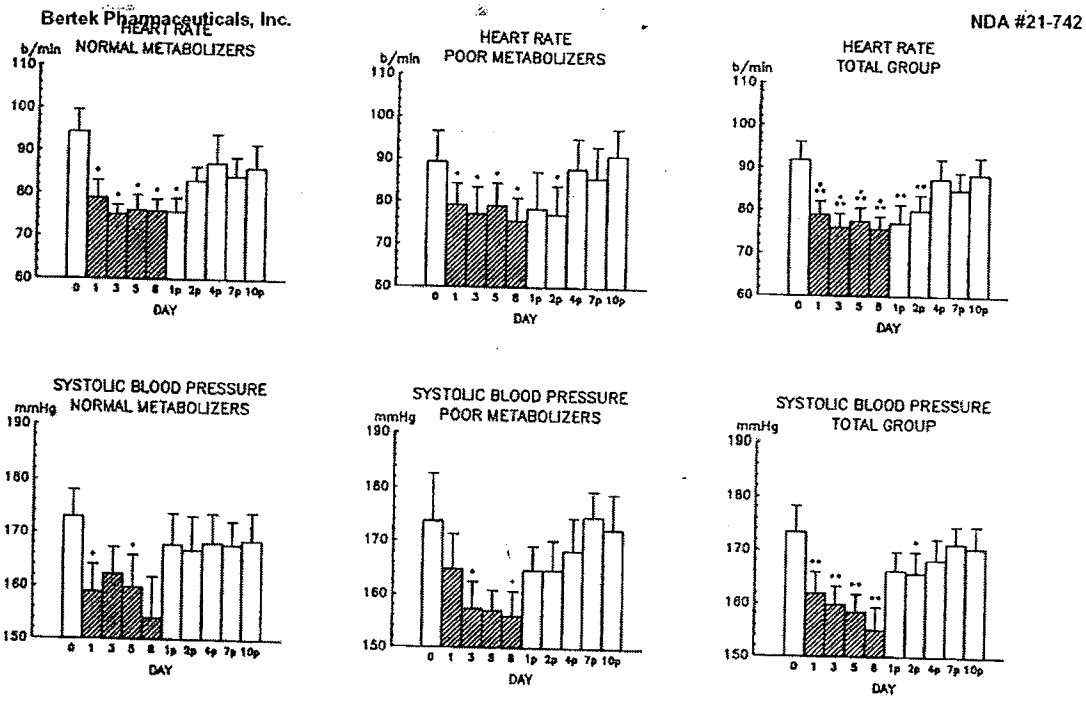
Table 68. Exercise-Induced Increase of Systolic Blood Pressure, Before, During, and After Discontinuation of An 8-Day Treatment with Nebivolol in 6 Poor and 6 Normal Metabolizers (BEL-4/Part I)

	Pre exercise	During exercise			Post exercise		
		3 min	6 min	9 min	1 min	3 min	6 min
	Mean±SEM p	Mean±SEM p	Mean±SEM p	Mean±SEM p	Mean±SEM p	Mean±SEM p	Mean±SEM p
Normal metabolizers							
Day 0	146±3.8 --	153±4.6 --	165±6.3 --	180±6.2 --	173±5.1 --	157±5.7 --	151±4.3 --
1	136±5.5 n.s.	143±5.4 n.s.	149±4.2 n.s.	171±8.6 n.s.	159±5.1 0.03	147±5.8 n.s.	139±4.1 0.03
3	133±6.0 n.s.	134±4.5 0.03	143±5.6 0.03	165±8.0 0.03	162±5.0 n.s.	146±4.8 0.03	142±3.3 0.03
5	134±5.1 0.03	133±4.4 0.03	143±6.1 0.03	168±7.3 n.s.	160±6.0 0.03	146±5.0 n.s.	138±5.7 n.s.
8	137±6.0 n.s.	131±3.7 0.03	146±7.6 0.03	163±9.2 n.s.	154±7.8 n.s.	139±5.8 0.03	135±5.8 0.03
Day 1 post	134±4.7 0.03	137±2.5 0.03	155±7.5 n.s.	173±8.5 n.s.	168±5.8 n.s.	150±4.8 n.s.	146±4.8 n.s.
2	131±4.9 0.03	138±4.0 0.03	153±7.5 0.03	174±8.8 n.s.	167±6.3 n.s.	146±5.9 n.s.	139±3.6 0.03
4	135±4.8 n.s.	142±4.6 n.s.	152±5.6 n.s.	172±5.9 n.s.	168±5.5 n.s.	150±5.2 0.03	145±3.9 n.s.
7	141±5.4 n.s.	143±6.1 n.s.	147±4.9 0.03	173±6.7 n.s.	168±4.4 n.s.	149±5.4 n.s.	145±4.0 n.s.
10	143±4.8 n.s.	138±5.4 0.03	150±4.5 n.s.	170±9.0 n.s.	169±5.2 n.s.	149±3.7 0.03	146±4.9 n.s.
Poor metabolizers							
Day 0	140±3.3 --	147±4.0 --	160±4.7 --	179±5.5 --	174±9.0 --	153±6.6 --	146±7.2 --
1	133±6.6 n.s.	138±6.6 n.s.	143±4.8 0.03	155±5.0 0.03	165±6.5 n.s.	149±5.3 n.s.	147±6.0 n.s.
3	133±5.9 n.s.	131±4.9 0.03	140±5.8 0.03	154±4.2 0.03	157±5.1 0.03	142±3.4 n.s.	137±3.5 n.s.
5	134±3.9 n.s.	133±5.7 n.s.	142±6.0 n.s.	158±4.4 0.03	157±3.9 n.s.	138±4.0 n.s.	135±3.1 n.s.
8	133±3.3 n.s.	133±5.1 n.s.	143±4.4 0.03	161±3.3 0.03	156±4.7 0.03	140±4.9 n.s.	135±5.1 0.03
Day 1 post	133±5.8 n.s.	133±4.4 0.03	141±5.4 0.03	161±3.0 0.03	165±4.4 n.s.	146±4.3 n.s.	141±6.5 n.s.
2	139±8.3 n.s.	138±5.7 0.03	148±7.0 n.s.	167±6.0 n.s.	165±5.5 n.s.	149±4.2 n.s.	142±2.8 n.s.
4	141±4.2 n.s.	137±6.7 n.s.	158±8.3 n.s.	168±5.9 n.s.	168±6.1 n.s.	150±5.7 n.s.	141±6.1 n.s.
7	141±4.6 n.s.	143±4.8 n.s.	152±5.6 n.s.	170±6.2 n.s.	175±4.8 n.s.	154±4.1 n.s.	144±4.7 n.s.
10	141±3.7 n.s.	137±5.3 n.s.	154±7.2 n.s.	169±5.7 n.s.	172±6.7 n.s.	155±6.0 n.s.	148±6.3 n.s.
Total group							
Day 0	143±2.6 --	150±3.0 --	163±3.8 --	180±4.0 --	173±4.9 --	155±4.2 --	149±4.1 --
1	135±4.1 0.02	140±4.1 0.008	146±3.2 0.001	163±5.3 0.002	162±4.0 0.007	148±3.8 n.s.	143±3.7 0.05
3	133±4.0 0.005	133±3.2 0.0004	142±3.9 0.0004	160±4.6 0.0004	160±3.5 0.002	144±2.9 0.001	140±2.4 0.008
5	134±3.1 0.001	133±3.5 0.001	143±4.1 0.001	163±4.3 0.001	158±3.4 0.003	142±3.3 0.005	136±3.1 0.01
8	135±3.3 0.005	132±3.0 0.001	144±4.2 0.0004	162±4.7 0.001	155±4.4 0.001	139±3.6 0.001	135±3.7 0.0004
Day 1 post	134±3.6 0.002	135±2.5 0.0004	148±4.9 0.002	167±4.7 0.002	166±3.5 n.s.	148±3.1 0.02	144±3.9 n.s.
2	135±4.8 n.s.	138±3.3 0.0004	151±5.0 0.001	170±5.2 0.04	166±4.0 0.05	148±3.5 0.02	140±2.2 0.02
4	138±3.1 n.s.	139±3.9 0.003	155±4.9 n.s.	170±4.0 0.004	168±3.9 n.s.	150±3.7 0.001	143±3.5 n.s.
7	141±3.4 n.s.	143±3.7 0.02	149±3.6 0.001	172±4.4 0.004	171±3.3 n.s.	152±3.3 n.s.	145±2.9 n.s.
10	142±2.9 n.s.	138±3.6 0.002	152±4.1 0.01	170±5.1 0.006	171±4.1 n.s.	152±3.5 n.s.	146±3.8 n.s.

p-value : Wilcoxon m.p.s.r. test, 2-tailed probability versus Day 0-values.

(Reproduced from Sponsor, BEL-4/Part I, Table 2, page 9)

Figure 84. Effects on Heart Rate and Systolic Blood Pressure 1 Minute after Exercise, Before, During, and After Discontinuation of An 8-Day Treatment with Nebivolol in 6 Poor and 6 Normal Metabolizers (BEL-4/Part I)



(Reproduced from Sponsor, BEL-4/Part I, Figure 1, page 13)

There were significant decreases in resting heart rate prior to and 6 hours post dosing in both poor and extensive metabolizers receiving nebivolol. In subjects receiving nebivolol, however, there was no significant reduction in resting blood pressure in either the poor or extensive metabolizers.

In extensive metabolizers only, there was significant shortening of PEP_c and $PEP_c/LVET_c$. In both poor and extensive metabolizers, there was shortening of $LVET_c$ post-exercise, but this shortening was reduced in a comparable fashion in both extensive and poor metabolizers receiving nebivolol, as seen in Figure 85.

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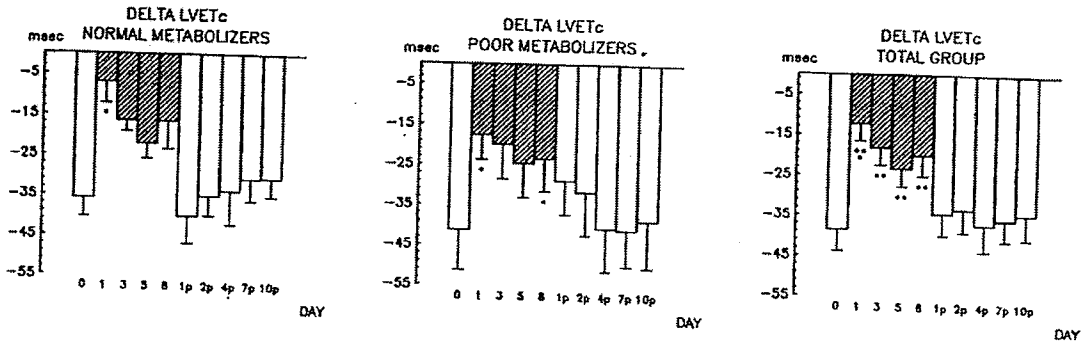
Figure 85. Exercise-Induced Shortening of LVETc Before, During, and After Discontinuation of an 8-Day Treatment with Nebivolol in 6 Poor and 6 Normal Metabolizers (BEL-4/Part I)



(Reproduced from Sponsor, BEL-4/Part I, Figure 3, page 15)

1.53 LMD No. 62269. Study ID 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") (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the effect of 8 days of oral nebivolol 5 mg on ECG parameters in poor and extensive metabolizers.

Methods: Twelve healthy males (6 poor and 6 extensive metabolizers), ages 18 to 65, received nebivolol solution (10 mg) for one day followed by 7 days of nebivolol solution (5 mg). 12-lead ECGs were performed on the control day and on Days 8 and 10 (post completion of nebivolol therapy). QT intervals were corrected for heart rate according to Bazett (QT_c) and Hodges (QT_m). Investigators used the Wilcoxon matched-pairs signed-ranks test and 2-tailed probability for statistical analysis.

Results: Six poor and six extensive healthy male metabolizers, median age 34.5 years, participated in this study. Subjects received nebivolol 10 mg on the first day followed by 7 days of nebivolol 5 mg. Heart rate decreased, and QTc shortened. QTm was unchanged. The ratio QT/QS_2 slightly decreased, but in a nonsignificant fashion. Findings were similar in both poor and extensive metabolizers.

Table 69. Heart Rate and ECG-Intervals measured Before, During, and After a 8-Day Intake of Nebivolol in 6 Poor and 6 Normal Metabolizers (BEL-4/Part II)

	Poor metabolizers (n = 6)					Normal metabolizers (n = 6)				
	Day 0	Day 8		Day 10 post		Day 0	Day 8		Day 10 post	
	Mean±SEM	Mean±SEM	p	Mean±SEM	p	Mean±SEM	Mean±SEM	p	Mean±SEM	p
HR (beats/min)	67±5.3	59±1.9	n.s.	63±4.2	n.s.	65±5.4	57±3.4	n.s.	61±4.0	n.s.
PQ (msec)	152±14.7	155±13.1	n.s.	153±13.6	n.s.	147±9.9	145±9.6	n.s.	143±9.9	n.s.
QRS (msec)	100±5.8	98±6.5	n.s.	98±6.5	n.s.	105±3.4	105±3.4	n.s.	103±3.3	n.s.
QT (msec)	367±10.2	378±4.0	n.s.	373±4.9	n.s.	365±9.6	377±10.5	n.s.	370±11.3	n.s.
QT_c (msec)	383±6.4	374±4.6	0.03	380±9.1	n.s.	375±8.6	366±7.5	n.s.	370±6.4	n.s.
QT_m (msec)	379±4.2	376±3.1	n.s.	379±3.9	n.s.	373±5.3	369±6.7	n.s.	372±6.9	n.s.
QT/QS_2	0.92±0.022	0.95±0.019	n.s.	0.91±0.025	n.s.	0.91±0.014	0.94±0.019	n.s.	0.91±0.014	n.s.

p-value: 2-tailed probability by Wilcoxon m.p.s.r. test versus Day 0.

(Reproduced from Sponsor, BEL-4/Part II, Table 1, page 5)

Figure 86. Individual and Mean Values of QTc- and QTm-Intervals and QT/QS_2 Ratio Before, During, and After a 8-Day Intake of Nebivolol in 6 Poor and 6 Normal Metabolizers (BEL-4/Part II)

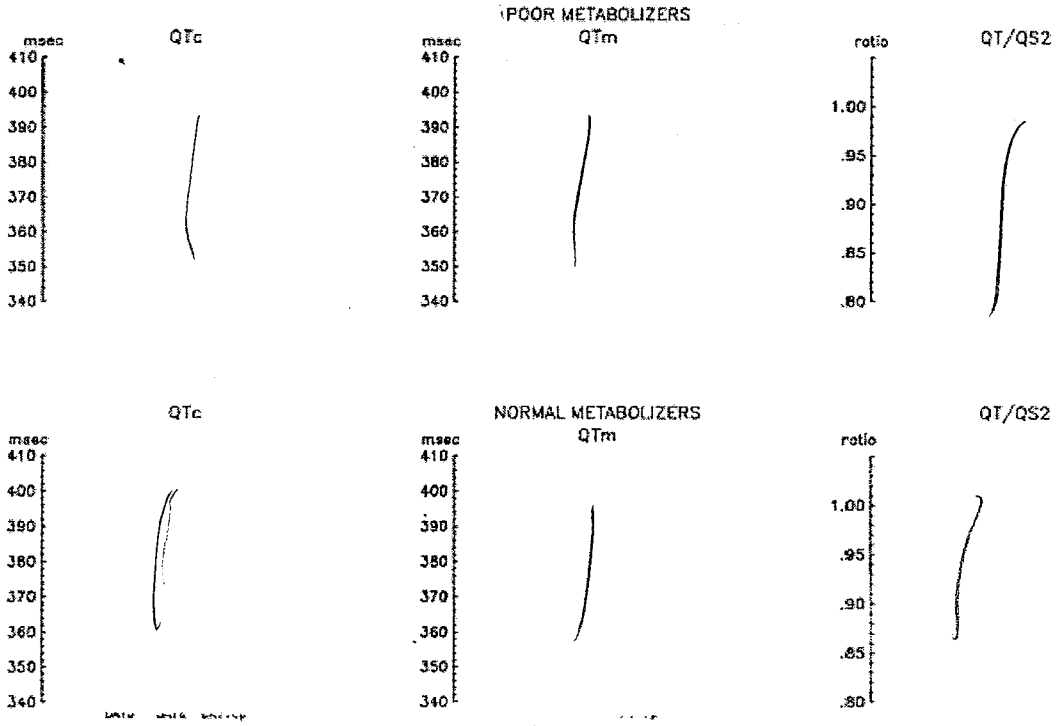


Figure 1: Individual and mean values of QT_c- and QT_m-intervals and QT/QS_2 ratio before, during and after a 8-day intake of nebivolol in 6 poor and 6 normal metabolizers.

(Reproduced from Sponsor, BEL-4/Part II, Figure 1, page 6)

1.54 LMD No. 62270. Study ID 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") (Trial Period: November 18, 1987 – February 11, 1988) (Reviewer: Karen A. Hicks, M.D.)

Objective: Same population as described in Part II. The objective of the study was to determine the effect of multiple days of nebivolol therapy on hematology, chemistry, and urinalysis results.

Methods: As previously described in Part II. Investigators obtained serum and urine samples on Days 0, 8, and 15.

Results: There were no significant changes in hematology, chemistry, or urine results following 8 days of nebivolol therapy. There were no significant differences in laboratory results between extensive and poor metabolizers.

1.55 LMD No. 69145. Study ID BEL-17/Part I. ("Effect of Nebivolol on Dopamine Related Phenomena. Part I: Hormonal Effects. Clinical Research Report NEB-BEL-17. June 1989") (Trial Period: October 11, 1988 – December 21, 1988) (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the effect of a 7-day treatment with nebivolol on hormones related to the dopaminergic system.

Methods: This was a double-blind placebo-controlled cross-over trial in 10 healthy men, ages 18 to 65. Subjects were randomly assigned to either nebivolol 5 mg oral tablet or a placebo tablet once daily for one week. There was a 1 week wash-out period between the two study sessions. On the control day and 24 hours after the last study dose on Day 8, subjects received an intravenous injection of 10 mg metoclopramide, administered over 5 minutes. On the control day and Day 8, investigators obtained serum samples for prolactin, vasopressin, plasma renin activity, and aldosterone before the metoclopramide injection, at 5 minutes (end of injection), and at 15, 25, 35, and 45 minutes after the initiation of the IV metoclopramide. Biochemistry evaluations were performed on the control day prior to IV metoclopramide, as well as on Day 8, 45 minutes after the initiation of IV metoclopramide.

The Wilcoxon signed-rank tests (two-tailed) were used for statistical analysis.

Results: Ten male subjects, median age 41 years, participated in the study. Following an intravenous injection of 10 mg metoclopramide in 10 subjects, plasma prolactin and aldosterone levels increased but were not significantly different between the nebivolol treatment group and placebo. Plasma renin activity, noted to be reduced in the supine

position on day 0, was also comparably reduced on day 8, 24 hours following the last nebivolol dose. There was no significant difference in plasma renin activity between the nebivolol treatment group and placebo. Plasma vasopressin levels, only determined in 4 subjects, were unchanged. There were no statistically significant differences in biochemistry results in the nebivolol treatment group. The sponsor concluded nebivolol had no effect on the dopaminergic system after 7 days of therapy.

1.56 LMD No. 101048. Study ID BEL-52. ("Effects of Nebivolol on Hormonal Responses to Insulin Induced Hypoglycaemia. Clinical Research Report NEB-BEL-52. December 1993") (Trial Period: November 10, 1992 – November 27, 1992) (Reviewer: Karen A. Hicks, M.D.)

Objective: To evaluate the effects of nebivolol (5 mg once daily) on the hormonal response to insulin-induced hypoglycemia.

Methods: This was a single center, open-label trial in 12 healthy male and premenopausal female volunteers, ages 18 to 45 years old. Subjects received nebivolol 5 mg once daily for 7 days. Investigators measured hormone levels on Days 0 (baseline) and 7 (endpoint) immediately before the bolus injection of insulin 0.15 U/kg and at frequent intervals for two hours following the injection (10, 20, 40, 60, 90, and 120 minutes). The study plan was as follows:

Table 70. Study Plan (BEL-52)

DAY	TIME	ACTION
Baseline -7		haematology, biochemistry, urinalysis
-1	08.00 **urine collection**	
0	08.00 10.00	 insulin provocation
1	08.00	start nebivolol 5 mg
2-5	08.00	take nebivolol 5 mg
Endpoint 6	08.00 **urine collection**	take nebivolol 5 mg
7	08.00 10.00	take nebivolol 5 mg haematology, biochemistry, urinalysis insulin provocation

(Reproduced from Sponsor, BEL-52, page 12)

Results: Six men and six women with a median age of 24 years participated in the study. There were no adverse events or withdrawals from the study. One patient, however, had an increase in ASAT up to 3-fold the upper limits of normal.

Table 71. Safety Results (BEL-52)

Adverse Events/Laboratory Data		Nebivolol 5 mg once daily
• Adverse events (AE) Total number of subjects assessed No. (%) of subjects with one or more AE		12 0
• Clinical laboratory parameters No. of subjects with baseline and endpoint data Parameters with code-4 abnormality, i.e. pathological value at end of treatment and not before treatment, n (value)		12
	normal range	
- gamma GT	14-41 U/l	1 (96 U/l)
- ASAT	16-48 U/l	1 (163 U/l)

(Reproduced from Sponsor, BEL-52, page 8)

Nebivolol therapy significantly decreased steady state levels of plasma cortisol ($p = 0.003$), which was accompanied by a decrease in 24-hour urinary levels of cortisol ($p = 0.034$) and in urinary excretion of cortisol ($p = 0.002$) relative to urinary creatinine. There were no significant changes in steady state levels of ACTH, active renin, aldosterone, glucose, growth hormone, luteinizing hormone, prolactin, or testosterone. Additionally, there were no significant changes in 2 hour AUC or peak concentrations (Cmax) of ACTH, glucose, growth hormone, or prolactin.

The investigators concluded nebivolol was well tolerated and had no statistically significant effect on the hormonal response to hypoglycemia based on the 2 hour AUC or Cmax of ACTH, glucose, growth hormone, or prolactin. Although the AUC for cortisol was statistically significantly reduced ($p = 0.016$) at the end of the 7 day treatment period, compared to baseline, the investigators felt this change was a reflection of lower steady state levels rather than reduced responsiveness, because Cmax was not significantly changed.

Table 72. Efficacy Results (BEL-52)

RESULTS Effectiveness	Day 0 (n = 12)	Day 7 (n =12)
• Steady state hormone levels (mean)		
- ACTH, ng/l	19.7	14.9
- Active renin, ng/l	12.6	12.4
- Aldosterone, ng/l	88.3	78.6
- Cortisol, µg/l	114.1	78.4**
- Glucose, mg/dl	74.9	74.4
- Growth hormone, mU/l	4.2	5.4
- Luteinising hormone, U/l	5.4	4.8
- Prolactin, mU/l	264.4	226.4
- Testosterone, µg/l	2.1	2.4

Asterisks refer to differences between Day 7 and Day 0
Levels of significance: ◊ $p \leq 0.1$; * $p \leq 0.05$; **$p \leq 0.01$, ***$p \leq 0.001$

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Effectiveness		Day 0 (n = 7)	Day 7 (n =12)
• Insulin provocation test (mean C_{max}; AUC)			
- ACTH	ng/l; ng/l.min	12823; 247.5	13703; 295.8
- Cortisol	µg/l; µg/l.min	21754; 230.7	19940*;219.1
- Glucose	mg/dl; mg/dl.min	5008; 79.9	5150; 80.7
- Growth hormone	mU/l; mU/l.min	6480; 98.4	7648; 113.9
- Prolactin	mU/l; mU/l.min	138229; 2004.6	122010; 1619.8
• Urinary hormone levels (mean)			
- Urine volume, ml		1467.5	1389.2
- Total creatinine, g		1.4	1.6
- Total aldosterone, µg		10.0	10.2
- Total cortisol, µg		52.9	38.1*
- Aldosterone/gram creatinine, µg/g		7.3	7.4
- Cortisol/gram creatinine, µg/g		41.0	26.6**

Asterisks refer to differences between Day 7 and Day 0
Levels of significance: 0 p ≤ 0.1; * p ≤ 0.05; **p ≤0.01, ***p ≤0.001

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Table 73. Changes in Steady State Hormone Levels Immediately Prior to Insulin Administration (t = 0 min) (BEL-52)

	Mean (SEM)			95% confidence interval for the mean change from baseline	Change from baseline (Wilcoxon test) p-value
	Baseline (Day 0)	Endpoint (Day 7)	Change (Day 0 to Day 7)		
ACTH (ng/l)	19.7 (3.6)	14.9 (2.3)	-4.8 (3.1)	-11.5; 1.9	0.233
Active renin (ng/l)	12.6 (1.6)	12.4 (2.5)	-0.3 (2.6)	-6.0; 5.4	0.389
Aldosterone (ng/l)	88.3 (15.5)	78.6 (12.9)	-9.7 (18.7)	-50.9; 31.6	0.850
Cortisol (µg/l)	114.1 (16.5)	78.4 (12.1)	-35.6 (12.4)	-62.9; -8.4	0.003**
Glucose (mg/dl)	74.9 (1.6)	74.4 (1.9)	-0.5 (1.8)	-4.5; 3.5	0.966
Growth hormone (mU/l)	4.2 (1.8)	5.4 (1.9)	1.2 (1.5)	-2.2; 4.5	0.322
Luteinising hormone (U/l)	5.4 (0.9)	4.8 (1.0)	-0.6 (1.4)	-3.6; 2.4	0.762
Prolactin (mU/l)	264.6 (14.4)	226.4 (15.7)	-38.2 (19.0)	-80.0; 3.7	0.110
Testosterone (µg/l)	2.1 (0.6)	2.4 (0.7)	0.2 (0.2)	-0.1; 0.6	1.000

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Table 74. Changes in Plasma Cortisol Levels (µg/l) During the Insulin Provocation Tests (BEL-52)

Time (minutes)	Baseline (Day 0)		Endpoint (Day 7)		Change from baseline to endpoint (Wilcoxon test) p-value
	Mean (SEM)	95% CI of mean	Mean (SEM)	95% CI of mean	
-30	136.1 (14.8)	103.5; 168.6	96.5 (10.7)	72.8; 120.1	
-15	117.8 (14.8)	85.3; 150.3	84.9 (11.1)	60.6; 109.3	
0	114.1 (16.5)	77.7; 150.4	78.4 (12.1)	51.8; 105.1	
+10	104.8 (13.6)	74.8; 134.8	75.3 (11.7)	49.5; 101.1	
+ 20	100.3 (12.5)	72.8; 127.7	72.0 (11.4)	46.9; 97.0	
+ 30	127,7 (11.8)	101.9; 153.6	104.0 (9.9)	82.2; 125.9	
+ 40	188.8 (9.5)	167.8; 209.7	173.4 (9.7)	152.0; 194.8	
+ 60	214.1 (7.7)	197.3;230.9	207.6 (9.1)	187.5; 227.6	
+ 90	219.0 (9.1)	199.1; 238.9	210.0 (8.5)	191.4; 228.7	
+ 120	206.8 (10.0)	184.9; 228.8	196.3 (10.7)	172.7; 219.8	
AUC ($\mu g.l^{-1}.min$)	21754 (844)	19896; 23612	19940 (932)	17888; 21992	0.016*
C_{max} ($\mu g.l^{-1}$)	230.7 (8.5)	211.9; 249.4	219.1 (8.9)	199.5; 238.7	0.519

There was a significant decrease in plasma cortisol levels from -30 min to 0 min at both the baseline ($p < 0.001$) and endpoint visits ($p = 0.001$ Friedman test). Hence 0 min was used as a reference for evaluating the response to insulin provocation

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Table 75. Changes in 24-h Urinary Hormone Levels (BEL-52)

	Mean (SEM)			95% CI for the mean change from baseline	Change from baseline (Wilcoxon test) p-value
	Baseline (Day 0)	Endpoint (Day 7)	Change (Day 0to Day 7)		
Urine volume (ml)	1467.5 (145.4)	1389.2 (171.0)	-78.3 (121.3)	-345.3; 188.6	0.596
Total creatinine (g)	1.4 (0.2)	1.6 (0.2)	0.2 (0.1)	0.0; 0.4	0.064
Total aldosterone (µg)	10.0 (2.4)	10.2 (2.1)	0.2 (2.2)	-4.6; 5.0	0.910
Total cortisol (µg)	52.9 (8.3)	38.1 (3.9)	-14.8 (6.2)	-28.5; -1.1	0.034*
Aldosterone/creatinine (µg/g)	7.3 (2.0)	7.4 (1.5)	0.1 (1.8)	-4.0; 4.1	0.910
Cortisol/creatinine (µg/g)	41.0 (6.1)	26.6 (3.2)	-14.3 (4.2)	-23.6; -5.1	0.002**

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1.57 LMD No. 107434. Study ID 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") (Trial Dates: October 21, 1992 – February 7, 1994) (Reviewer: Karen A. Hicks, M.D.)

Objective: To evaluate the possible interference of chronic nebivolol treatment with glucose metabolism, lipid profile, and blood viscosity parameters in patients with insulin-dependent (IDD) and non-insulin dependent (NIDDM) diabetes.

Methods: This Phase III randomized double blind parallel group study evaluated nebivolol 5 mg daily versus atenolol 50 mg daily for 8 weeks in 16 patients with IDD and

16 patients with NIDDM. Investigators performed the following assessments according to Table 76:

Table 76. Assessments (BEL-39)

Assessments	Baseline		4 weeks	8 weeks	
	0 h	2 h	0 h	0 h	2 h
• Diabetic control parameters					
- glucose	x	x		x	x
- C-peptide	x	x		x	x
- insulin	x	x		x	x
- HgbA1c	x			x	
- fructosamine	x			x	
- glucose urine	x			x	
- microalbumin urine	x			x	
- creatinine urine	x			x	
• Rheological parameters				x	
- plasma viscosity		x			x
- whole blood viscosity		x			x
- RBC filterability		x			x
• Blood pressure, sitting, standing	x		x	x	
• Heart rate, sitting, standing	x		x	x	
• Body weight	x		x	x	
• ECG	x			x	
• Laboratory data					
- Haematology	x			x	
- Biochemistry	x			x	
• Adverse events	x		x	x	
Statistical methods	ANOVA				

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The primary parameters were the glucose and C-peptide level, the hemoglobin A_{1c} concentration ($HgbA_{1c}$), and the fructosamine level. The trial was conducted according to the "Declaration of Helsinki." Patients returned for control after 4 and 8 weeks of treatment. Patients were on a stable dose of antidiabetic medication for 3 months prior to study entry, and these medications remained unchanged during the study. If the patient was on antihypertensive medications or diuretics prior to study entry, these medications were gradually tapered until they were completely discontinued 4 weeks before the first trial visit. The study prohibited the use of tricyclic antidepressants, MAO inhibitors, corticosteroids, H_1 antagonists, and lipid lowering drugs during the study.

As shown in Table 76 above, investigators performed assessments at randomization (visit 1) and after 4 and 8 weeks of double-blind therapy (visits 2 and 3) at the same time each morning. On the morning of these study visits, the patients were fasting and had not taken their usual antidiabetic medication. Investigators obtained baseline blood tests (glucose, C-peptide, insulin, HgbA1c, fructosamine, lipid profile, hematology and chemistry), vital signs, body weight, and electrocardiograms. The subjects subsequently ate breakfast and received their usual antidiabetic medication. At visit 3, subjects also received study medication. Two hours after breakfast, blood tests were again performed for glucose and C-peptide levels, whole blood and plasma viscosity, and for red blood cell filterability. Urine collection continued for approximately 3 hours following the early morning collection. At 4 weeks (visit 2), only a physical examination was performed with vital signs and body weight.

Blood pressure and heart rate were measured after the patient rested for 5 minutes. Three consecutive sitting blood pressure measurements were obtained at 2 minute intervals.

The patient then stood for two minutes, and a standing blood pressure was obtained. Heart rate was measured after the sitting blood pressure was determined and once during the standing blood pressure measurement. Regarding ECGs, QT-intervals were corrected for heart rate according to Bazett (QTcB) or Hodges (QTcM).

Results: Thirty-two patients participated in the trial. The patient group was comprised of 18 males and 14 females between 30 and 71 years of age. The median age was 52 years. Eight of these patients were regular smokers, and the $HgbA_{1c}$ levels at baseline ranged from 6.70 to 10.95 (median: 8.85%). One NIDDM patient dropped out after 49 days of atenolol treatment due to the serious adverse event of arterial thrombosis in the leg, requiring hospitalization. A total of 6 patients had concomitant illnesses. Concomitant illnesses in the IDDM group included diabetic retinopathy, hypothyroidism, and neuropathy. Concomitant illnesses in the NIDDM group included Crohn's disease, depression and dyspepsia, and leg fatigue with ambulation.

There was a compliance rate exceeding 90% in all patients during double-blind randomization.

The results of the study are summarized in the following tables.

Table 77. Results (BEL-39)

Results		IDD		NIDD	
		nebivolol	atenolol	nebivolol	atenolol
		Baseline / 8 weeks			
(n = number of patients with data)		(n = 8/8)	(n = 8/8)	(n = 8/8)	(n = 8/7)
• **Diabetic control parameters**					
- Glucose (mg/dl)	- F	227/217	173/210	166/157	178/192
	- NF	277/322	269/288	215/225	240/245
- C-peptide (pmol/l)	- F	155/81	117/185	667/774	499/602
	- NF	270/260	347/344	1186/1202	1489/1261
- Insulin (µIU/ml	- F	19.5/19.2	43.8/45.3	8.4/15.6	10.0/9.2
	- NF	49.3/50.1	68.2/68.1	31.1/32.2	50.8/34.0
- $HgbA_{1c}$ (%)	- F	10.2/10.5	9.1/9.7	8.6/9.6	9.4/9.0
- Fructosamine (mmol/l)	- F	3.5/3.5	3.6/3.6	3.0/2.8	3.4/3.0
- Glucose urine (mg/dl)	- F	1517/2020	202/1621	659/826	750/141
- Microalbumin urine (µg/min)	- F	18.2/8.3	9.0/10.2	6.4/6.2	38.1/34.3
- Creatinine urine (mg/24 h)	- F	953/1246	1155/1068	946/1013	923/842
• **Rheological parameters**					
- Plasma viscosity (mPa.s)		1.37/1.30	1.35/1.31	1.31/1.26	1.39/1.32
- Whole blood viscosity (mPa.s)- shear rate 20.4**		7.28/6.99	7.57/7.68	7.22/6.84	7.54/7.21
- shear rate 51.2*		5.92/5.80	6.01/6.21	6.07/5.94	6.28/6.13
- shear rate 94.5**		5.27/5.19	5.29/5.50	5.54/5.38	5.65/5.66
- RBC filterability (ml/min)		2.73/2.47	2.82/2.69	2.48/2.39	2.02/2.16

F = fasting ; NF = non-fasting
Asterisks refer to significant p-values for treatment effect in reduced ANOVA model.
*Levels of significance: * $p \leq 0.05$; ** $p \leq 0.01$*

	Shift Baseline / 8 weeks	
	Nebivolol (n = 16)	Atenolol (n = 15)
• **Blood pressure** (mm Hg)		
- SBP sitting	- 6.0	- 6.6
standing	- 6.6	- 5.2
- DBP sitting	- 3.0	- 4.4
standing	- 3.8	- 4.3
- MAP sitting	- 4.0	- 5.0
standing	- 4.5	- 4.8
• **Heart rate** (b/min)		
sitting	- 8.1	- 6.7
standing	- 7.9	- 6.4
• **Body weight** (kg)	- 0.1	0.6
• **ECG** PQ (ms)	2.5	- 2.0
QRS (ms)	- 0.3	0.7
QT (ms)	20.6	16.7
QTc (ms)	1.3	- 6.1
QTm (ms)	9.9	2.3

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Table 78. Parameters for Diabetic Control: Statistics (BEL-39)

			IDD (n = 16)						NIDD (n = 16)					
			Nebivolol			Atenolol			Nebivolol			Atenolol		
			Mean	(SEM)	95 %CI of mean	Mean	(SEM)	95 % CI of mean	Mean	(SEM)	95 % CI of mean	Mean	(SEM)	95 % CI of mean
Glucose mg/dl	B	F	227	(33)	150 ; 305	173	(34)	93 ; 253	166	(13)	136 ; 195	178	(14)	145 ; 212
		NF	277	(26)	216 ; 339	269	(32)	194 ; 344	215	(18)	172 ; 258	240	(32)	163 ; 316
	8 w	F	217	(32)	142 ; 292	210	(39)	118 ; 301	157	(15)	120 ; 193	192	(21)	140 ; 244
		NF	322	(45)	217 ; 428	288	(15)	254 ; 323	225	(7)	209 ; 241	245	(29)	175 ; 316
Glucose urine mg/dl	B	F	1517	(727)	-202 ; 3236	202	(112)	-63 ; 468	659	(324)	-108 ; 1426	750	(464)	-347 ; 1848
	8 w	F	2020	(650)	482 ; 3557	1621	(739)	-126 ; 3367	826	(472)	-328 ; 1980	141	(39)	47 ; 236
Hg A_{1c} %	B	F	10.2	(0.48)	9.1 ; 11.4	9.1	(0.35)	8.3 ; 10.0	8.6	(0.40)	7.7 ; 9.6	9.4	(0.87)	7.3 ; 11.5
	8 w	F	10.5	(0.67)	8.9 ; 12.1	9.7	(0.34)	8.9 ; 10.5	9.6	(0.47)	8.5 ; 10.7	9.0	(0.75)	7.1 ; 10.8
C-peptide pmol/l	B	F	155	(58)	17 ; 293	117	(50)	-0.5 ; 234	667	(167)	273 ; 1061	499	(94)	277 ; 721
		NF	270	(112)	5 ; 534	347	(191)	-104 ; 798	1186	(303)	470 ; 1902	1489	(443)	443 ; 2536
	8 w	F	81	(20)	35 ; 127	185	(79)	-0.6 ; 371	774	(250)	184 ; 1364	602	(142)	253 ; 950
		NF	260	(113)	-8 ; 529	344	(172)	-61 ; 750	1202	(317)	453 ; 1950	1261	(366)	365 ; 2156
Fructosamine mmol/l	B	F	3.5	(0.18)	3.1 ; 4.0	3.6	(0.25)	3.0 ; 4.2	3.0	(0.16)	2.6 ; 3.4	3.4	(0.26)	2.8 ; 4.0
	8 w	F	3.5	(0.19)	3.1 ; 4.0	3.6	(0.25)	3.0 ; 4.2	2.8	(0.11)	2.6 ; 3.1	3.0	(0.30)	2.3 ; 3.8
Insulin µlU/ml	B	F	19.5	(4.77)	8.2 ; 30.7	43.8	(21.1)	-6.2 ; 93.7	8.4	(2.06)	3.5 ; 13.3	10.0	(3.18)	2.5 ; 17.6
		NF	49.3	(10.5)	24.4 ; 74.1	68.2	(31.0)	-5.2 ; 141.6	31.1	(6.95)	14.7 ; 47.5	50.8	(25.41)	-9.3 ; 110.9
	8 w	F	19.2	(4.98)	7.4 ; 31.0	45.3	(22.5)	-7.9 ; 98.6	15.6	(6.73)	-0.3 ; 31.5	9.2	(3.85)	-0.3 ; 18.6
		NF	50.1	(10.6)	25.1 ; 75.1	68.1	(30.0)	-2.8 - 139.0	32.2	(7.66)	14.1 ; 50.3	34.0	(19.43)	-13.6 ; 81.5
Microalbumin urine µg/min	B	F	18.2	(10.8)	-7; 44	9.0	(1.40)	6 ; 12	6.4	(1.16)	3.6 ; 9.1	38.1	(17.7)	-3.8 ; 80.1
	8 w	F	8.3	(1.55)	5 ; 12	10.2	(2.58)	4 ; 16	6.2	(1.48)	2.5 ; 9.8	34.3	(23.7)	-23.8 ; 92.3
Creatinine urine mg/24 h	B	F	953	(191)	500 ; 1405	1155	(111)	893 ; 1418	946	(133)	632 ; 1259	923	(183)	491 ; 1356
	8 w	F	1246	(267)	615 ; 1877	1068	(146)	722 ; 1413	1013	(148)	650 ; 1375	842	(159)	454 1231

CI = confidence interval
B = baseline ; 8 w = 8 weeks , F = fasting ; NF = not fasting
p-value : no significant treatment or patient groups effect

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Table 79. Safety Results (BEL-39)

Safety	Nebivolol	Atenolol
• **Laboratory parameters**		
- Total no. of patients assessed	16	16
- No. (%) of patients with code 4* abnormalities	4 (25)	6 (37.5)
WBC		3
Platelet count	1	
Triglycerides		2
Blood urea nitrogen		1
Glucose in urine	3	1
• **Adverse events (AE)**		
- Lumbar pain		1
- Headache	1	
- Dizziness		1
- Hoarseness		1
- Diarrhoea	1	
- Gastroenteritis		1
- Nausea		1
- Hypoglycaemia		1
- Muscle pain	1	
- Tendinitis		1
- Thrombosis arterial leg		1
- Irritability		1
- Bronchitis		1
- Throat sore		1
- Rhinitis	3	1
- Folliculitis	1	
- Urinary tract infection	1	
- Peripheral coldness		1
Total No. of patients assessed	16	16
No. (%) of patients with one or more AE	6 (37.5)	9 (56.25)
No. (%) of drop-outs because of AE	0	1 (6.25)

* code 4 = important abnormality in at least two samples during treatment, or in last sample, and before treatment sample being not pathologic.

(Reproduced from Sponsor, BEL-39, page 10)

Nebivolol significantly reduced whole blood viscosity at 20.4, 51.2, and 94.5 s^{-1} ($p = 0.002$, 0.03, and 0.009, respectively), compared with atenolol, as seen in Table 80.

Table 80. Mean Blood Viscosity at Shear Rate (BEL-39)

	Mean blood viscosity at shear rate					
	20.4 s^{-1}		51.2 s^{-1}		94.5 s^{-1}	
	Baseline	8 weeks	Baseline	8 weeks	Baseline	8 weeks
Nebivolol	7.25	6.91	6.00	5.87	5.40	5.28
Atenolol	7.56	7.46	6.14	6.17	5.47	5.57

(Reproduced from Sponsor, page 20)

Both nebivolol and atenolol reduced sitting and standing blood pressure and heart rate at 4 weeks and the end of the study, as shown in Table 81 and Table 82.

Table 81. Sitting and Standing Blood Pressure: Statistics (BEL-39)

			Nebivolol (n = 16)			Atenolol (n = 16)		
Position	Parameter	Time	Mean	SEM	95% CI of mean	Mean	SEM	95% CI of mean
Sitting	SBP (mmHg)	Baseline	129	3.2	123;136	131	4.5	121;141
		4 weeks	120	3.0	114;127	125	4.2	116;134
		8 weeks	123	3.2	117;130	126	2.9	119;132
		Shift Baseline-8weeks	-6.0	2.50	-11.33;-0.67	-6.6	4.68	-16.53;3.40
	DBP (mmHg)	Baseline	81	2.0	77;86	83	2.2	79;88
		4 weeks	75	1.6	72;78	78	2.0	73;82
		8 weeks	78	2.0	74;83	79	1.7	76;83
		Shift Baseline-8weeks	-3.0	1.75	-6.73;0.73	-4.4	2.41	-9.58;0.70
	MAP (mmHg)	Baseline	98	2.4	92;103	99	2.9	93;105
		4 weeks	90	2.0	86;95	94	2.8	88;99
		8 weeks	94	2.4	88;99	95	2.0	91;99
		Shift Baseline-8weeks	-4.0	1.90	-8.04;0.04	-5.0	3.02	-11.43;1.43
Standing	SBP (mmHg)	Baseline	128	3.6	120;136	130	4.6	120;140
		4 weeks	121	3.6	113;129	127	3.8	119;135
		8 weeks	121	4.0	113;130	125	3.7	117;133
		Shift Baseline-8weeks	-6.6	2.76	-12.45;-0.67	-5.2	4.37	-14.50;4.13
	DBP (mmHg)	Baseline	81	2.3	76;86	83	2.3	78;88
		4 weeks	75	1.7	72;79	80	2.0	76;84
		8 weeks	77	2.5	72;82	79	2.0	75;83
		Shift Baseline-8weeks	-3.8	1.94	-7.88;0.38	-4.3	2.64	-9.94;1.31
	MAP (mmHg)	Baseline	97	2.7	91;102	99	3.1	92;105
		4 weeks	91	2.3	86;96	96	2.6	90;101
		8 weeks	92	2.9	86;98	94	2.5	89;100
		Shift Baseline-8weeks	-4.5	2.00	-8.75;-0.25	-4.8	3.21	-11.60;2.10

CI = confidence interval
p-value: no significant treatment effect

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Table 82. Sitting and Standing Heart Rate: Statistics (BEL-39)

		Nebivolol (n = 16)			Atenolol (n = 16)		
		Mean	SEM	95% CI of mean	Mean	SEM	95% CI of mean
Sitting HR	Baseline	76	3.2	69;83	78	3.8	70;86
	4 weeks	69	2.6	63;74	70	3.4	62;77
	8 weeks	68	3.5	60;75	71	3.2	64;78
	Shift baseline-8 week	-8.1	1.71	-11.77;-4.48	-6.7	1.74	-10.40;-2.98
Standing HR	Baseline	82	2.6	76;87	81	3.0	74;87
	4 weeks	73	2.7	67;79	72	3.0	66;78
	8 weeks	74	3.7	66;82	74	3.3	67;81
	Shift baseline-8 week	-7.9	2.03	-12.20;-3.55	-6.4	2.32	-11.31;-1.44

CI = confidence interval
p-value: no significant treatment effect

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Table 83. ECG Parameters: Statistics (BEL-39)

		Nebivolol (n = 16)			Atenolol (n = 16)		
		Mean	SEM	95% CI of mean	Mean	SEM	95% CI of mean
HR (b/min.)	Baseline	72	2.7	66;78	76	3.4	69;83
	8 weeks	66	3.7	58;74	68	3.0	61;74
	Shift baseline-8 weeks	-6.1	1.70	-9.75 ;-2.50	8.2	2.57	-13.71;-2.69
PQ (msec)	Baseline	144	5.8	131;156	144	5.9	131;156
	8 weeks	146	7.5	130;162	142	6.5	128;156
	Shift baseline-8 weeks	2.5	2.81	-3.50;8.50	-2.0	2.00	-6.29;2.29
QRS(msec)	Baseline	98	2.5	92;103	100	5.6	88;112
	8 weeks	98	2.3	93;102	101	5.3	90;113
	Shift baseline-8 weeks	-0.3	0.96	-2.37;1.74	0.7	1.18	-1.87;3.20
QT (msec)	Baseline	367	6.2	354;380	371	7.4	356;387
	8 weeks	388	7.4	372;403	391	8.2	374;409
	Shift baseline-8 weeks	20.6	5.66	8.56;32.69	16.7	5.99	3.82;29.51
QTc (msec)	Baseline	400	7.2	384;415	415	6.2	402;428
	8 weeks	401	6.5	387;415	412	5.3	400;423
	Shift baseline-8 weeks	1.30	5.0	-9.38;12.00	-6.1	2.76	-11.99;-0.14
QTm (msec)	Baseline	388	5.6	376;400	400	5.3	388;411
	8 weeks	398	4.7	388;408	405	5.2	394;416
	Shift baseline-8 weeks	9.9	4.67	-0.02;19.90	2.3	2.93	-3.94;8.61

CI = confidence interval
p-value: no significant treatment effect

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Table 84. Haematology, Biochemistry, and Urinalysis: Descriptive Statistics and Changes from Baseline to End of an 8 Week Treatment Period with Nebivolol (BEL-39)

Study group:nebivolol

Laboratory test	Unit	SBPG : start N	SBPG : start Mean	SBPG : start Sem	SBPG : start Median	DBPG : endpoint N	DBPG : endpoint Mean	DBPG : endpoint Sem	DBPG : endpoint Median	(a) (b) (c)	Below B	Below W	Below A	Below M	Within B	Within W	Within A	Within M	Above B	Above W	Above A	Above M	N
Biochemistry																							
Calcium	mmol/l	16	2.28	0.02	2.30	2.25	0.02	2.26								16							16
Potassium	mmol/l	16	4.42	0.07	4.50	4.33	0.08	4.35				1		1		14							16
Sodium	mmol/l	16	141	0.76	141	141	0.48	141			1			2		12				1			16
Total protein	g/l	16	71.5	0.96	72.5	70.6	0.81	70.0								16							16
Albumin	g/l	16	44.9	0.58	44.0	44.9	0.40	45.5								16							16
Total cholesterol	mmol/l	16	6.04	0.21	6.06	5.96	0.26	5.96								9	3			4	2		16
Triglycerides	mmol/l	16	1.73	0.32	1.37	1.67	0.47	1.06								11	1				4		16
Apolipoprotein B/A1	Ratio	16	0.86	0.09	0.86	0.90	0.08	0.80						1		14					1		16
HDL	g/l	16	0.63	0.07	0.53	0.64	0.06	0.64				2				7				3	4		16
LDL	g/l	16	1.40	0.07	1.43	1.34	0.09	1.38				1				9	1			2	4		16
Apolipoprotein A1	g/l	15	1.43	0.07	1.46	1.47	0.08	1.54			2					13						1	16
Apolipoprotein B	g/l	16	1.26	0.10	1.09	1.28	0.10	1.24								12	1			1	2		16
Total bilirubin	micmol/l	16	10.5	0.92	10.4	11.2	1.07	11.3								16							16
Alkaline phosphatase	U/l	16	91.1	7.23	88.0	89.6	7.32	85.5								12	1				3		16
GGT	U/l	16	34.6	9.73	18.0	33.1	7.53	20.0								15					1		16
AST	U/l	16	20.8	1.31	20.0	21.3	1.63	20.5								15				1			16
ALT	U/l	16	22.8	2.55	20.5	23.1	2.77	20.5								15							16
Blood urea nitrogen	mmol/l	16	6.13	0.28	6.12	6.20	0.29	5.98								13	2			1			16
Creatinine	micmol/l	16	83.8	2.47	84.4	84.3	3.26	81.8								15				1			16
Uric acid	micmol/l	16	250	13.8	235	256	14.3	265								15					1		16
Haematology																							
Haemoglobin	g/l	16	143	2.69	143	142	2.46	142			3			1		12							16
RBC	tera/l	16	4.66	0.11	4.60	4.66	0.08	4.65			3			2		11							16
Haematocrit	vol-%	16	41.4	0.84	41.3	40.9	0.67	41.4			4	3		2		7							16
MBC	giga/l	16	6.13	0.35	6.30	6.32	0.40	5.60								16							16
Segm neutrophils	%	16	54.8	2.04	56.0	53.2	2.54	53.4			1	1				13				1			16
Lymphocytes	%	16	32.8	1.79	33.1	33.3	2.18	32.8			1					14					1		16
Monocytes	%	16	9.20	0.29	9.30	9.39	0.51	10.1								16							16
Eosinophils	%	16	2.68	0.40	2.55	3.34	0.66	3.05								14				2			16
Basophils	%	16	0.56	0.09	0.45	0.78	0.13	0.60								16							16
Platelet count	giga/l	16	216	12.2	206	213	16.4	204			1	1				14							16
Urine																							
Occult blood	Code	15	1.00	0.00	1.00	1.13	0.09	1.00															
Protein	Code	16	1.19	0.14	1.00	1.00	0.00	1.00								13		1		2			16
Glucose*	Code	16	2.38	0.13	2.00	2.25	0.17	2.00								14	2						16
																	2				16		16

(a) No. of laboratory values below, within and above normal range at the end of treatment
(b) No. of laboratory values below (B), within (W) and above (A) normal range, or missing (M), before trial
(c) Shifts of values from one class (B, W, A) to another (- or -- ; decrease, + or ++ ; increase)
*Urinary protein and glucose code: 1: normal (negative or within normal range)
2: dubious (slightly above normal range)
3: abnormal (clearly above normal range)

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The sponsor concluded the following:

1. Neither nebivolol nor atenolol influenced diabetic control of NIDDM and IDDM patients in a clinically relevant or statistically significant way.
2. Nebivolol but not atenolol significantly reduced whole blood viscosity at all shear rates tested (20.4, 51.2, and 94.5 s^{-1}).
3. There were no clinically relevant shifts in haematological, biochemical, urinary, and electrocardiographic parameters. There were no significant changes in the lipid profile.
4. 37.5% and 56.25% of patients in the nebivolol and atenolol treatment groups, respectively, experienced adverse events. One patient in the atenolol treatment group had to discontinue the study due to developing an arterial thrombosis in his leg for which he required hospitalization.

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