#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
					21 AEs experienced by 10 subjects during study (sluggishness, fatigue, chest pressure, nausea, vomiting, congestion, toothache). Lab, vital sign, and ECG monitoring indicated no safety risk. A single 10 mg dose of nebivolol given to healthy volunteers on Day 1 produced an average decrease of 5 mm Hg and 7 mm Hg in all subjects for SBP and DBP, respectively. By Day 17 (steady-state), decrease of 7 mm hg and 12 mm Hg for SBP and DBP. HR slightly decreased but effect was variable.
140	N/A	NEB-0128	A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction of Hydrochlorothiazide and Nebivolol HCL in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label	Randomized, open-label, multiple dose, one period, two parallel groups study. 16 subjects enrolled, ages 19-45.. 13 subjects completed the study. 2 subjects withdrew due to personal reasons, and 1 patient withdrew due to low hemoglobin (pt menstruating). Subjects received 10 doses of 10 mg nebivolol alone, 10 doses of 10 mg nebivolol given concomitantly with 25 mg of HCTZ, and 10 doses of 25 mg HCTZ alone. 24 AEs experienced by 8 subjects (headaches, dizziness, insomnia). <u>Results</u>: 1. Laboratory, vital sign, and ECG monitoring indicated no safety risk associated with oral dosing of 10 mg nebivolol HCL tablets alone or concomitantly with 25 mg (2 x 12.5 mg) hydrochlorothiazide capsules. 2. No PK changes. 3. Steady-state dosing of 10-mg nebivolol given to healthy volunteers produced, on average, a 10 mm Hg decrease in DBP with small variable changes seen in SBP and pulse rate. Steady-state dosing of 25 mg HCTZ in healthy subjects produced increases in SBP and pulse rate, with a small decrease in DBP. The concomitant administration of both drugs under steady-state conditions produced small and variable changes in SBP and pulse rate, with a 10 mm Hg decrease in DBP. This was similar to changes seen with nebivolol. However, the BP changes induced by nebivolol, HCTZ, or both given concomitantly did not produce associated clinical symptoms in any subjects.

#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
141	N/A	NEBI-0174	A Phase I Open-Label Study Comparing the Interaction of Nebivolol HCL on the Pharmacokinetics of Digoxin in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label	Open-label, one-period, one-sequence, two-treatment study in 16 healthy, nonsmoking males and females, ages 21-53. 13 subjects (12 EM, 1 PM) completed the study. Subjects 6, 15 and 16 were discontinued by the investigator due to low pulse rates (50, 48, 46 bpm). Subjects received a 0.25 mg dose of digoxin BID on Day 1. On Day 2 through Day 17, subjects received a 0.25 mg dose of digoxin once daily. On Day 8 through Day 17, subjects received a once daily dose of 10 mg nebivolol HCL concomitantly with digoxin. 14 AEs in 6 subjects (low backache, headache, stiff neck, nasal congestion, vomiting, fever). Results: 1. No significant changes in digoxin pk parameters when digoxin administered concomitantly with nebivolol. 2. Laboratory, vital sign, and ECG monitoring indicated no safety risk associated with oral dosing of 10 mg nebivolol HCL tablets alone or given concomitantly with 0.25 mg digoxin. No dose adjustments necessary.
142	N/A	NEBI-0181	A Phase I Open-Label Study Comparing the Interaction of Steady-state Nebivolol HCL on the Pharmacokinetics and Pharmacodynamics of Warfarin Sodium in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label	Open-label, one-period, one-sequence, two-treatment study. Subjects received a single 10 mg dose of Coumadin® on Day 1. On Day 8 through Day 22, subjects received a once daily 10 mg nebivolol HCL tablet. On Day 17, subjects once again received a single dose of 10 mg warfarin sodium. 16 subjects enrolled. Subject 12 and 13 discontinued by the investigator prior to Day 17 for abnormal pre-dose lab values. 14 subjects (11 EM and 3 PM) healthy, non-smoking, male and female subjects between the ages of 19 and 50 completed this study. Subject 15 and 16 received warfarin on Day 15 instead of Day 17—not included in statistical analyses. 4 AEs in 3 subjects (shakiness, fatigue, headache, and nausea). Results: 1. Overall, steady-state administration of 10 mg nebivolol HCL alone or concomitantly with a single 10 mg dose of warfarin to healthy volunteers is safe and well tolerated. No clinically significant change in the pk of R- or S-warfarin. Warfarin protein binding in human plasma was independent of the absence or presence of nebivolol. No dose

#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
					adjustments necessary. 2. Assessments of clinical lab results and ECGs were generally unremarkable. 3. Single dose nebivolol produced expected decreases in SBP (9 mm Hg), DBP (10 mm hg), and pulse rate (9 bpm). These cardiovascular effects were maintained with daily dosing of 10 mg nebivolol. The concomitant administration of both drugs produced small and variable changes in SBP, DBP, and pulse rate, primarily due to the beta blockade effects of nebivolol. The BP changes induced by nebivolol, warfarin, or both given concomitantly did not produce associated clinical symptoms in any subjects.
143	N/A	NEBI-0184	A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction of Fluoxetine Hydrochloride and Nebivolol HCL in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label	Open-label, one-period, multiple-dose study. Each subject received a single oral 10 mg dose of nebivolol HCL tablets administered with 240 mL of water at ambient temperature on Day 1. On Days 8 through 28, a 20 mg capsule dose of fluoxetine HCL was administered once daily to all subjects. On Day 28, in addition to the fluoxetine dose, a single oral dose of 10 mg nebivolol HCL tablet was administered. 13 subjects reported to the drug study unit; however, 1 volunteer was not dosed due to abnormal pre-dose lab values. 12 subjects entered the study, and 10 subjects completed the study. Subject 6 failed to report on Day 8 due to personal reasons. Subject 7 was discontinued prior to dosing on Day 20 due to a protocol deviation. 9 AEs in 3 subjects (headache, lightheadedness, somnolence, swelling of feet, sleeplessness, nausea, occasional vomiting, occasional loose stools). <u>Results</u>: 1. Lab, vital sign, and ECG monitoring indicated no safety risk associated with the oral dosing of 10 mg nebivolol hydrochloride tablets. 2. Coadministration of fluoxetine interfered with the apparent clearance of d,l-nebivolol from the body leading to increased AUCL, AUCI, and CPEAK values on the order of approximately 7, 7, and 2.5 fold higher, respectively, than when fluoxetine was not coadministered. 3. Plasma concentrations of nebivolol, when co-administered with fluoxetine and/or other CYP2D6 inhibitors, may become elevated,

#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
					but an increase in adverse events has not been shown. 4. A single dose of nebivolol HCL on Day 1, a single dose of fluoxetine HCl on Days 8 through 27, and a single dose of nebivolol HCl concomitantly with a single dose of fluoxetine HCl on Day 28 produced, on average, a 10% and 18% decrease in both SBP and DBP, respectively. This effect was the greatest at 6 hours after drug administration. However, the BP reduction induced by nebivolol and/or fluoxetine did not produce associated clinical symptoms in any subjects. Likewise, pulse rate was also slightly decreased; however, the effect was variable, but did not produce any clinically significant symptoms.
144	N/A	NEBI-0213	A Phase I Open-Label Study of the Pharmacokinetic Interaction between Furosemide and Nebivolol HCL in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label	Open-label, one-period study. 15 (12 EMs, 3 PMs) healthy, non-smoking, male and female subjects, ages 20-43, were enrolled and completed this study. On Day 1, volunteers were administered a single furosemide tablet (1 x 40 mg) and blood samples were collected for up to 10 hours post-dose. On Days 2 through 11, volunteers received a single nebivolol tablet (10 mg) once daily. On Day 11, a single 40 mg furosemide tablet was concomitantly administered with nebivolol and serial blood samples were collected for up to 96 hours. 11 AEs in 6 subjects (headache, pharyngitis, dysmenorrhea, pharyngitis in nebivolol or nebivolol + furosemide). In furosemide, dizziness, vomiting, and headache. <u>Results</u>: 1. Laboratory, vital sign, and ECG monitoring indicated no safety risk associated with oral dosing of 10 mg nebivolol HCL tablets alone or concomitantly with 40 mg furosemide tablets. Most drug-related adverse events were associated with furosemide administration. 2. Steady-state plasma concentrations were achieved by Day 8 or 9 for d-nebivolol, l-nebivolol, and d, l-nebivolol in EM and PM subjects. 3. Confidence intervals for parameters measuring the rate of furosemide elimination (Cl/F, KEL and HALF) were slightly outside of 80% to 125%, but are not considered clinically significant. 4. No drug interactions that would affect the clinical PK profile or the safety of either

#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
					nebivolol HCl or furosemide upon co-administration of the two drugs. 5. Small and variable changes in SBP, DBP, and pulse rate with nebivolol and furosemide.
145	N/A	NEBI-0214	A Phase I Open-Label Multiple-Dose Study of the Pharmacokinetic Interaction between Nebivolol HCL and Spironolactone in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label	Randomized, open-label, two treatment, multiple-dose, one-period, two parallel group study in 16 patients (12 EM and 4 PM). 8 subjects received a single nebivolol HCL tablet (10 mg) once daily for 10 days. On Day 11 through Day 20, 25 mg (1 x 25 mg) of spironolactone was co-administered once daily with a single nebivolol HCL tablet. On Day 21 through Day 30, subjects received a single 25-mg dose of spironolactone once daily. The other 8 subjects received drugs in the reverse order. A total of 15 subjects completed the study. 28 AEs in 12 subjects (loose stool, headache, light-headed, sore-throat, dizziness, itchy throat, achy right shoulder, fatigue, numbness in two fingers, constipation, rectal bleeding, difficulty concentrating). Results: 1. Laboratory, vital sign, and ECG monitoring indicated no safety risk. 2. In EMs, LNCSS and LNAUCTAU for d-nebivolol were slightly above 125%. At most, these changes reflect a 14% increase in plasma drug concentrations for nebivolol co-administered with spironolactone in EM subjects. 3. There were no drug interactions that would affect clinical PK profile. 4. Steady-state plasma nebivolol concentrations were reached within 10 days whether nebivolol was administered alone or concomitantly with spironolactone. 5. Multiple doses of nebivolol alone, spironolactone alone, or multiple doses of nebivolol administered concomitantly with spironolactone resulted in both small and variable changes in SBP, DBP, and Pulse Rate.
146	N/A	NEBI-0220	A Phase I Open-Label Multiple-Dose Study of the Pharmacokinetic Interaction between Ramipril and Nebivolol HCL in Healthy Volunteers	Pharmacokinetic, Drug interaction Open-label	Open-label, multiple-dose, one-period, two parallel group study. Two groups, 8 subjects each (6 EMs and 2 PMs). Group 1 received a single nebivolol HCL tablet (10 mg) once daily for 10 days. On Day 11 through Day 20, 5 mg ramipril co-administered once daily with a single nebivolol HCL tablet (10 mg). On day 21 through Day 30, subjects received a single 5

#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
			Study conducted from October 9, 2002 – November 14, 2002.		mg dose of ramipril once daily. Group 2 subjects received a single 5 mg dose of ramipril once daily for 10 days. On Day 11 through Day 20, nebivolol HCL 10 mg was co-administered once daily with a 5 mg dose of ramipril. On Day 21 through Day 30, pts received nebivolol HCL 10 mg once daily. 15 (12 EM and 3 PM) healthy, non-smoking male and female subjects between the ages of 19 and 69 completed this study. 58 AEs experienced by 10 subjects during the study (headache, dry throat, sore throat, fatigue, decreased cognitive ability, abdominal pain, diarrhea, hot flashes, yeast infection, light-headed, upset stomach, vomiting, back pain, abdominal pain, felt drunk, gas, upset stomach, dry lips, constipation). Results: 1. Lab, vital sign, and ECG monitoring indicate no safety risk associated with oral dosing of 10 mg nebivolol HCL tablets alone or concomitantly with 5 mg (1 x 5 mg) ramipril capsules. 2. Steady-state plasma concentrations achieved by Day 10, Day 20 and/or Day 30 for d-nebivolol, l-nebivolol, d,l nebivolol in EM and PM subjects and/or ramiprilat in EM subjects. 3. No tx differences observed, when ramipril co-administered with nebivolol (as compared to nebivolol alone), in mean CSS, AUCTAU, HALF, apparent KEL and apparent Cl/F for l-nebivolol or d,l-nebivolol in EM subjects. Additionally, CSS and AUCTAU for l-nebivolol and d,l-nebivolol showed no treatment differences in PM subjects. 4. No sig drug interaction between nebivolol HCL or ramipril upon co-administration.
147	N/A	NEBI-02104	A Phase I Open-Label Single-Dose Study of the Pharmacokinetic Interaction between Nebivolol HCL and Losartan Potassium in Healthy Volunteers All subjects dosed from January 20, 2003 through February 17, 2003.	Pharmacokinetic, Drug interaction Open-label	Single-dose, open-label, randomized, two-sequence, two-treatment, three period study between nebivolol HCL (10 mg) and losartan potassium (Cozaar®) (50 mg) in 24 healthy volunteers (20 EMs and 4 PMs), between the ages of 18 and 55. 21 subjects (18 EMs and 3 PMs) completed the study. Subjects treated with nebivolol alone, nebivolol in combination with losartan, and losartan alone. Each tx given as a single dose with a 14-day washout period between treatments. Group 1 and Group 2 consisted of 12 subjects each (10 EMs and 2 PMs).

#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
					30 AEs reported in 14 subjects (headache, light-headed, left shoulder pain, right ear pressure, fever, malaise, menstrual cramps, somnolence, rhinitis, sinusitis, vomiting, dizziness, left otitis media, URI). Subject 9 withdrew prior to Day 29 dose administration due to personal reasons. Subject 16 withdrew prior to Day 15 due to personal reasons. Subject 20 was dropped by Mylan's PK department prior to Day 29 due to an upper respiratory infection. Results: 1. Clinical laboratory, vital sign, and ECG monitoring indicated no safety risk. 2. Concomitant administration of losartan and nebivolol did not produce any substantial changes in the PK of d, l, and d,l nebivolol in both EMs and PMs. CPEAK, AUCL, or AUCI were slightly decreased by no greater than 21% for EM and 13% for PM subjects. 3. Comparisons of the PK parameters of losartan and EXP-3174 in the presence or absence of nebivolol indicated that there were slight decreases in both AUCL (14%) and AUCI (14%) and slight increases in Cl/F (17%) and Vd/F (21%) of losartan upon coadministration with nebivolol, while the disposition of EXP-3174, which is responsible for most of the Angiotensin II receptor antagonism that follows losartan treatment, was not affected by nebivolol. 4. Overall, a single dose of nebivolol resulted in a 12% (14 mm Hg) decrease in mean SBP, maximal at 8 hrs post-dose, a 13% (9 mm Hg) decrease in mean DBP that was maximal at 8 hours post-dose, and a 19% (13 bpm) decrease in mean pulse rate that was maximal at 4 hours post-dose. Overall, a single dose of losartan resulted in approximately a 7% (8 mm Hg) decrease in mean SBP that was maximal 24 hours post-dose, a 9% (6 mm Hg) decrease in mean DBP that was maximal 6 hours post-dose, and a 9% (6 bpm) decrease in mean pulse rate that was maximal 2 hours post-dose. Overall, a single dose of nebivolol concomitantly with losartan resulted in a 9% (10 mmHg) decrease in mean SBP that was maximal 6 hours post-dose, a 12% (8 mm Hg) decrease in mean DBP that was maximal at 6 hours post-dose, and a 15% (10 bpm) decrease in mean pulse rate that

#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
					was maximal 4 hours post-dose. Similar findings seen in EMs and PMs. 5. No significant drug interaction with concomitant administration of losartan and nebivolol.
148	N/A	NEBI-02118	A Phase I Open-Label Study of the Effect of Repeated-Dose Activated Charcoal on the Pharmacokinetics of Nebivolol HCL in Healthy Volunteers January 18, 2003 – March 10, 2003.	Pharmacokinetic, Drug interaction Open-label	Open-label, randomized, two-period, crossover study. Oral administration of 10 mg nebivolol HCL tablets with repeated-dose (8x50 g/240 mL or 25 g/240 mL) activated charcoal suspension. 15 EMs and 4 PMs, healthy, males and females, ages 20-51. Only 9 subjects (6 EMs and 3 PMs) completed the study. 28 AEs (dizziness, vomiting, headache, watery or loose stools, nausea). More AEs with higher dose of charcoal. No significant lab, vital sign, or ECG changes with nebivolol 10 mg alone or with activated charcoal (25g/240mL) <u>Results</u>: 1. Effects of activated charcoal appear to differ slightly between EMS and PMs. 2. In EMs, repeated doses of charcoal resulted in no significant changes in AUCL, AUCI, and Cl/F of d-, l-, and d, l-nebivolol. For glucuronides, there was a 15% decrease in AUCL and AUCI, and a 19% increase in Cl/F. 3. In PMs, 24-30% decreases in mean AUCL and AUCI, and 31-41% increases in the mean Cl/F of d-, l-, d, l-nebivolol observed following activated charcoal treatment. Also a 21% decrease in the mean AUCL and AUCI, and a 27% increase in the mean CL/F of G-UD in PMs. 4. Variable and inconsistent changes in HALF and Vd/F (Vd/F for G-UD) in individuals following activated charcoal tx. <u>Summary</u>: Nebivolol and G-UD tend to exhibit more enterohepatic recycling in PMs compared to EMs. Therefore, enterohepatic recycling of nebivolol and/or its metabolites likely exists in humans, but the extent of its involvement or significance is still unknown. Nebivolol + activated charcoal resulted in approximately a 13 mm Hg drop (12% decrease) in SBP 6 hrs post nebivolol dosing and an 11 mm Hg drop (15% decrease) in DBP 8 hrs post nebivolol dosing. (compared with 3 mm Hg (3% decrease) and 10 mm (14%

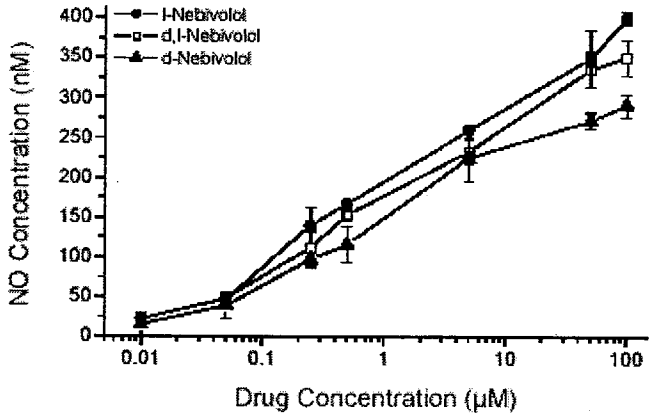
#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
					decrease) in SBP and DBP 8 hrs post dosing with nebivolol + distilled water. Nebivolol + activated charcoal resulted in 8 bpm drop (12%) in sitting mean pulse rate at 4 hrs post nebivolol dosing. Nebivolol + distilled water led to 6 bpm (9% decrease) at 6 hrs post dosing.
149	N/A	NEBI-0124	A Phase I, Open-Label Study Investigating the Effects of Hepatic Impairment on the Single-Dose Pharmacokinetics of Nebivolol Hydrochloride Dosing dates: September 13, 2001 - October 17, 2001 for impaired subjects. Dosing dates: October 17, 2001 – October 22, 2001.	Pharmacokinetic, Special populations Open-label	8 healthy adult volunteers and 8 pts with moderate hepatic impairment. 6 women. 10 men. 16 total subjects. All EMs. 4 pts with Hepatitis C. All subjects completed the study. Ages 41-64. Open-label, one-period, single-dose study. 5 mg nebivolol. <u>Results</u>: 1. AUCL for d, l-nebivolol 4.5 fold higher for moderate hepatic impaired individuals (range 14.80 ng*hr/mL to 145.5 ng*hr/mL) compared to healthy individuals (range: 0.80 to 56.13). 2. CPEAK 3.5 fold larger in moderate hepatic impaired group 3. Mean time to peak plasma concentrations for both moderate hepatic impaired and healthy individuals was comparable (1.5 hrs vs. 1.75 hrs, respectively) 4. Mean t1/2 and mean apparent clearance of nebivolol was roughly 3 fold larger (22.2 hrs vs. 7.4 hrs) and 10-fold smaller (168.2L/hr vs. 1937 L/hr), respectively, for the hepatic impaired subjects compared to healthy controls. <u>For nebivolol glucuronides</u>: 1. Mean AUCL approximately 1.7 fold higher for moderate hepatic impaired individuals (NS) 2. CPEAK approximately equal between 2 groups 3. Mean time to reach peak plasma concentrations for both the moderate hepatic impaired and healthy individuals comparable (2.6 hrs vs. 2.4 hrs) 4. Mean apparent volume of distribution was nearly identical for both groups for the nebivolol glucuronide moiety. 5. Mean apparent clearance for nebivolol glucuronides approximately double for the healthy subjects relative to hepatic impaired volunteers. 6. Only statistically significant ($p < 0.05$) value was the glucuronide half-life for moderate hepatic impairment almost 3 fold

#	LMD No.	Study ID	Title	Study Category/ Type/Design	Results
151	N/A	NEB-122	A Randomized, Parallel-Group Safety Evaluation of Electrocardiographic Intervals and Blood pressure in Normal Healthy Volunteers after Nebivolol, Atenolol, Moxifloxacin, or Placebo Administration after Single and Repeated Doses	Cardiovascular, Double-blind, Randomized, Placebo and Active-Controlled Study of QT Effects	Please see the complete review of NEB-122 under Safety in the Review by Karen A. Hicks, M.D..

1.1 Report Number: 1270_01_00. ("Comparative Effects of Nebivolol, Nebivolol Enantiomers, Atenolol, Metoprolol, Carvedilol, and Bucindolol on Human Endothelial Cell Nitric Oxide Release Following Acute Treatment") (June 25, 2002) (Reviewer: Karen A. Hicks, M.D.)

Study 1270.01.00 compared the effects of nebivolol, nebivolol enantiomers, atenolol, metoprolol, carvedilol, and bucindolol on the release of nitric oxide from human umbilical vein endothelial cells (HUVEC) following acute treatment. The concentrations of nebivolol and its enantiomers ranged from 100 nM to 100 µM. HUVEC released 400 nM, 300 nM, and 350 nM of nitric oxide in response to 100 µM concentrations of *l*-nebivolol, *d*-nebivolol, and racemic mixture of nebivolol, respectively, as seen in Figure 1.

Figure 1. Nitric Oxide Release from Endothelial Cells Following Acute Treatment with Nebivolol and Its Enantiomers



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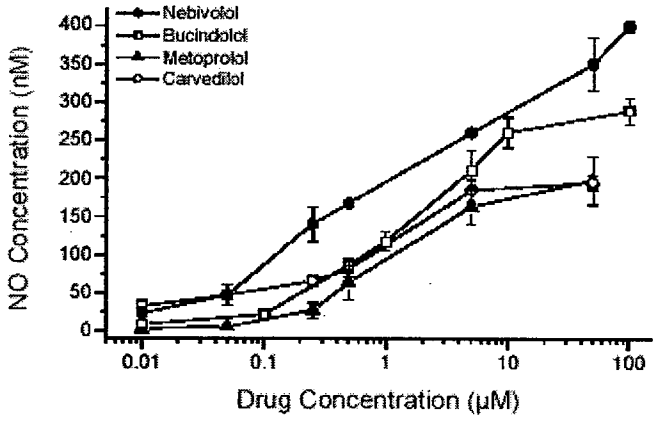
The racemic mixture of nebivolol and its enantiomers increased NO release from HUVEC and were superior to the other agents tested. At a 5 µM concentration of study drug, HUVEC released 40 nM of nitric oxide for atenolol, over 200 nM for *d*-nebivolol and the racemic mixture, and over 250 nM for *l*-nebivolol. At 500 nM, HUVEC released over 160 nM of nitric oxide for racemic nebivolol, compared to slightly over 85 nM of nitric oxide for Bucindolol, and less than 85 nM of nitric oxide for Metoprolol and Carvedilol. Nitric oxide release for these compounds is shown in Figure 2.

Figure 2. Nitric Oxide Release Following Acute Treatment with Nebivolol, Bucindolol, Metoprolol, and Carvedilol



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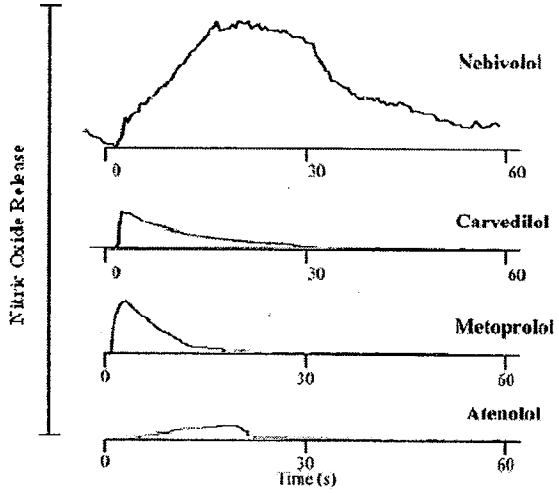
Following nebivolol, nitric oxide release from HUVEC occurred gradually over 15 seconds and then plateaued for an additional 15 seconds, prior to declining over the subsequent 30 seconds, as seen in Figure 3. The release kinetics for carvedilol, metoprolol, and bucindolol, however, were different, and were marked by a rapid onset and shorter plateau phase. The release kinetics for atenolol were not sufficiently studied. It is not known whether or not rapid release kinetics increase the concentration of superoxide and free radical formation, thereby depleting nitric oxide and resulting in cellular toxicity.

Figure 3. Nitric Oxide Releasing Effect of Various Beta-Blockers on Human Endothelial Cells



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X-ray diffraction analyses found that nebivolol was located in the membrane hydrocarbon core, as were carvedilol and metoprolol, two compounds which also increased nitric oxide release. Atenolol, a hydrophilic compound, however, had its equilibrium location in the charged headgroup, as seen in Figure 4 and Figure 5. It is not

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

Figure 4. Nebivolol and its Enantiomers Partition to a Similar Membrane Location

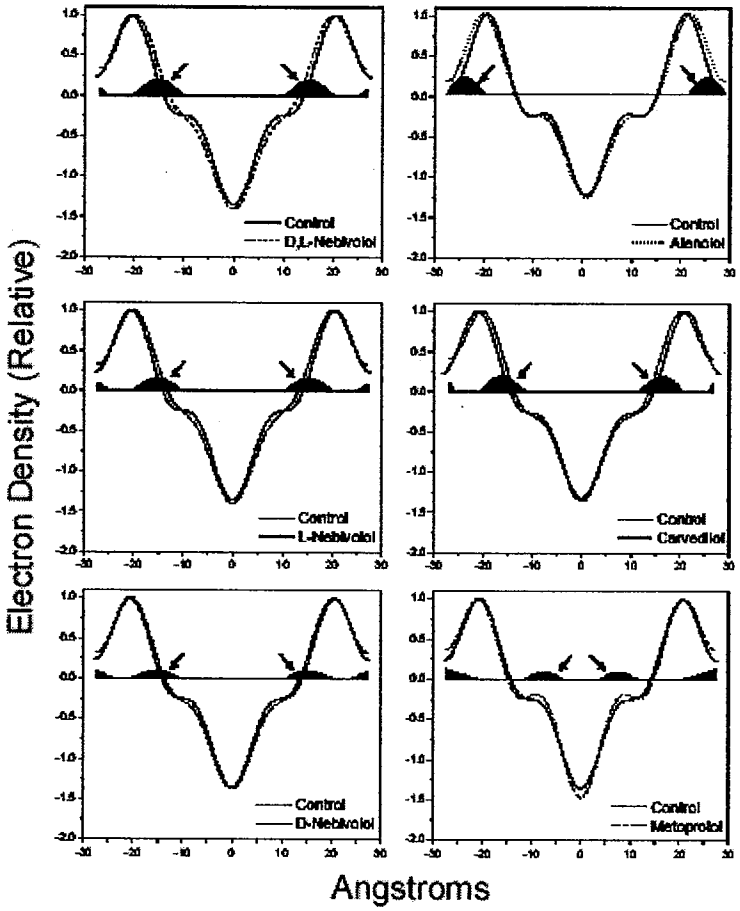

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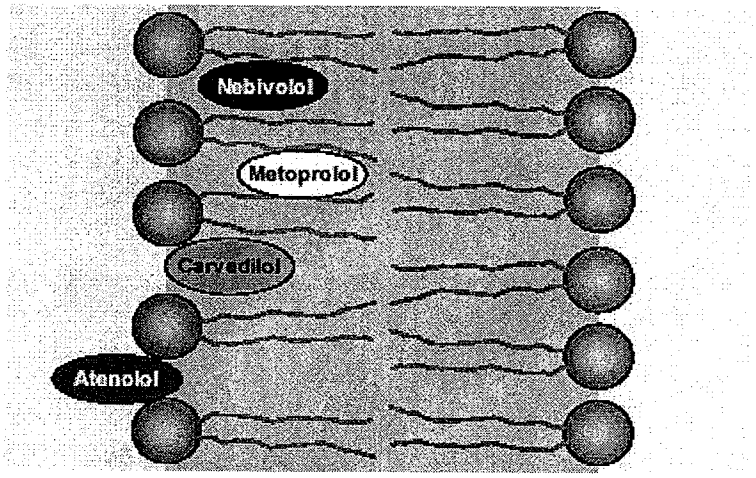
Figure 5. Predicted Location of Nebivolol, Metoprolol, Carvedilol, and Atenolol in Cell Membrane



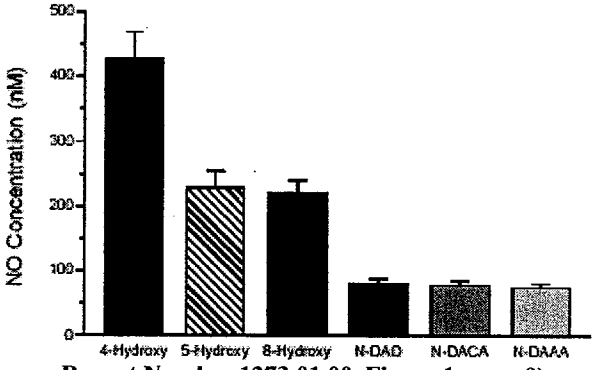
(Reproduced from Sponsor, Figure 7, page 16)

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

1.2 Report Number: 1273_01_00. ("Comparative Effects of Nebivolol, Nebivolol Enantiomers, and Six Nebivolol Metabolites on Endothelial Nitric Oxide Release from Human Endothelial Cells following Acute Treatment") (July 25, 2002) (Reviewer: Karen A. Hicks, M.D.)

Study 1273.01.00 compared the effects of nebivolol, nebivolol enantiomers, and six nebivolol metabolites (4-hydroxy nebivolol, 5-hydroxy nevibolol, 8-hydroxy nebivolol, N-dealkylated carboxylic acid (N-DACA), N-dealkylated diol (N-DAD), and N-dealkylated amino alcohol (N-DAAA) on nitric oxide release from human endothelial cells following acute treatment. At concentrations of 10 µM of 4-hydroxy nebivolol, 5-hydroxy nebivolol, and 8-hydroxy nebivolol, HUVEC released nitric oxide at concentrations of 420 nM, 230 nM, and 230 nM, respectively, as seen in Figure 6. The remaining three metabolites resulted in peak NO levels less than 90 nM. At concentrations of 5 µM, 4-hydroxy nebivolol and nebivolol resulted in peak NO concentrations of greater than 400 nM and of 225 nM, respectively, as seen in Figure 7. Additionally, the peak NO concentration achieved after 4-hydroxy nebivolol approximated the concentration usually measured with acetylcholine, and both agents demonstrated rapid early release kinetics.

Figure 6. Peak NO Release Following Acute Treatment with Nebivolol Metabolites (10μM)



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

Figure 7. Peak NO Release Following Treatment with Acetylcholine, Nebivolol, and Nebivolol Metabolites (5 μM Treatment)

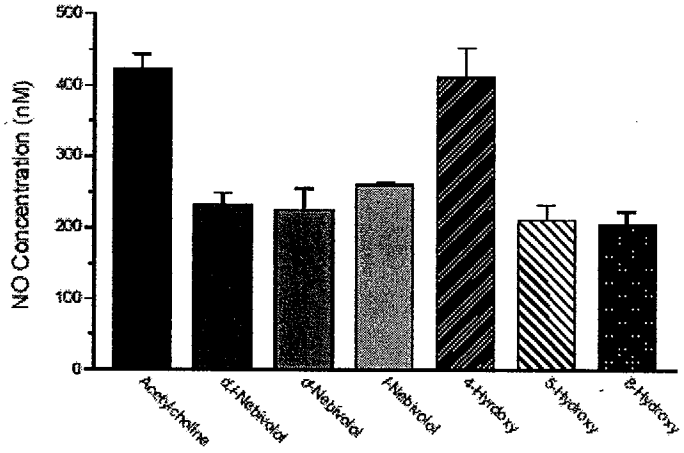


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Table 3. Relative Magnitude of NO Bioavailability for Nebivolol, Its Enantiomers, and Major Metabolites

Compound	Relative Magnitude of Effect (500nM Compound)
Nebivolol	***
d-Nebivolol	**
l-Nebivolol	***
4-hydroxy-5-phenol nebivolol	***
4-hydroxy-8-phenol nebivolol	***
Nebivolol glucuronide	**
4-hydroxy nebivolol	****
5-hydroxy nebivolol	**
8-hydroxy nebivolol	*
N-dealkylated amino alcohol	-
N-dealkylated diol	-
N-dealkylated carboxylic acid	-

- = No appreciable binding; * = ≤100nM; ** = 101-150nM; *** = 151- 200nM; **** = >200nM
(Mason, 2003a)

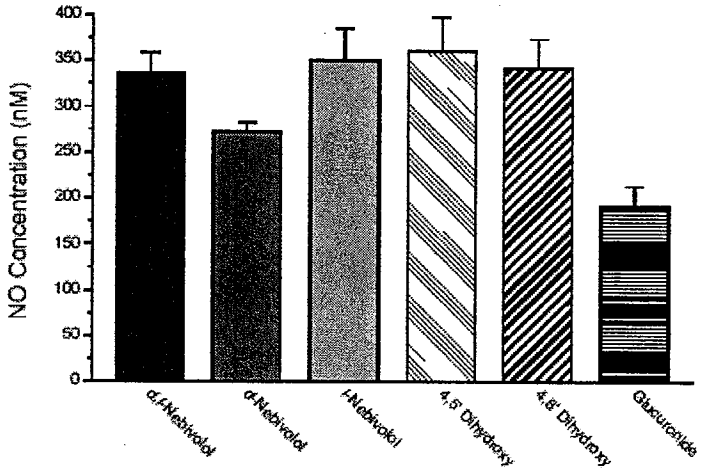
(Reproduced from Sponsor, Table 4.3-01, Integrated Summary of Efficacy, page 34)

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

1.3 Report Number: 1332_00_00. ("Comparative Effects of Nebivolol Metabolites 4,5'-dihydroxy, 4,8'-dihydroxy, Glucuronide, Nebivolol, and Nebivolol Enantiomers on Endothelial Nitric Oxide Release in Human Endothelial Cells following Acute Treatment") (March 2003) (Reviewer: Karen A. Hicks, M.D.)

Acute treatment with 50 μM of nebivolol or nebivolol metabolites in Study 1332.00.00 demonstrated that 4,5'-dihydroxy nebivolol, 4,8'-dihydroxy nebivolol, and nebivolol glucuronide increased NO release from HUVEC in a concentration-dependent manner. At a concentration of 50 μM, 4,5' and 4,8'-dihydroxy nebivolol resulted in peak NO release of 330-350 nM, while the glucuronide metabolite resulted in a peak NO release of 190 nM, as shown in Figure 8.

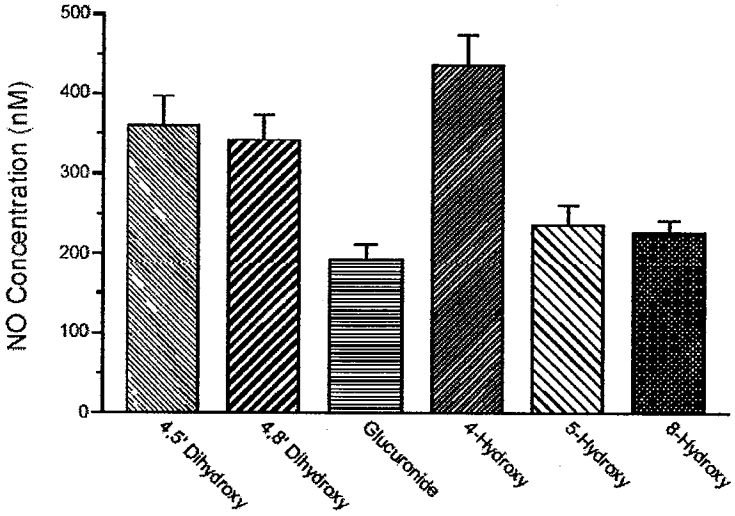
Figure 8. Effects of Nebivolol and Metabolites on Peak NO Release from Human Endothelial Cells Following Acute Treatment (50 µM)



(Reproduced from Sponsor, Report Number: 1332.00.00, Figure 2, page 10)

In Figure 9, the sponsor shows the more potent effect of dihydroxy metabolites compared with the previously studied nebivolol metabolites, with the exception of 4-hydroxy nebivolol.

Figure 9. Effects of Nebivolol and Nebivolol Metabolites on Peak NO Release from Human Endothelial Cells Following Acute Treatment (50 µM)



(Reproduced from Sponsor, Report Number 1332.00.00, Figure 3, page 11)

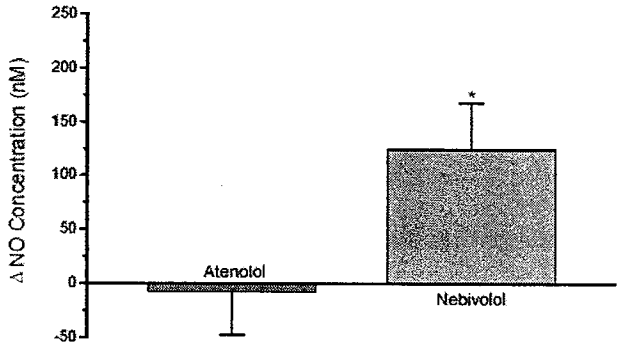
Conclusions: 4-hydroxy nebivolol had the highest peak NO release from HUVEC, followed by 4,5' dihydroxy and 4,8' dihydroxy nebivolol.

1.4 Report Number: 1333_00_00. ("Comparative Effects of Nebivolol and Atenolol on Nitric Oxide Release from Human Endothelial Cells following Chronic Treatment") (August 2, 2002) (Reviewer: Karen A. Hicks, M.D.)

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

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

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



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

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

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

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

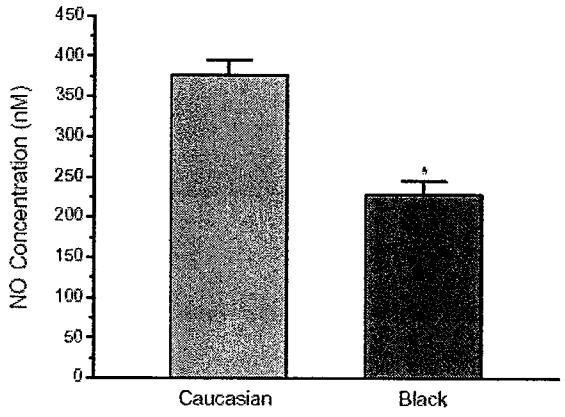
Conclusion: Peak NO release from HUVEC is a concentration-dependent phenomenon after chronic treatment with nebivolol. Although the mechanism of NO release is not

known, some investigators postulate a mechanism independent of ß1-adrenergic receptor inhibition, because atenolol at the concentration tested had no significant effect on peak NO release.

1.5 Report Number: 1334_00_00. ("Comparative Effects of Nebivolol and Atenolol on Nitric Oxide Release in Black and Caucasian Endothelial Cells following Chronic Treatment") (September 20, 2002) (Reviewer: Karen A. Hicks, M.D.)

Study 1334.00.00 studied the effects of nebivolol and atenolol on nitric oxide release in Black and Caucasian endothelial cells following chronic treatment. Prior to drug therapy, baseline nitric oxide release after stimulation with acetylcholine (1 µM) was 375 nM and 225 nM in Caucasian and Black HUVEC preparations, respectively, suggesting that there may be racial differences in basal levels of nitric oxide release, as seen in Figure 11.

Figure 11. Comparison of Acetylcholine (1 µM) Stimulated NO Release from Caucasian and Black Donor Endothelial Cells

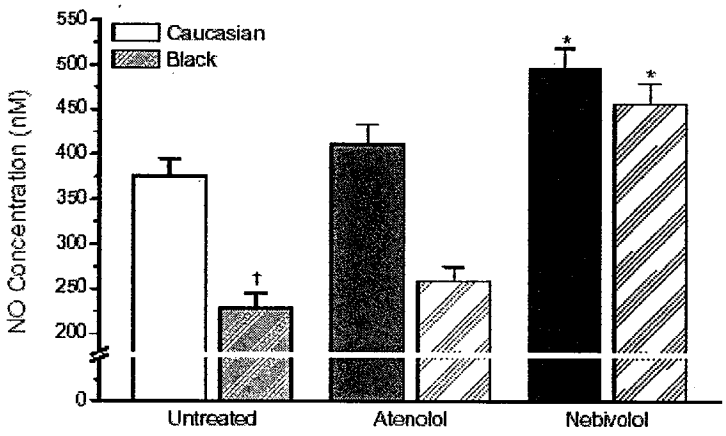


* $p < 0.01$ vs. Caucasian (NO Release stimulated with ACh alone); n = 5-7

(Reproduced from Sponsor, Study 1334.00.00, Figure 1, page 9)

After chronic treatment (24 hours) with 10 µM of nebivolol and atenolol in the Black HUVEC preparation, however, nitric oxide release increased from ~225 nM to ~450 nM in the nebivolol group and from ~225 nM to ~260 nM in the atenolol group following stimulation with acetylcholine (1 µM). In the Caucasian HUVEC preparation, nitric oxide release increased from ~375 nM to ~500 nM with nebivolol and from ~375 nM to ~420 nM with atenolol. Figure 12 shows the results of chronic treatment with nebivolol and atenolol in Black and Caucasian HUVEC preparations. These findings suggest nebivolol stimulates native endothelial cells to increase nitric oxide release in the setting of endogenous agonists such as acetylcholine or bradykinin.

Figure 12. Release of NO after Chronic Treatment with β_1-Adrenoceptor Blockers (10 µM) Followed by Stimulation with Acetylcholine (1 µM)



*$p < 0.01$ vs. cognate control (NO Release stimulated with ACh alone); n = 5-7
†$p < 0.001$ vs control from Caucasian donors

(Reproduced from Sponsor, Study 1334.00.00, Figure 2, page 10)

The above data suggest the magnitude of the NO response after chronic therapy with nebivolol is greater in Black than in Caucasian HUVEC preparations, almost completely eliminating the racial difference. Additionally, chronic treatment with atenolol had no significant effect on nitric oxide release in either Black or Caucasian HUVEC preparations.

Conclusions: Using Black and Caucasian HUVEC preparations in vitro, this study suggests there may be an ethnic difference regarding basal levels of NO release following stimulation with acetylcholine. After chronic treatment with nebivolol and atenolol, NO release increased in both HUVEC preparations, although the magnitude of increase was greater with nebivolol.

1.6 Report Number: 1271_00_00. ("Effects of Nebivolol and ACE-Inhibitors on Endothelial Nitric Oxide Release in Black and Caucasian Donor Endothelial Cells following Chronic Treatment") (May 2003) (Reviewer: Karen A. Hicks, M.D.)

Study 1271.01.00 studied the effects of chronic nebivolol and ACE-Inhibitor treatment on nitric oxide release from Black and Caucasian donor endothelial cells. HUVEC preparations from 6 Black and Caucasian donors were utilized. Basal nitric oxide release after stimulation with acetylcholine (1 µM), a receptor-dependent agonist, was 196 nM in Black cells and 316 nM in Caucasian cells, while after stimulation with a calcium ionophore (1 µM), a receptor-independent agonist, was 301 nM and 465 nM, respectively, in Black and Caucasian cells.

Nitric oxide release in Black and White donors following stimulation with acetylcholine (1 µM) was concentration dependent after chronic treatment with nebivolol in doses

ranging from 0.01 μM to 10 μM. In Black donors, ACh-stimulated NO release increased from 196 nM (untreated) to 430 nM, and the percent increase in NO release ranged from approximately 38% to 120% over the nebivolol dose range tested. In Caucasian donors, Ach-stimulated NO release increased from 316 nM (untreated) to approximately 420 nM, and the percent increase in NO release ranged from 10% to 30% over the nebivolol dose range tested.

Nitric oxide release in Black and White donors following stimulation with calcium ionophore (1 μM) was also concentration dependent after chronic treatment with nebivolol in the same dose range. In Black donors, NO release increased from 301 nM (untreated) to approximately 700 nM, and the percent increase in NO release ranged from approximately 62% to 120% over the nebivolol dose range tested. In Caucasian donors, NO release increased from 465 nM (untreated) to approximately 670 nM, and the percent increase in NO release ranged from approximately 10% to 40% over the nebivolol dose range tested.

After chronic treatment with ramiprilat (0 to 10 μM) followed by treatment with nebivolol (1 μM), there was a concentration dependent increase in nitric oxide release from Black and Caucasian HUVEC preparations. The magnitude of nitric oxide release appeared to be greater in the Black donors. In Black donors, NO concentration increased from approximately 175 nM (untreated) to approximately 480 nM in the setting of nebivolol and increasing doses of ramiprilat. In Caucasian donors, NO concentration increased from approximately 250 nM (untreated) to 460 nM in the setting of nebivolol and increasing doses of ramiprilat.

There were similar results after chronic treatment with enalapril (0 to 10 μM) followed by treatment with nebivolol (1 μM).

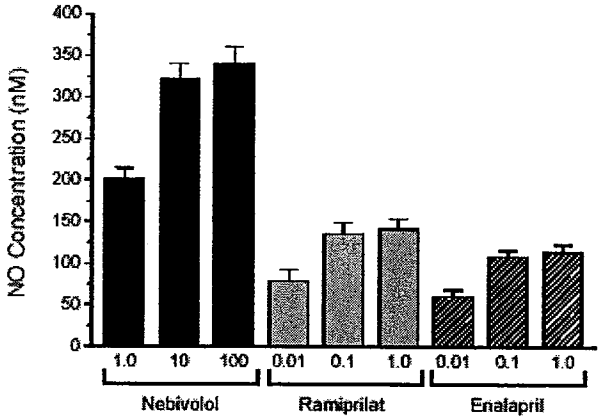
Conclusions: Following stimulation with acetylcholine (1 μM) or calcium ionophore (1 μM) after chronic treatment with nebivolol (0.01 to 10 μM), peak nitric oxide release increased in both Black and Caucasian HUVEC preparations. After chronic treatment with ramiprilat or enalapril, following stimulation with nebivolol (1 μM), there was a concentration dependent increase in nitric oxide release in both Black and Caucasian HUVEC preparations. Although at baseline, nitric oxide release was less in Black compared with Caucasian endothelial donors, following treatment with nebivolol or following ramiprilat or enalapril in combination with nebivolol, peak nitric oxide release in Black donors exceeded that seen in Caucasian donors.

1.7 Report Number: 1269_01_00. ("Separate and Combined Effects of Nebivolol and ACE-Inhibitors on Human Endothelial Cell Nitric Oxide Release following Acute Treatment") (August 5, 2002) (Reviewer: Karen A. Hicks, M.D.)

Study 1269.01.00 examined peak nitric oxide release from HUVEC following acute treatment with nebivolol, ramiprilat, or enalapril. The study showed that nebivolol in

doses ranging from 1.0 to 100 μM and ramiprilat or enalapril, in doses ranging from 0.01 to 1.0 μM acutely increased nitric oxide release from HUVEC. Doses of ramiprilat or enalapril greater than 1.0 μM, were not studied. Figure 13 shows the acute treatment effects of these agents.

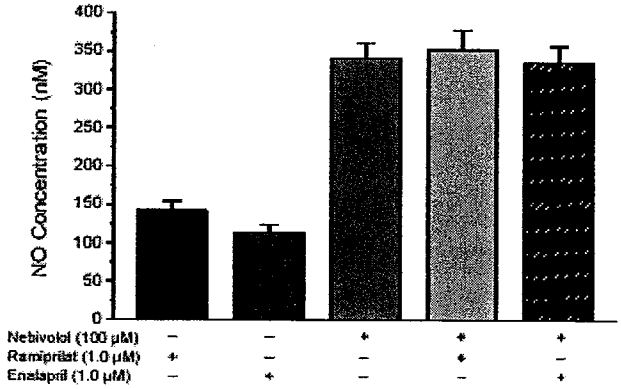
Figure 13. Effects of Acute Treatment with Nebivolol, Ramiprilat, and Enalapril on Peak Nitric Oxide Release from Human Endothelial Cells



(Reproduced from Sponsor, Study 1269.01.00, Figure 1, page 8)

The study also examined the individual and combined effects of nebivolol, ramiprilat, and enalapril following acute treatment. As seen in Figure 14, when either ramiprilat or enalapril were acutely administered with nebivolol, there was no significant increase in peak NO release from HUVEC, compared with nebivolol alone. Higher doses of ramiprilat or enalapril were not studied.

Figure 14. Separate and Combined Effects of Acute Treatment with Nebivolol and ACE Inhibitors on Peak NO Release from Human Endothelial Cells



(Reproduced from Sponsor, Study 1269.01.00, Figure 2, page 9)

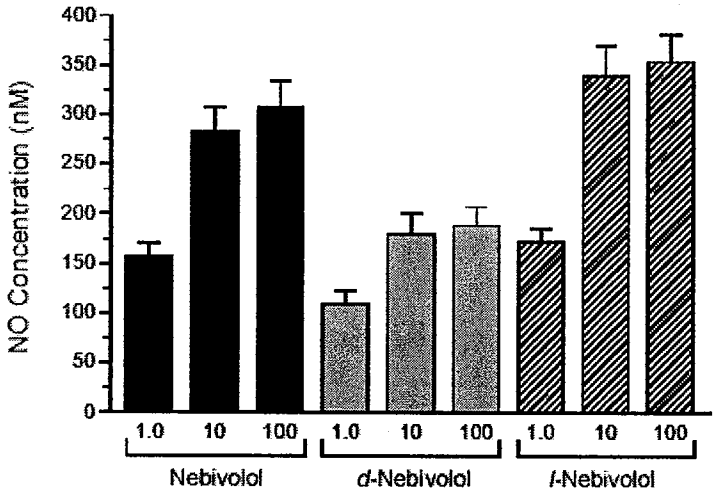
Conclusion: Acute treatment with nebivolol (1.0 to 100 μM), ramiprilat (0.01 to 1.0 μM), or enalapril (0.01 to 1.0 μM), increased peak NO release from HUVEC. Acute treatment with nebivolol, in combination with either ramiprilat or enalapril, however, did not significantly enhance peak NO release from HUVEC compared with nebivolol alone.

1.8 Report Number: 1268_01_00. ("Effects of Acute Nebivolol Treatment on Nitric Oxide Release and Vascular Function in Normal versus Diseased Mesenteric Arteries") (September 2, 2002) (Reviewer: Karen A. Hicks, M.D.)

Study 1269.01.00 examined the effect of nebivolol and its enantiomers on nitric oxide release from small resistance mesenteric arteries from both normotensive Wistar-Kyoto (WKY) and stroke-prone spontaneously hypertensive (SHR) rats. The investigator compared these results to peak nitric oxide release seen in WKY and SHR rats after administration of 1.0 μM of acetylcholine, a concentration which produces maximal NO release, and after administration of a calcium ionophore (1.0 μM). The calcium ionophore increases intracellular calcium through a receptor independent mechanism. After calcium binds to calmodulin, the complex serves as an essential co-factor to activate endothelial nitric oxide synthase (eNOS).

In control WKY rats, maximum NO release following acute treatment with *d*-nebivolol, *l*-nebivolol, and the nebivolol racemate in concentrations of 1.0 to 100 μM was 180 nM, 340 nM, and 280 nM, respectively, suggesting *l*-nebivolol was the most potent. The result for the WKY rats are shown in Figure 15.

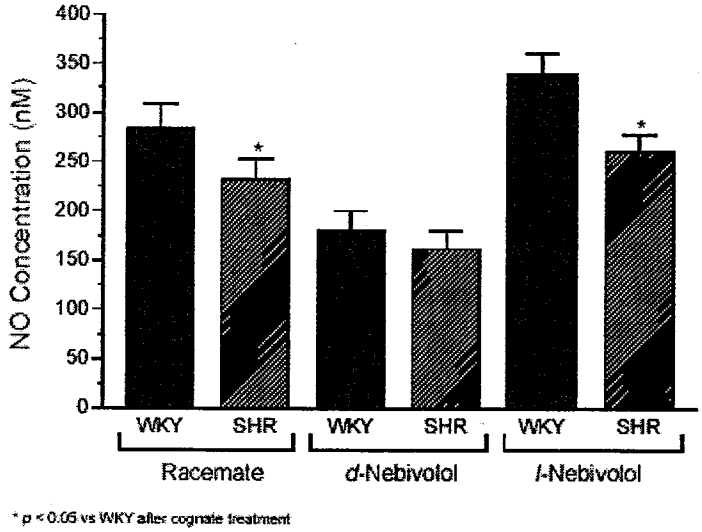
Figure 15. Effects of Nebivolol and Its Enantiomers (1, 10, and 100 μM) on NO Release from Endothelium-Intact WKY Rats



(Reproduced from Sponsor, Report Number 1268.01.00, Figure 1, page 9)

In SHR arteries, maximum NO release after acute treatment with *d*-nebivolol, *l*-nebivolol, and the nebivolol racemate was 160 nM, 260 nM, and 230 nM, respectively, also suggesting *l*-nebivolol was the most potent. The SHR results, compared with the WKY results, are shown in Figure 16 below.

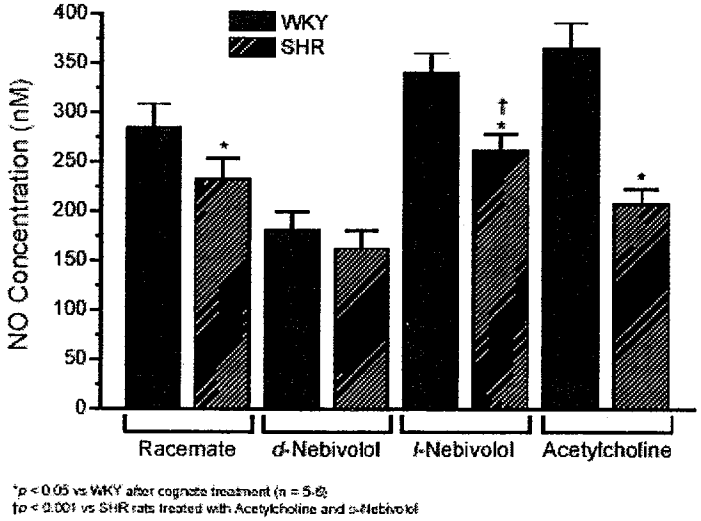
Figure 16. Effects of Nebivolol and Its Enantiomers (10 μM) on NO Release from Arteries of WKY and SHR Rats



(Reproduced from Sponsor, report Number 1268.01.00, Figure 2, page 10)

Peak NO release in WKY rat mesenteric arteries following acute treatment with 1.0 μM of acetylcholine was similar to that seen inWKY rat mesenteric arteries following acute treatment with *l*-nebivolol. In SHR rats, however, peak NO release following acute treatment with *l*-nebivolol was greater than that seen following acute treatment with acetylcholine (260 nM vs. 200 nM, respectively). The effects of nebivolol, nebivolol enantiomers, and acetylcholine on NO release are shown in Figure 17 below.

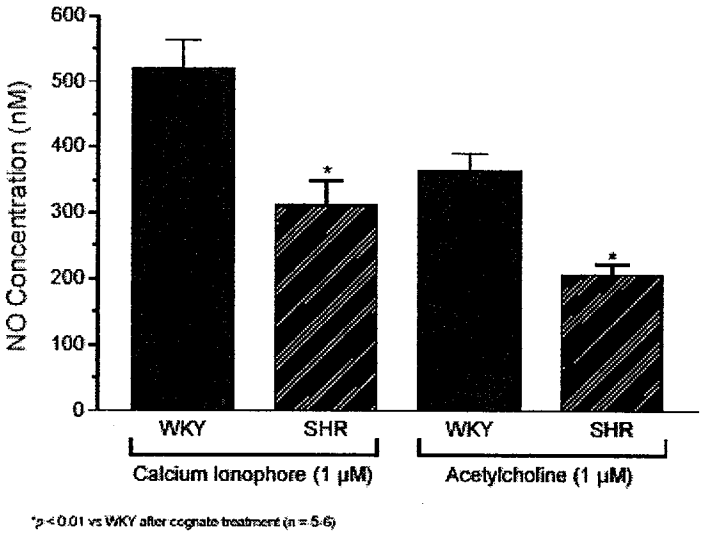
Figure 17. Effects of Nebivolol (10 M), Nebivolol Enantiomers (10 μM), and Acetylcholine (1 μM) on NO Release from Endothelium-Intact Rat Arteries



(Reproduced from Sponsor, Report Number 1268.01.00, Figure 3, page 11)

Following acute treatment with a calcium ionophore (1 μM), peak NO release was 40% less in SHR arteries, compared with WKY arteries, as seen in Figure 18 below.

Figure 18. Effects of Calcium Ionophore and Acetylcholine (1 μM) on NO Release from Endothelium-Intact Rat Arteries



(Reproduced from Sponsor, Study 1268.01.00, Figure 4, page 12)

Conclusions: Acute treatment with nebivolol and its enantiomers increased peak nitric oxide release in WKY and SHR small (200μM) resistance arteries. *l*-Nebivolol appeared to be the most potent stimulator of nitric oxide release at the doses tested. Nitric oxide release was greater in WKY compared with SHR arteries. In SHR arteries, peak nitric oxide release was reduced following acute treatment with nebivolol, nebivolol enantiomers, acetylcholine, and a calcium ionophore. At the doses tested, acute treatment with *l*-nebivolol resulted in a greater release of nitric oxide than acetylcholine in the SHR model.

1.9 Report Number: 1312_01_00. ("Adrenergic Receptor Pharmacology of Nebivolol in the Human Heart") (February 9, 2004) (Reviewer: Karen A. Hicks, M.D.)

In Report 1312.01.00, Bristow and colleagues examined the $ß_1/ß_2$ binding selectivity of nebivolol, as there had been discrepancies in the literature regarding the extent of selectivity (Bristow 2004). Bristow previously found nebivolol had a 183 fold higher affinity for human cardiac $ß_1$ adrenergic receptors compared with $ß_2$ receptors. In Bohm's laboratory (Bohm 2001) and in Schwinger's laboratory (Schwinger 2001), however, the ß1/ß2 selectivity was only 3-4 fold and 41 fold, respectively.

In this study, Bristow and colleagues used a longer incubation time (4 hours vs. the previous 2 hours) and a higher assay volume (450 μL vs. the previous 250 μL) than studies performed in other laboratories to determine if the prior studies were performed at steady-state conditions and were affected by radioligand or cold ligand depletion.

Using a high-yield crude membrane preparation from a 5 gram aliquot of freshly explanted left ventricular myocardium, Bristow examined beta adrenergic selectivity with a nonselective radioligand ^{125}[I]CYP (^{125}Iodocyanopindolol) assay in the presence or absence of nebivolol. Bristow studied different concentrations of nebivolol. Donor myocardium was obtained from 5 nonfailing heart donors (2 females, 3 males; average age 54 years) and 5 end-stage dilated cardiomyopathy transplant recipients (1 female, 4 males; average age 58 years; 3 idiopathic dilated cardiomyopathies; and 2 ischemic cardiomyopathies).

Bristow found the β_1 selectivity increased as the incubation time increased from 2 to 4 hours. Table 4 below shows the difference in $\beta_1\beta_2$ selectivity at the two incubation times.

Table 4. Data Summary of Nebivolol Binding Constants with Incubations at 2 and 4 Hours

Incubation Time	Nebivolol $K_H(\beta_1)$ (n = 10)	Nebivolol $K_L(\beta_2)$ (n = 10)	β_1/β_2 Selectivity
2 Hrs	0.79±0.24	137±37	202±93
4 hrs	0.70±0.10	225±28	*352±37

K_is are in nM ± SE): *, $p < .05$ vs. 2 hours

(Reproduced from Bristow, 2004, Report Number 1312.01.00, Table 1, page 10)

Bristow compared the binding parameters of numerous other beta-blockers, incubated at two hours, to that seen with nebivolol after four hours of incubation. Table 5 shows the various binding parameters of these beta-blockers.

Table 5. Binding Parameters (K_i) for Multiple ß-Blocking Agents in Human Cardiac Membranes

Compound	n	$K_H(\beta_1)$ nM	$K_L(\beta_2)$ nM	β_1/β_2 Selectivity
propranolol	18	3.63±0.64	3.63±0.64	1.0
bucindolol	§5	2.35±0.62	2.35±0.62	1.0
carvedilol	§7	3.84±1.22	3.84±1.22	1.0
betaxolol	23	6.19±0.92	*576±172	93
metoprolol	12	43.0±18.0	*3186±1400	67.8±17.8
bisoprolol	6	36.5±22.7	*3751±2142	103
celiprolol	§12	120±24	*8292±2862	69
nebivolol	10	0.70±.10	*225±28	†352±37

K_H = high affinity binding site. High affinity sites assumed to be β_1 receptor sites.
K_L = low affinity binding site. Low affinity sites assumed to be β_2 receptor sites.
*, $p < .05$ vs. K_L; †, $p < .05$ vs. nebivolol. ‡, $p < .05$ vs. metoprolol §, binding performed in the presence of Gpp(NH)p to eliminate agonist binding, 1 site fit curves only

(Reproduced from Bristow, 2004, Report Number 1312.01.00, Table 2, page 10)

To determine α_1-adrenergic receptor binding of nebivolol, Bristow evaluated nebivolol's ability to displace ^{125}[I]BE 2254 binding from human cardiac membranes after two hours of incubation. According to Bristow, after 2 hours of incubation ^{125}[I]BE 2254 binding becomes unstable. Nebivolol had a Ki of 330 nM for α_{1c} adrenergic receptors in the human heart, consistent with a weak affinity.

Conclusions: Bristow determined a 4 hour (240 minutes) incubation of nebivolol was necessary to achieve steady state, and low assay volumes (250 µL) identified only a single class of binding sites with similar affinity to the $ß_2$ receptor.

Bristow concluded nebivolol was highly $ß_1$ selective. According to Bristow, nebivolol had a 352 fold higher affinity for human cardiac $ß_1$ versus $ß_2$–adrenergic receptors and a $ß_1α_1$ selectivity exceeding 400 fold. Additionally, Bristow stated nebivolol had a higher selectivity than all other beta-adrenergic blockers currently in clinical use, but he compared binding data for other beta-blockers incubated for only two hours to nebivolol incubated at four hours. Bristow stated the other beta blockers took only two hours to reach steady state.

1.10 Report Number 1311_01_00. ("Adrenergic Receptor Pharmacology of Nebivolol, Its Enantiomers and Nine Metabolites in the Human Heart") (February 9, 2004) (Reviewer: Karen A. Hicks, M.D.)

Study 1311.01.00 used a high-yield crude membrane preparation from a 5 gram LV free wall aliquot from 4 end stage heart failure patients with left ventricular ejection fractions less than 25% undergoing transplantation (2 idiopathic dilated cardiomyopathies and 2 ischemic cardiomyopathies). Nonselective radioligand ^{125}[I]-ICYP (^{125}Iodocyanopindolol) in the presence or absence of varying nebivolol isomer or metabolite concentrations following 4 hours of incubation evaluated the beta selectivity of nebivolol and nine of its metabolites. The nine metabolites included N-dealkylated amino alcohol, 4-hydroxy nebivolol, 5-hydroxy nebivolol, 8-hydroxy nebivolol, N-dealkylated diol, N-dealkylated carboxylic acid, 4-hydroxy-5-phenol nebivolol, 4-hydroxy-8-phenol nebivolol, and nebivolol glucuronides. *d*-Nebivolol, *l*-nebivolol, and racemic nebivolol were also studied. The results of the nonselective radioligand assay are shown in Table 6.

Table 6. Summary of K_i Values for All Compounds in the Nebivolol Series

Compound	# Experiments	# Binding Sites	K_H ($β_1$ if 2 site fit)	K_L ($β_2$ if 2 site fit)
N-dealkylated amino alcohol	2	1, low affinity	–	$1.43x10^{-6}$M
4-hydroxy nebivolol	4	2	$6.81x10^{-10}$M	$1.01x10^{-7}$M
5-hydroxy nebivolol	4	2	$9.72x10^{-10}$M	$5.09x10^{-8}$M
8-hydroxy nebivolol	5	2	$4.52x10^{-9}$M	$3.06x10^{-7}$M
N-dealkylated diol	3	1, low affinity	–	$1.08x10^{-6}$M
N-dealkylated carboxylic acid	1	1, low affinity	–	$1.61x10^{-6}$M
4-hydroxy-5-phenol nebivolol	4	(2) 1 site (2) 2 sites	- $5.65x10^{-9}$M	$5.02x10^{-7}$M $6.79x10^{-8}$M
4-hydroxy-8-phenol nebivolol	4	2	$1.98x10^{-9}$M	$3.97x10^{-7}$M
Nebivolol glucuronides	4	2	$1.05x10^{-9}$M	$5.80x10^{-7}$M
Nebivolol	10	2	$7.00x10^{-10}$M	$2.25x10^{-7}$M
d-Nebivolol	4	2	$4.01x10^{-10}$M	$1.01x10^{-7}$M
l-Nebivolol	4	1	-	$7.15x10^{-7}$M

K_H = high affinity binding site. High affinity sites assumed to be $β_1$ receptor sites.
K_L = low affinity binding site. Low affinity sites assumed to be $β_2$ receptor sites.

(Reproduced from Bristow, Report Number 1311.01.00, Table 1, page 19)

Four nebivolol metabolites had a nanomolar or subnanomolar affinity for the β_1 adrenergic receptor, similar to the nebivolol racemate. These four metabolites were 4-hydroxy nebivolol, 5-hydroxy nebivolol, 8-hydroxy nebivolol, and 4-hydroxy-5-phenol nebivolol. Four-hydroxy nebivolol had a β_1 versus β_2 receptor selectivity exceeding 100 fold, while, 5-hydroxy nebivolol and 8-hydroxy nebivolol had selectivities exceeding 50 fold.

The study also showed *d*-nebivolol and racemic nebivolol had β_1 versus β_2 selectivity of 250 and 320 fold, respectively. The investigator accounted for the higher β_1 selectivity of the racemate by stating *l*-nebivolol had a weak affinity for the receptor. In the *in vivo* competition assays with the nebivolol racemate, *l*-nebivolol would bind to the β_2 site. According to the investigator, based on the assumption that the *l*-isomer did not actually bind to β_2-receptors, the presumed $\beta_1\beta_2$ selectivity for racemic nebivolol is probably 250 fold, as opposed to 320 fold.

Conclusions: Four nebivolol metabolites had β_1 versus β_2-adrenergic receptor selectivity exceeding 50 fold.

1.11 LMD No. 59897. ("Response to Isoprenaline after a Single Intravenous and Oral Application of Nebivolol: Time Course. Clinical Research Report. January 1988") (Reviewer: Karen A. Hicks, M.D.)

Study report only. No protocol available for review. Investigators in the Netherlands performed this open label, non-placebo controlled study in healthy volunteers in 1987. Six normotensive volunteers were assigned to three single-dose groups: nebivolol 1.5 mg IV, nebivolol 5 mg IV, and nebivolol 5 mg po. After volunteers rested supinely for 1 hour, investigators administered a 1 µg bolus of isoprenaline 5, 10, 20, 30, 40, and 50 minutes prior to and 1, 1.25, 1.5, 2, 3, 4.5, 6, and 8 hours following nebivolol. Investigators recorded subsequent blood pressures and heart rates over a 360 minute time period, following 15 minutes of supine rest.

Nebivolol 5 mg IV appeared to better suppress the isoprenaline-induced increase in heart rate, compared with nebivolol 1.5 mg IV. In both doses, there seemed to be a suppression of heart rate at two time points: 30 minutes and 3-5 hours. After oral nebivolol administration, heart rate appeared to be suppressed at approximately 4 to 5 hours. Only half of the volunteers participated in both the IV and PO portions of this study. Mean arterial pressure (MAP) appeared to be slightly more decreased after the 5 mg intravenous nebivolol dose, compared with the 1.5 mg intravenous dose.

Conclusions: I cannot draw any firm conclusions from this study report. Nebivolol appears to affect heart rate and blood pressure, but there was no control group for comparison.

1.12 LMD No. 59988. Study ID NED-6. ("Isoprenaline Dose-Response in Man After a Single 5 mg Intravenous Dose of Nebivolol and After Oral Application of Nebivolol 5 mg Once Daily for One Week. Clinical Research Report NEB-NED-6. February 1988") (Trial Period: June 18, 1987 – November 25, 1987) (Reviewer: Karen A. Hicks, M.D.)

Study report only. No protocol submitted for review. This open-label non placebo-controlled study was performed in the Netherlands in 1987. This study evaluated 9 normotensive volunteers receiving nebivolol 5 mg IV and 10 normotensive volunteers receiving oral nebivolol 5 mg daily for one week. Investigators monitored heart rate and blood pressure in response to intravenous injections of isoprenaline. Investigators administered isoprenaline in increasing doses (0.25, 0.5, 1, 2, 4, 8 μg). When the difference between peak heart rate after injection of isoprenaline and heart rate prior to injection was more than 30 bpm, no additional doses of isoprenaline were administered.

Thirty minutes following a single 5 mg IV dose of nebivolol, twice the dose of isoprenaline was required to increase heart rate to the same extent as prior to nebivolol administration. The dose ratio four hours post IV nebivolol was identical to the dose ratio at 30 minutes.

Four hours after the last 5 mg oral dose given daily for one week, the dose ratio averaged 2.5 and the ability to block beta receptors appeared to be higher than after IV dosing.

Conclusions: IV and PO nebivolol appear to affect heart rate. There was no placebo group for comparison.

1.13 LMD No. 84265. Study ID GBR-20. ("Clinical Pharmacology of Nebivolol (Drug Investigation; 3 (suppl. 1): 31-32, 1991)") (Trial Period: 1988-1989) (Reviewer: Karen A. Hicks, M.D.)

This journal article, published in 1991, provided results from two studies. No protocols were submitted for review. The first study was a randomized, double blind study in twelve healthy volunteers who received single oral doses of nebivolol 2.5, 5, and 10 mg, atenolol 50 mg, propranolol 40 mg, and placebo at weekly intervals. The study measured resting, standing, and exercise heart rate, blood pressure, and cardiac output (by an acetylene rebreathing technique) at 0, 1, 2, 4, 8, 24, and 48 hours following study drug. All active treatments affected heart rate. For nebivolol 2.5, 5, and 10 mg, the maximum percentage inhibition of exercise tachycardia was 9.6, 14.5, and 17.4%, respectively. For atenolol 50 mg and propranolol 40 mg, the maximum percentage inhibition of exercise tachycardia was 24.2% and 18.9%, respectively. At 48 hours, nebivolol was the only active drug studied that inhibited exercise tachycardia. All active treatments lowered standing diastolic blood pressure. All active treatments reduced postexercise cardiac index except nebivolol 5 mg. At 2 and 4 hours postexercise, the difference in cardiac index between nebivolol and atenolol was statistically significant. During these time points, atenolol reduced cardiac index by 22% and 15.7%, respectively.

Study two was a randomized double-blind placebo-controlled trial in 12 normal subjects to evaluate $ß_1$ and $ß_2$ adrenergic receptor blocking activity. No protocol was submitted for review. Following incremental isoprenaline infusions aiming to increase heart rate by 25 bpm (I_{25}), investigators measured changes in heart rate, systolic and diastolic blood pressure, finger tremor, and cardiac output. Investigators determined the dose of isoprenaline required to increase finger tremor by 500% (IT_{500}) and to increase calf blood flow by 50% (IF_{50}). At weekly intervals, subjects received the same drugs and dosages previously mentioned in study one. Investigators calculated individual dose-response curves and dose ratios. Following the isoprenaline infusion, subjects underwent routine stress testing. Nebivolol had the lowest dose ratios for finger tremor and calf blood flow, as seen in Table 7 below.

Table 7. Isoprenaline (Isoproterenol) Dose Ratios for ß-Adrenoceptor Antagonists

	Nebivolol			Atenolol 50mg	Propranolol 40mg
	5mg	10mg	20mg		
IT_{500}	1	1.2	2	3.6	13.9
IF_{50}	1.9	4	5	6.3	8.6

Abbreviations: IT_{500} = dose of isoprenaline required to increase finger tremor by 500%; IF_{50} = dose of isoprenaline required to increase calf blood flow by 50%.

(Reproduced from McLay JS, N Irvine, DG McDevitt, Clinical Pharmacology of Nebivolol, Short Communication, 1991, First International Nebivolol Investigators' Meeting, Antwerp, Belgium, September 13-15, 1990, Drug Investigation 3(supplement 1):31-32)

Nebivolol 5, 10, and 20 mg inhibited exercise tachycardia by 5%, 13.1%, and 16.4%, respectively. Atenolol and propranolol inhibited exercise tachycardia by 20.9% and 12.3%, respectively.

LMD No. 92890. Study ID GBR-20. ("A Comparative Study of the Relative Beta-Blocking Potency, and Beta-1 Selectivity of Nebivolol, Propranolol, and Atenolol in Healthy Volunteers") (Reviewer: Karen A. Hicks, M.D.)

In this Phase II randomized, placebo-controlled, single dose, single blind crossover study in 10 male volunteers, investigators assessed heart rate, blood pressure, finger tremor, calf blood flow, and cardiac output at rest and during exercise both during and following isoprenaline infusion. No protocol was submitted. Only a study report was available for review. Subjects were healthy volunteers, ages 18-40 years. Subjects received single doses of nebivolol 5, 10, or 20 mg, propranolol 40 mg, atenolol 50 mg, and placebo separated weekly.

Investigators obtained resting vital signs in the supine and standing positions and used a piezo resistive accelerometer attached to the dorsal surface of the distal phalynx to measure finger tremor in ten second intervals. Subjects followed the acetylene rebreathing method for determination of cardiac output. Exercise consisted of subjects stepping on and off a box 46 cm high to achieve 30 steps/minute for 3 minutes.

Investigators measured heart rate (supine/standing), blood pressure (supine/standing), calf blood flow, finger tremor, cardiac output, Borg Score, VAS for fatigue and breathlessness, and adverse events at 2.5 hours post-dose in the control period, during the isoprenaline infusion (1-20 mcg/min IV for 10 minutes), and during the exercise test phase 4.5 hours post dose. With the isoprenaline infusion, investigators sought to increase the heart rate and blood pressure by 50 beats/minute and 50 mm Hg, respectively.

Statistical methods included an analysis of variance for a cross-over design, linear regression analyses, and dose response slope comparison.

For all parameters, investigators constructed a log dose-response curve of isoprenaline dose versus effect. Beta-1 receptor blockade was reflected by the ability of nebivolol to inhibit exercise-induced tachycardia. Beta-2 receptor blockade was estimated by shifts in the dose response curves for both finger tremor and calf blood flow.

Results: The mean age of the male volunteers was 25.1 years, with a range from 20.0 to 38.0. Investigators recorded supine resting vital signs every 5 minutes from 2 hours 30 minutes to 3 hours post dose. Nebivolol 10 and 20 mg, propranolol 40 mg, and atenolol 50 mg significantly reduced resting heart rate and systolic blood pressure ($p < 0.05$). For nebivolol 10 mg, propranolol 40 mg, and atenolol 50 mg, mean resting heart rate was reduced by -5.4 bpm, -6.4 bpm, and -3.5 bpm, respectively, and systolic blood pressure was reduced by 5.0 mm Hg, 7.2 mm Hg, and 6.6 mm Hg, respectively. Nebivolol 20 mg reduced systolic blood pressure by 4.8 mm Hg. Diastolic blood pressure, cardiac output, finger tremor, and calf blood flow at rest were not significantly changed during this time period.

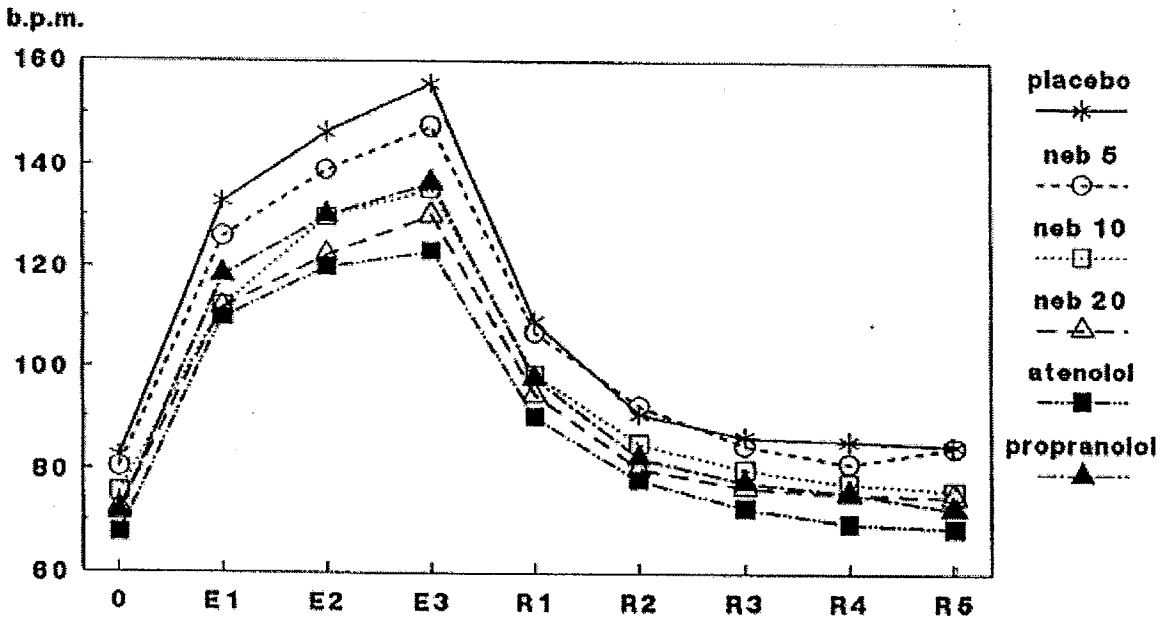
Investigators performed an isoprenaline infusion at 1-20 mcg/min IV for 10 minutes at approximately 3 hours post-dose. During isoprenaline infusion, there was a good correlation for heart rate ($r^2 = 0.58 – 0.80$), a moderate correlation for systolic pressure ($r^2 = 0.20 – 0.73$) and finger tremor ($r^2 = 0.31 – 0.43$), and a poor correlation for cardiac index ($r^2 = 0.19 – 0.35$), calf blood flow ($r^2 = 0 – 0.21$), and diastolic blood pressure ($r^2 = 0.02 – 0.1$). For heart rate, nebivolol 20 mg, atenolol, and propranolol had significantly different slopes from placebo, consistent with non-parallel shifts of the dose-response curve to the right. Nebivolol 5 and 10 mg, however, shifted the curve to the right in a parallel fashion, reflecting competitive beta receptor antagonism. For systolic blood pressure, all active treatments shifted the curve to the right in a parallel fashion. For finger tremor, propranolol was unique in shifting the dose-response curve to the right in a non parallel fashion, consistent with $ß_2$ receptor antagonism.

Following isoprenaline infusion at approximately 4 hours 30 minutes post-dose, investigators measured heart rate and blood pressure.. In the placebo group, heart rate increased from 9.2 bpm in the supine position to 25.4 bpm in the standing position after isoprenaline. Nebivolol 20 mg, atenolol, and propranolol compared with placebo significantly decreased heart rate following isoprenaline in both supine and standing positions ($p < 0.03$). Nebivolol had a dose-related effect on standing heart rate.

Nebivolol 10 mg and atenolol significantly decreased ($p < 0.05$) systolic blood pressure in the supine position, when compared with placebo. There were no significant differences in cardiac output and stroke work.

Subjects performed three minutes of standardized exercise at approximately 4 hours 30 minutes post-dose. Following standardized exercise, all active treatments significantly reduced heart rate ($p < 0.02$). Nebivolol had a dose-dependent effect on exercise heart rate. Nebivolol 5 mg, 10 mg, and 20 mg, reduced exercise heart rate by 5%, 13.1%, and 16.4%. Atenolol and propranolol decreased exercise heart rate by 20.9% and 12.3%, respectively, as seen in Figure 19.

Figure 19. Exercise Heart Rate



(Reproduced from Sponsor, LMD No. 92890, GBR-20, Figure 13, page 22)

At five minutes of recovery, all active treatments except for nebivolol 5 mg continued to significantly affect heart rate ($p < 0.01$).

There were no subject drop-outs in this study. By the study account, subjects did not report any adverse events.

More patients on propranolol noted sleepiness, but the difference was not statistically significant.

Conclusions: Nebivolol 10 mg and 20 mg, propranolol 40 mg, and atenolol 50 mg decreased resting heart rate and systolic blood pressure. All active treatments shifted isoprenaline dose response curves for heart rate and systolic blood pressure to the right, consistent with ß adrenergic receptor blockade. Only propranolol shifted the dose response curve to isoprenaline for finger tremor to the right, consistent with $ß_2$ receptor antagonism.

Compared with placebo, all active treatments reduced exercise heart rate, consistent with ß1 blockade. Nebivolol 20 mg, atenolol 40 mg, and propranolol 40 mg reduced exercise tachycardia by 16.4%, 20.9%, and 12.3%, respectively.

LMD No. 106646. Study ID GBR-20. ("A Comparative Study of the Potency and Relative Beta-1 Selectivity of Nebivolol, Propranolol, and Atenolol in a Group of Healthy Volunteers. Clinical Research Report NEB-GBR-20, May 1994") (Trial Period 1988-1989) (Reviewer: Karen A. Hicks, M.D.)

Same study report as LMD No. 92890.

1.14 LMD No. 108078. Study ID BEL-20. ("Determination of the Acute and Subacute Beta-Sympathicolytic Activity of *d*-, *l*-, and *d,l* Nebivolol Compared to Atenolol and Placebo, in Inhibiting Exercise-Induced Tachycardia. Synoptic Clinical Research Report NEB-BEL-20. April 1994") (Trial Period: March 31, 1989 – January 23, 1990) (Reviewer: Karen A. Hicks, M.D.)

Study report only. No protocol was available for review. This Phase II double-blind, placebo controlled, 7-way crossover trial evaluated 14 healthy male volunteers over 18 years of age. Subjects received placebo or a single dose of nebivolol 2.5 mg, 5 mg, 10 mg, *l*-nebivolol 2.5 mg, *d*-nebivolol 2.5 mg, or atenolol 50 mg, with a wash-out period of at least 7 days between doses. Investigators measured heart rate, systolic blood pressure, and systolic time intervals on Day 1 (0 and 3 hours), Day 2 (0 hours), Day 7 (3 hours), and Day 8 (0 hours). An electrocardiogram was performed on Days 0, 1, 2, 7, and 8 at the hours indicated above. An exercise test was performed on Days 1, 2, 7, and 8 at the same time.

The investigators analyzed the data using ANOVA-model for a 7-way cross-over, with Duncan's multiple range test.

There were no significant electrocardiographic effects. Adverse events increased with increasing nebivolol doses. Nebivolol 10 mg had 6 subjects with adverse events, compared with 7 subjects each for *l*-nebivolol 2.5 mg and *d*-nebivolol 2.5 mg. Atenolol also had 7 subjects with adverse events. There were no deaths in this study.

Efficacy results are listed in Table 8.

Table 8. Summary of Results (BEL-20)

Effectiveness, mean (n = 14)	Baseline Day 1,0h	Day 1,3h (peak)	Day 2,0h (trough)	Day 7,3h (peak)	Day 8,0h (trough)
• At rest:					
- Heart rate, bpm					
neb 2.5 mg	72.2	71.0	68.1	64.0	65.6
neb 5 mg	71.3	69.0	64.6	61.2	63.8
neb 10 mg	70.9	65.3	60.9	58.9	61.7
l-neb 2.5 mg	72.9	71.5	62.6	56.9	59.4
d-neb 2.5 mg	70.5	77.7	68.4	71.8	74.5
atenolol	69.6	59.1	60.7	56.7	60.7
placebo	73.9	73.4	69.4	75.0	68.6
- Systolic blood pressure, mmHg					
neb 2.5 mg	130.4	128.1	122.4	122.9	128.6
neb 5 mg	128.6	126.5	123.2	121.6	126.4
neb 10 mg	130.9	119.6	120.4	119.1	121.9
l-neb 2.5 mg	125.5	125.4	123.8	122.1	122.3
d-neb 2.5 mg	127.1	132.6	125.4	128.3	127.4
atenolol	126.4	120.6	119.0	120.1	121.2
placebo	127.5	126.9	125.1	128.1	132.1
- Diastolic blood pressure, mmHg					
neb 2.5 mg	76.8	77.0	75.2	75.2	76.9
neb 5 mg	78.1	76.8	75.6	73.3	73.2
neb 10 mg	79.6	73.5	73.6	71.2	73.1
l-neb 2.5	77.5	79.0	76.5	78.2	76.7
d-neb 2.5	77.9	76.8	76.5	73.3	73.8
atenolol	76.9	71.9	73.1	71.3	73.1
placebo	78.0	76.1	76.9	76.9	79.4

(continued)

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Table 8. Summary of Results (BEL-20) (continued)

Effectiveness, mean	Baseline Day 1,0h	Day 1,3h (peak)	Day 2,0h (trough)	Day 7,3h (peak)	Day 8,0h (trough)
* At maximal exercise (9 min):					
- Heart rate, bpm					
neb 2.5 mg	144.7	139.6**	137.9**	129.2**	133.0*
neb 5 mg	149.0	135.3**	133.4*	125.1**	128.5*
neb 10 mg	144.6	126.0**	128.3*	117.4*	120.9**
l-neb 2.5 mg	144.3	145.8*	144.1*	143.1*	143.4*
d-neb 2.5 mg	145.0	134.3**	130.1*	121.9**	125.8**
atenolol	145.4	115.9	129.2	116.1	131.1
placebo	143.7	145.5	140.9	143.8	140.9
- Systolic blood pressure, mmHg					
neb 2.5 mg	167.9	161.8**	159.3*	158.9*	161.4
neb 5 mg	166.8	156.4**	160.4*	153.2*	159.6
neb 10 mg	168.9	152.9**	153.9*	152.1*	156.8*
l-neb 2.5 mg	170.7	166.1*	165.7*	164.6*	163.9
d-neb 2.5 mg	169.6	155.7*	158.6*	157.1*	160.0
atenolol	168.2	151.1	159.6	156.8	160.0
placebo	169.6	168.6	162.1	166.8	167.5
* Systolic time intervals					
- Pre-ejection phase (PEP), ms					
neb 2.5 mg	102.9	101.9	106.6	99.4	105.5
neb 5 mg	103.7	107.9	108.6	96.6	106.4
neb 10 mg	107.1	105.1	107.5	99.1	108.6
l-neb 2.5 mg	106.0	106.2	110.7	101.1	109.7
d-neb 2.5 mg	109.2	99.6	107.1	101.4	105.3
atenolol	103.6	108.7	107.9	100.1	105.6
placebo	104.1	102.1	112.7	97.9	109.8
- Left ventricular ejection time (LVET), ms					
neb 2.5 mg	306.4	304.9	313.3	316.1	314.1
neb 5 mg	307.9	303.4	315.6	319.9	319.5
neb 10 mg	308.7	311.2	317.1	321.4	324.9
l-neb 2.5 mg	304.5	301.3	314.9	316.2	322.2
d-neb 2.5 mg	309.9	301.4	306.4	301.9	304.7
atenolol	309.6	316.0	319.7	322.5	327.8
placebo	311.8	302.4	312.5	298.4	308.1
- PEP/LVET					
neb 2.5 mg	0.336	0.335	0.340	0.319	0.336
neb 5 mg	0.337	0.356	0.345	0.302	0.333**
neb 10 mg	0.347	0.338	0.340	0.309	0.336
l-neb 2.5 mg	0.348	0.353	0.352	0.320	0.341
d-neb 2.5 mg	0.354	0.333	0.351	0.336	0.346
atenolol	0.335	0.345	0.338	0.310	0.323
placebo	0.335	0.339	0.362	0.329	0.357
- Total electromechanical systole (QS2C), ms					
neb 2.5 mg	392.7	388.4	395.4	385.8	396.6
neb 5 mg	395.7	390.6	398.6	389.1	395.5
neb 10 mg	399.2	393.8	397.3	391.4	400.9
l-neb 2.5 mg	395.4	393.0	401.4	390.1	402.3
d-neb 2.5 mg	399.9	388.8	395.0	389.6	393.8
atenolol	394.9	396.9	396.9	390.2	403.6
placebo	397.3	388.3	402.7	384.9	397.6

* significant difference in shifts from placebo compared to atenolol at the 5% level

* significant difference in shifts from placebo between l-nebivolol 2.5 mg and d-nebivolol 2.5 mg or dl-nebivolol 5 mg

** significant difference in shifts from baseline between nebivolol 5 mg and placebo

(Reproduced from Sponsor, BEL-20, page 3)

Conclusions: Beta-blockade with racemic nebivolol was more profound following one week of therapy, compared with atenolol which had a significant beta-blocking effect after the initial dose. *l*-Nebivolol at maximal exercise did not appear to significantly affect heart rate, although resting heart rate following one week of therapy appeared to be significantly decreased, unless these data points were supposed to represent results for *d*-nebivolol.

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1.15 LMD No. 108084. Study ID NED-5. ("Time Course of Beta-Blockade with Nebivolol. Synoptic Clinical Research Report NEB-NED-5. January 1988") (Trial Period: March 17, 1987 – June 19, 1987) (Reviewer: Karen A. Hicks, M.D.)

Study report only. No protocol was available for review. This Phase I open label, dose finding trial in a total of 12 healthy male and female volunteers examined the effect of nebivolol on blood pressure and heart rate over 6 hours following an isoprenaline IV infusion (?1 µg or 1 mg). There was no placebo control group. 6 patients received three single doses of intravenous nebivolol 1.5 mg, intravenous nebivolol 5 mg, and oral nebivolol 5 mg, separated by at least 2 days.

Investigators recorded heart rate at 0, 5, 10, 20, 30, 40, and 50 minutes following isoprenaline, as well as blood pressure at 1, 1.25, 1.5, 2, 3, 4, 5, and 6 hours post dose.

The median age for the intravenous group was 22 (19-26) and for the oral group was 22 (19-25).

The investigator supplied limited results. According to the investigator, the beta-blocking effect, as seen by the inhibition of isoprenaline-induced tachycardia, was more pronounced with the 5 mg intravenous nebivolol dose, compared with the 1.5 mg intravenous dose. Following dosing, the author reported decrements in heart rate after ± 30 minutes and 3-5 hours following intravenous nebivolol 5.0 mg. The ± 30 minute decrement was reportedly not seen with oral nebivolol. The author stated blood pressure reduction was more pronounced with 5 mg intravenous nebivolol, compared with the 1.5 mg intravenous dose. The investigator did not provide data to support the blood pressure conclusions, and there was no placebo group for comparison.

The investigator stated there were no adverse events.

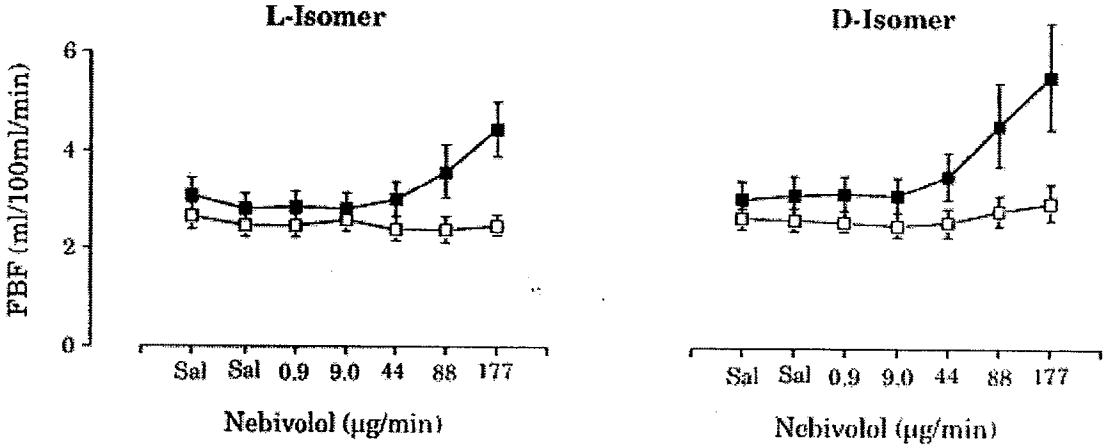
Conclusions: There was no control group in this study. Nebivolol may affect heart rate.

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

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

Both *l*- and *d*-nebivolol significantly increased blood flow in the infused arm, compared with a saline infusion, as seen in Figure 20. The formulation of the individual isomers, however, contained cyclodextrin, which could have affected the results.

Figure 20. Forearm Blood Flow with Nebivolol Isomers (GBR-29) (Mean +/- SE)



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

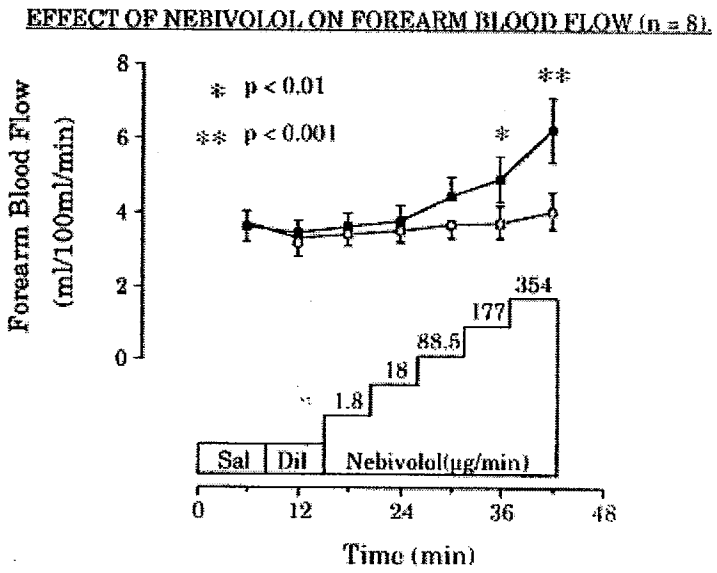
There were no drop-outs in this study. The investigator stated there were no adverse events and no significant changes in laboratory parameters. No laboratory data was available for review.

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

1.17 LMD No. 107421. Study ID GBR-23. ("A Study to Investigate the Possible Vasodilator Effect of Nebivolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-23") (Trial Period August 16, 1992 – August 27, 1992) (Reviewer: Karen A. Hicks, M.D.)

This Phase II open-label study in 8 healthy, non-smoking male volunteers aged 18 to 50 years evaluated the effect of nebivolol on forearm blood flow. Investigators administered a series of consecutive 6 minute infusions, consisting of intravenous nebivolol in concentrations ranging from 1.8 µg/min to 354 µg/min followed by a final intravenous sodium nitroprusside infusion at 3 µg/min. Nebivolol demonstrated a dose-dependent increase in forearm blood flow, as measured by venous occlusion plethysmography. The percent increase in forearm blood flow of 25.84 ($p < 0.01$)and 50.05% ($p < 0.001$) at 177 and 354 µg/min nebivolol was statistically significant. The percent change in forearm blood flow for sodium nitroprusside was 178.27. The mean ± SEM blood flow during saline, diluent, and nebivolol infusions are shown in Figure 21.

Figure 21. Effect of Nebivolol on Forearm Blood Flow (GBR-23) (Mean ± SEM)



(Reproduced from Sponsor, GBR-23, Figure 1, page 8)

There were no drop-outs in this study. One patient had one or more adverse events, but the type of adverse event was not indicated. The investigator stated there were no significant changes in laboratory parameters or ECGs, but this data was not provided for review.

Conclusions: At doses of 177 and 354 µg/min, nebivolol significantly increased forearm blood flow.

1.18 LMD No. 107422. GBR-25. ("A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-25") (Trial Period: January 18, 1993 – February 15, 1993) (Reviewer: Karen A. Hicks, M.D.)

This Phase II open-label crossover study in 9 healthy, non-smoking male volunteers, ages 18 to 50 years, examined the effect of nebivolol on forearm blood flow. On three study days, one week apart, subjects received a 12 minute infusion of nebivolol (354 µg/min), carbachol (0.2 µg/min), or sodium nitroprusside (1 µg/min) with coinfusion of L-NMMA (4 µmol/min) for the last 6 minutes. Sodium nitroprusside, carbachol, and nebivolol increased forearm blood flow, compared with saline (n=3). When L-NMMA was coadministered with these agents, the percentage change in forearm blood flow for sodium nitroprusside, carbachol, and nebivolol was -22%, -49%, and -65%, respectively, as seen in Figure 22.

Figure 22. Efficacy Findings (GBR-25)

Effectiveness (n = 3)	Sodium Nitroprusside	Carbachol	Nebivolol
Venous occlusion plethysmography Increase in forearm blood flow (ml/100ml/min) drug alone vs saline	5.7	3.9	2.2
Percentage change in forearm blood flow drug + L-NMMA vs drug alone	-22%	-49%*	-65%**
Secondary parameters None			

* = P < 0.05
** = P < 0.01, versus nitroprusside

(Reproduced from Sponsor, GBR-25, page 2)

Of the 9 male subjects, 1 discontinued the study due to "failure to respond to nebivolol." It is unclear how the investigator defined nebivolol failure. According to the study, subjects did not report any adverse events, and there were no clinically significant changes in laboratory or ECG parameters. The investigator did not present laboratory or ECG data for review.

Conclusions: Nebivolol, sodium nitroprusside, and carbachol increased forearm blood flow, compared with placebo, but the number of subjects evaluated was small. Concomitant administration of these agents with L-NMMA significantly reduced forearm blood flow with carbachol and nebivolol, suggesting the possible involvement of the L-arginine/nitric oxide pathway. The investigator could not exclude desensitization during the nebivolol infusion as an explanation for the above findings.

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

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

minutes of each 6 minute infusion. The regimen for the Study Visits is further described in Table 9.

Table 9. GBR-28 Drug Regimen

Treatment				
Form - intra-arterial				
Medication	Nebivolol 0.5 mg/ml	L-NMMA	L-arginine	Saline
Batch number	92F02/F7	209039 & 251060	212/62	1 ml/min
Dosage	354 µg/min	4 µmol/min	10 mg/min	
Duration	variable - as per protocol, 3 study days, 1 week apart. Visit 1 : Nebivolol for 6 minutes Visit 2 : L-arginine : min 1 - 18 co-infused with nebivolol : min 6 - 18 and L-NMMA : min 12 - 18 Visit 3 : Nebivolol : min 1 - 12 co-infused with L-NMMA : min 6 - 12			

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

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

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

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

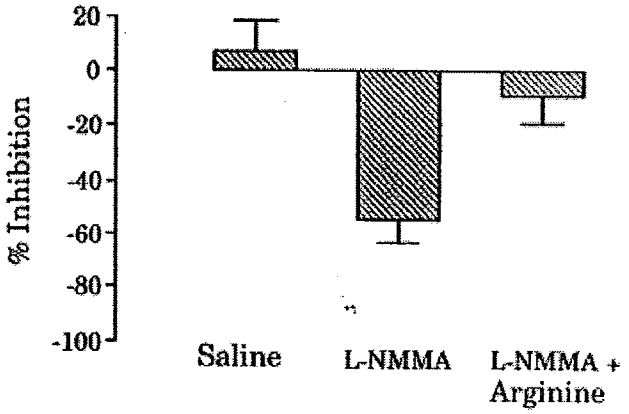
During all three study visits, nebivolol increased mean forearm blood flow following the 6 minute infusion. During Visit 1, nebivolol increased mean forearm blood flow from 3.80 ± 0.24 to 6.17 ± 0.36. During Visit 2, nebivolol increased mean forearm blood flow from 3.42 ± 0.46 (during L-arginine alone)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

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

During Visit 2, L-arginine almost completely counteracted the inhibitory effect of L-NMMA on nebivolol. At 6 minutes following an infusion of nebivolol with L-arginine,

the mean blood flow was 6.29 ± 0.68, compared with a blood flow of 6.09 ± 0.74 at 12 minutes during the nebivolol infusion with L-NMMA and L-arginine. The percentage inhibition of the nebivolol response at 6 and 12 minutes is summarized by the investigator in Figure 23.

Figure 23. Effect of L-Arginine and L-NMMA on Responses to Nebivolol During Visit 2 (GBR-28)



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

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

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

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

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

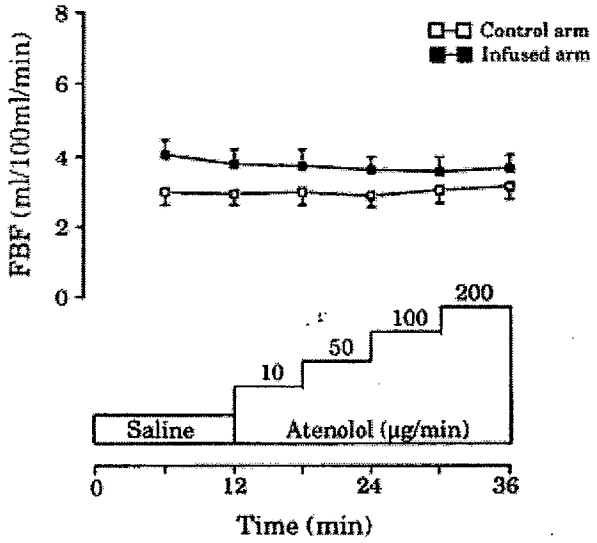
Table 10. GBR-27 Study Regimen

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

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

As seen in Figure 24, Atenolol had no significant effect on forearm blood flow.

Figure 24. Effect of Atenolol on Forearm Blood Flow (Mean ± SE) (GBR-27)



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

Nebivolol dose-dependently increased forearm blood flow, as show in Figure 25.

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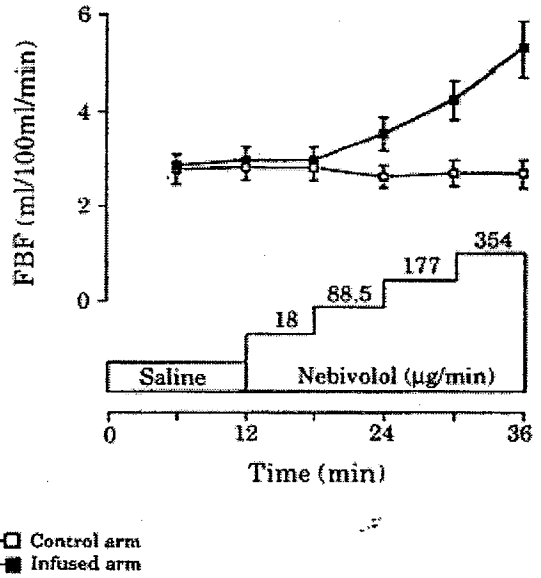
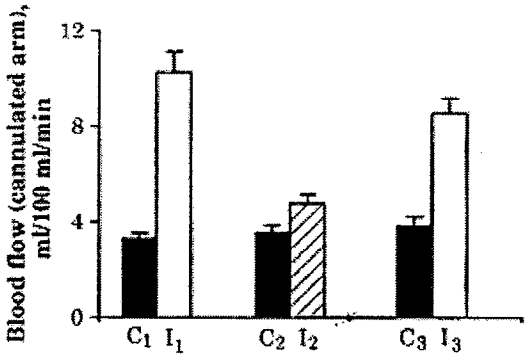
Figure 25. Effect of Nebivolol on Forearm Blood Flow (Mean ± SE) (GBR-27)



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

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

Figure 26. Saline Control (C) and Blood Flow During Isoprenaline (GBR-27) Before (I_1), During (I_2), and After (I_3) Atenolol



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

The percentage change in forearm blood flow, compared with saline, is shown in Table 11.

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Table 11. Efficacy Results (GBR-27)

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

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

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

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

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

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

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

The study drug dosages are shown in Table 12

Table 12. Medication Regimen (GBR-31)

Treatment			
Form - dosing route	Intra-aterial infusion into the brachial artery		
Medication	L - Nebivolol [RO85548 or placebo]	D - nebivolol [RO85547 or placebo]	DL - nebivolol [RO67555 or placebo]
Batch number	94EO9/F3 - active 95B13/F4-placebo	94EO6/F3 -active 95B13/F4-placebo	94E16/F7 -active 94E18/F8-placebo
Dosage (1l/min for 5 minutes each dose)	0.9l 9l 44.25l 88.5l 177l	0.9l 9l 44.25l 88.5l 177l	1.8l 18l 88.5l 177l 354l
Total Dosage for Study	1.6mg	1.6mg	3.35mg
Duration	30 minutes	30 minutes	30 minutes

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

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

Table 13 shows the schedule of evaluations and procedures for GBR-31.

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Table 13. Schedule of Evaluations/Procedures (GBR-31)

Treatment			
Form - dosing route	Intra-aterial infusion into the brachial artery		
Medication	L - Nebivolol [RO85548 or placebo]	D - nebivolol [RO85547 or placebo]	DL - nebivolol [RO67555 or placebo]
Batch number	94EO9/F3 - active 95B13/F4-placebo	94EO6/F3 -active 95B13/F4-placebo	94E16/F7 -active 94E18/F8-placebo
Dosage (1l/min for 5 minutes each dose)	0.9l 9l 44.25l 88.5l 177l	0.9l 9l 44.25l 88.5l 177l	1.8l 18l 88.5l 177l 354l
Total Dosage for Study	1.6mg	1.6mg	3.35mg
Duration	30 minutes	30 minutes	30 minutes
Disallowed medication	Any regular medication apart from paracetamol		

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

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

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

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

Efficacy results are shown in Table 15 and Table 15.

Table 14. Summary of Absolute Blood Flow Results (GBR-31)

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

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

Table 15. Efficacy Results (GBR-31)

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

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

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

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

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

1.22 LMD No. 101180. Study ID SWE-5. ("Nebivolol—Effects on Peripheral Arterial and Venous Blood Flow. Clinical Research Report NEB-SWE-5. November 1993") (Trial Dates: September 4, 1989 – June 28, 1990) (Reviewer: Karen A. Hicks, M.D.)

Objectives:
Primary: To determine the effect of nebivolol on peripheral arterial and venous blood flow, compared with placebo.
Secondary: To evaluate the antihypertensive effect of nebivolol in patients with uncomplicated essential hypertension.

Methods: This randomized, double blind, placebo-controlled crossover study in 15 hypertensive patients, ages 44 to 73 years, examined calf arterial and venous blood flow following a single dose of nebivolol 5 mg as well as four weeks of nebivolol 5 mg therapy. Patients underwent a 4-week run in, followed by two 4-week randomized

double blind periods in which they were treated with either placebo or nebivolol 5 mg, followed by a 5-week washout.

Uncomplicated essential hypertension was defined as "a diastolic blood pressure of at least 95 mm Hg but not higher than 110 mm Hg when not being treated for their hypertension."

At the time of inclusion, 6, 1, 1, 2, 2, and 3 patients were taking atenolol, metoprolol, a combination of metoprolol and hydrochlorothiazide, hydrochlorothiazide, enalapril, and no other medication, respectively.

There were nine study visits, and patients returned to the laboratory every two weeks for vital signs. Investigators performed plethysmographic measurements during Visits 3, 5, 7, and 9 prior to drug intake and 0.5, 1, 1.5, 2, 3, 4, 5, 6,12, and 24 hours post dose. Investigators determined plasma concentrations of *d*-nebivolol, *l*-nebivolol, and the hydroxylated metabolites by radioimmunoassay after the single 5 mg nebivolol dose and after the last 5 mg dose.

Exclusion Criteria

1. age < 40
2. pregnant women or women without adequate contraception or women with nursing children
3. previous intolerance to ß-adrenoceptor blockade
4. myocardial infarction or cerebrovascular attack within 6 months before start of the study
5. AV-block II or III or bundle branch blocks
6. congestive heart failure
7. obstructive lung disease
8. concomitant treatment with other drugs with cardiovascular effects which cannot be withdrawn prior to the study
9. alcohol or drug abuse or any other condition which may imply a bad compliance to the study procedures
10. extensive varicose veins or other signs of impaired venous function in the legs

Results: After the first dose, standing blood pressure was lower in the nebivolol group compared with placebo at three hours. On the first day, the blood pressure difference between nebivolol and placebo was statistically significant at 5 and 6 hours for supine and 4, 5, 6, and 24 hours for standing blood pressure. After the first dose, differences in heart rate between nebivolol and placebo were statistically significant at 5 and 12 hours for supine and 3.5, 4, 5, 6, 12, and 24 hours for standing heart rate.

After 1 month, treatment blood pressures were generally significantly lower in the nebivolol group compared with placebo, with the exceptions of 1 hour for supine diastolic blood pressure and 4 hours for standing systolic pressure. The difference in blood pressure between nebivolol and placebo was evident after two weeks of therapy.

After 1 month, treatment heart rate between nebivolol and placebo was statistically significant at all time points.

A summary of results is listed in Table 16.

Table 16. Main Features of the Trial Sample and Summary of the Results (SWE-5)

Effectiveness (n = number of patients with data)	Placebo (n = 15)	nebivolol (n = 15)
Primary parameters	mean ± SD (time(h))	mean ± SD (time(h))
• Arterial flow		
- Minimal - first dose	2.08 ± 0.72 (2)	2.12 ± 0.84 (2)
- Minimal - last dose	2.31 ± 1.24 (2)	2.72 ± 1.38 (2)
- Maximal - first dose	4.59 ± 1.60 (12)	3.68 ± 0.96 (12)
- Maximal - last dose	4.50 ± 2.11 (12)	3.82 ± 1.44 (12)
• Venous emptying over 3 sec.		
- Minimal - first dose	3.02 ± 0.87 (0)	2.95 ± 1.00 (0)
- Minimal - last dose	2.87 ± 0.86 (1)	2.85 ± 0.77 (1)
- Maximal - first dose	3.31 ± 0.81 (24)	2.74 ± 0.72** (24)
- Maximal - last dose	3.31 ± 0.87 (12)	3.05 ± 0.77 (12)
• Venous emptying maximal		
- Minimal - first dose	106 ± 20.9 (2)	110 ± 39.2 (2)
- Minimal - last dose	109 ± 31.3 (1.5)	108 ± 29.3 (1.5)
- Maximal - first dose	122 ± 28.2 (3)	99 ± 26.7*** (3)
- Maximal - last dose	125 ± 35.4 (12)	108 ± 22.4* (12)
• Venous volume		
- Minimal - first dose	5.30 ± 1.02 (2)	5.42 ± 1.17 (2)
- Minimal - last dose	5.21 ± 1.21 (0.5)	5.41 ± 0.86 (0.5)
- Maximal - first dose	5.90 ± 1.35 (12)	5.30 ± 1.37 (12)
- Maximal - last dose	5.63 ± 1.28 (12)	5.50 ± 1.05 (12)
Secondary parameters	mean ± SD	mean ± SD
• Supine blood pressure		
- 24 hours after first dose - SBP	158 ± 16.7	153 ± 15.1
- 24 hours after first dose - DBP	96 ± 8.1	92 ± 8.8
- 24 hours after last dose - SBP	162 ± 14.9	148 ± 14.3**
- 24 hours after last dose - DBP	95 ± 6.4	88 ± 6.5**
• Supine heart rate		
- 24 hours after first dose	68 ± 11.9	66 ± 13.1
- 24 hours after last dose	67 ± 11.5	61 ± 12.1*

Asterisks refer to differences with placebo
Levels of significance: * $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$

(Reproduced from Sponsor, SWE-5, page 10)

The pharmacokinetic results are shown in Table 17 and Table 18.

Table 17. Mean (SD) Plasma Concentrations of *l*- and *d*-Nebivolol Plus Their Hydroxylated Metabolites (SWE-5)

Time	d-nebivolol		l-nebivolol	
after dose	acute	chronic	acute	chronic
Before	ND	1.45 ± 0.87	ND	3.60 ± 3.87
0.5	1.87 ± 2.17	3.73 ± 1.54	2.26 ± 2.46	6.31± 3.13
1.0	4.64 ± 3.11	6.93 ± 2.75	6.75 ± 4.56	12.6 ± 4.5
1.5	6.26 ± 3.50	8.07 ± 2.97	10.3 ± 5.8	16.0 ± 4.6
2.0	6.20 ± 2.89	8.12 ± 2.55	10.6 ± 4.6	17.6 ± 3.8
3.0	6.06 ± 2.09	8.35 ± 2.24	10.7 ± 3.7	16.9 ± 3.3
4.0	5.13 ± 1.27	6.89 ± 1.53	9.49 ± 2.59	14.8 ± 3.2
5.0	4.60 ± 1.18	6.42 ± 1.56	8.42 ± 2.71	13.1 ± 3.6
6.0	4.41 ± 1.44	5.86 ± 1.35	7.82 ± 3.58	12.5 ± 3.8
12	2.18 ± 0.66	3.85 ± 1.14	3.37 ± 1.64	7.66 ± 4.70
24	ND	1.95 ± 1.06	ND	3.93 ± 4.16

ND = Not detectable, i.e. < 1.0 ng/ml
(Reproduced from Sponsor, SWE-5, page 34)

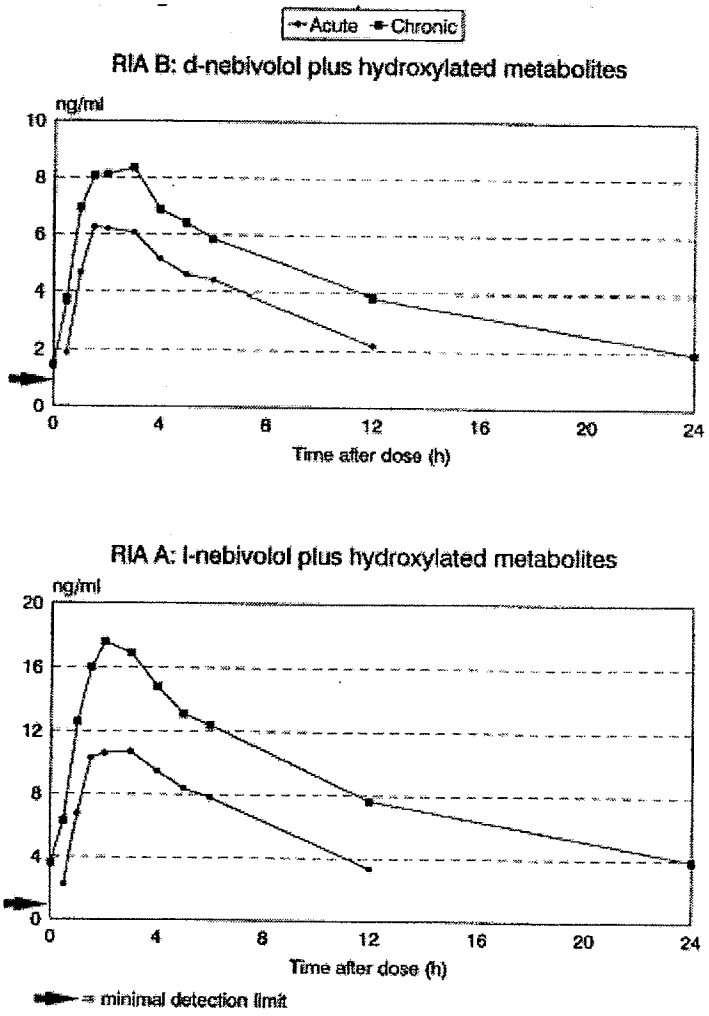
Table 18. Mean (SD) Pharmacokinetic Parameters of *l*- and *d*-Nebivolol Plus Their Hydroxylated Metabolites (SWE-5)

Parameter	d-nebivolol		l-nebivolol	
±	acute	chronic	acute	chronic
C_{0h} (ng/ml)	ND	1.45± 0.87	ND	3.60 ± 3.87
C_{24h} (ng/ml)	ND	1.95 ± 1.06	ND	3.93 ± 4.16
T_{max} (h)	2.50 ± 1.60	2.40 ± 1.20	2.60 ± 1.40	3.10 ± 2.60
C_{max} (ng/ml)	7.30 ± 2.52	9.07 ± 2.42	13.1 ± 4.20	19..0 ± 3.70
AUC_{0-24h} (ng.h/ml)	64.8 ± 14.9	104 ± 24	109 ± 32	212 ± 88

ND = Not detectable, i.e. < 1.0 ng/ml
(Reproduced from Sponsor, SWE-5, page 35)

Comparisons of *d*-nebivolol plus hydroxylated metabolites as well as *l*-nebivolol plus hydroxylated metabolites with nebivolol plasma concentrations are show in Table 19.

Table 19. Nebivolol Plasma Concentrations (SWE-5)



(Reproduced from Sponsor, SWE-5, Figure 11, page 46)

Safety: There were similar numbers of adverse events reported in the placebo and nebivolol treatment groups. According to the study report, there were no drop-outs and no significant changes in laboratory parameters. The QTc decreased significantly in the nebivolol group following one month of treatment. It is unclear which corrected QT calculation was used in this study. One patient demonstrated **"ischemic strain"** on the ECG, which was "accentuated at Visit 3 and remained unchanged therafter." The study report stated this patient was free of chest pain or chest discomfort. The safety results are seen in Table 20.

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Table 20. Safety Results (SWE-5)

Safety (n = number of patients with data)	Placebo (n = 15)	nebivolol (n =15)
Adverse events (AE)		
• Headache	3	3
• Dizziness	0	1
• Chest pain	1	0
• Foot oedema	1	0
• Tiredness	2	1
• Tachycardia	1	1
• Other	6	6
Total number of patients assessed	15	15
No. (%) with one or more AE	9 (60%)	8 (53%)
No. (%) with one or more serious AE	0 (0%)	0 (0%)
No. (%) treatment stopped due to AE	0 (0%)	0 (0%)
Clinical laboratory parameters	No clinically important change	
ECG		
First dose		
• PQ	171 ± 5.7	176 ± 5.2
• QT	391 ± 9.9	389 ± 8.4
• QT_c	395 ± 4.5	389 ± 6.0
Last dose		
• PQ	174 ± 5.1	173 ± 4.9
• QT	387 ± 9.1	399 ± 7.6
• QT_c	400 ± 3.4	381 ± 7.6*

(Reproduced from Sponsor, SWE-5, Safety Table, page 11)

Conclusions: Nebivolol decreased both supine and standing blood pressure. There were no consistent differences in calf arterial and venous blood flow between nebivolol and placebo treatment groups. The investigator stated the ECG QTc-interval was significantly shorter after two weeks of nebivolol treatment, compared with placebo. It is unclear which corrected QT calculation was used in this study. According to the study report, one patient manifested **"ischemic strain"** throughout the study (NEB-SWE-5) which was "accentuated at Visit 3 and remained unchanged therafter." This patient reportedly did not complain of chest pain or discomfort. No ECGs were available for review.

1.23 LMD No. 49278. Study ID: N/A. ("Effect of a Single Oral Intake of R 67555 (5 mg and 10 mg) and of a 7-Day Intake of R67555 (5 mg/day) on ECG. Clinical Research Report. February 1986") (Years of the Study: Not Recorded) (Reviewer: Karen A. Hicks, M.D.)

Objectives: To determine the effect of a single oral intake of R 67555 (5 mg or 10 mg) and of a 7-day intake of R 67555 (5 mg/day) on ECG parameters.

Methods: This open-label cross-over study had two parts. In Part 1, 8 healthy volunteers, ages 27 through 47, with body weights ranging from 54 to 76 kg, received single dose R 67555 5 mg on the first study day and single dose R 67555 10 mg on a second study day at least 7 days later. Investigators obtained ECGS at 3 and 6 hours on a baseline control day as well as 3 and 6 hours post dose. PQ, QRS, and QT intervals were obtained and QT_m- and QT_c-intervals were calculated.

In Part 2, 7 healthy volunteers, ages 24 through 47, with body weights between 54 and 77 kg, took R 67555 5 mg daily for one week. ECGs were obtained twice daily on the control day as well as days 1,2,3,4, and 7 days post dose and days 1, 2, and 7 following the one week intake period. ECGS were obtained just prior to study drug administration and 6 hours post dose.

Results: Table 21 and Table 22 show the study results for Part I and Part II, respectively.

Table 21. Heart Rate and ECG Intervals on a Control Day and Before and 3 and 6 Hours After Intake of 5 mg and 10 mg of R 67555 (LMD No. 49278)

		Control		R 67555 5 mg			R 67555 10 mg		
		3 hours after intake	6 hours after intake	before intake	3 hours after intake	6 hours after intake	before intake	3 hours after intake	6 hours after intake
HR (beats/ min)	mean	64.3	71.0	71.6	57.4	64.5	70.3	56.8	62.5
	S.E.M..	5.1	5.7	3.9	2.1	2.0	4.2	2.1	1.9
	p*versus before intake	-	-	-	0.02	n.s.	-	0.008	n.s.
	control day	-	-	-	n.s.	n.s.	-	n.s.	n.s.
PQ (msec)	mean	145	146	150	150	154	150	153	153
	S.E.M.	5	5	7	6	7	6	6	5
	p*versus before intake	-	-	-	n.s.	n.s.	-	n.s.	n.s.
	control day	-	-	-	n.s.	n.s.	-	n.s.	n.s.
QRS (msec)	mean	87.5	86.3	90.0	88.8	88.8	90.0	90.0	93.1
	S.E.M.	2.5	2.6	3.8	4.0	4.0	4.2	3.3	2.8
	p*versus before intake	-	-	-	n.s.	n.s.	-	n.s.	n.s.
	control day	-	-	-	n;s.	n.s.	-	n.s.	n.s.
QT (msec)	mean	394	378	371	395	386	369	407	387
	S.E.M.	11	10	6	4	4	4	6	9
	p*versus before intake	-	-	-	0.02	0.05	-	0.008	n.s.
	control day	-	-	-	n.s.	n.s.	-	n.s.	n.s.
QT_c (msec)	mean	403	406	403	388	400	397	395	394
	S.E.M.	9	8	7	7	7	10	7	8
	p*versus before intake	-	-	-	n.s.	n.s.	-	n.s.	n.s.
	control day	-	-	-	0.05	n.s.	-	n.s.	n.s.
QT_m (msec)	mean	401	397	392	392	392	385	401	392
	S.E.M.	5	5	3	5	6	6	5	8
	p*versus before intake	-	-	-	n.s.	n.s.	-	0.04	n.s.
	control day	-	-	-	n.s.	n.s.	-	n.s.	n.s.

* Wilcoxon matched-pairs signed-ranks test, two-tailed probability (n.s. = not significant)

(Reproduced from Sponsor, LMD No. 49278, Table 1, page 3)

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Table 22. Heart Rate and ECG-Intervals Before, During, and After a 7-Day Intake of R 67555 (5 mg/day)

		Before intake									6 hours after intake						
		Control day	Day 1	Day 2	Day 3	Day 4	Day 7	Day 1 post	Day 2 post	Day 7 post	Control day	Day 1	Day 4	Day 7	Day 1 post	Day 2 post	Day 7 post
HR (beats/min)	mean	72.3	71.9	69.1	64.4	65.7	66.1	64.7	67.6	73.7	67.1	67.4	62.3	62.3	63.0	69.0	68.6
	S.E.M.	6.1	3.8	4.5	3.5	3.8	4.8	3.5	4.6	3.6	1.8	2.5	3.0	3.6	1.9	2.3	4.0
	p*vs control day	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	p*vs before intake	-	-	-	-	-	-	-	-	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
PQ (msec)	mean	147	147	147	143	147	146	150	147	141	146	146	144	144	141	144	144
	S.E.M.	4	3	4	2	4	3	3	3	3	4	4	3	3	5	4	2
	p*vs control day	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	p*vs before intake	-	-	-	-	-	-	-	-	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
QRS (msec)	mean	95.7	91.4	94.3	91.4	94.3	92.9	92.9	91.4	91.4	94.3	94.3	94.3	90.0	91.4	92.9	91.4
	S.E.M.	2.0	2.6	3.0	3.4	2.0	2.9	2.9	3.4	3.4	2.0	3.7	2.0	3.1	3.4	2.9	3.4
	p*vs control day	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	p*vs before intake	-	-	-	-	-	-	-	-	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
QT (msec)	mean	370	373	380	391	384	386	388	383	376	380	387	388	387	390	383	383
	S.E.M.	10	7	9	5	5	6	6	5	6	7	9	3	7	4	4	10
	p*vs control day	-	n.s.	n.s.	0.02	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	p*vs before intake	-	-	-	-	-	-	-	-	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
QT_c (msec)	mean	402	406	405	403	400	402	401	404	413	401	408	393	393	399	409	406
	S.E.M.	9	9	9	10	9	10	7	10	6	6	6	8	9	6	6	6
	p*vs control day	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	p*vs before intake	-	-	-	-	-	-	-	-	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
QT_n (msec)	mean	392	394	396	399	395	396	396	396	400	393	400	392	391	395	399	398
	S.E.M.	5	6	5	6	5	5	4	5	4	6	6	5	6	4	4	5
	p*vs control day	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	p*vs before intake	-	-	-	-	-	-	-	-	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

* Wilcoxon matched-pairs signed-ranks test, two-tailed probability (n.s. = not significant)

(Reproduced from Sponsor, LMD No. 49278, Table 2, page 4)

Conclusions: For Parts 1 and 2 of this study, there were no significant changes in ECG parameters.

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

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

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

were examined in the opposite way, which allowed for a 3 week wash-out period between the two study sessions.

Results: Table 23 shows the baseline hemodynamic results for the eight patients prior to nebivolol.

Table 23. Individual and Mean Values of Haemodynamic Data Before Nebivolol Administration in 8 Healthy Volunteers (LMD No. 59987)

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

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

Table 24 shows the hemodynamic results following IV nebivolol administration.

Table 24. Individual and Mean Values of Haemodynamic Data After Intravenous Administration of Nebivolol in 8 Healthy Volunteers (LMD No. 59987)

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

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

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

Table 25 shows the hemodynamic results after oral nebivolol administration.

Table 25. Individual and Mean Values of Haemodynamic Data After Peroral Administration of Nebivolol in 8 Healthy Volunteers

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

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

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

The overall results comparing baseline hemodynamic measurements with those obtained after both IV and PO nebivolol are shown in Figure 27 and Figure 28.

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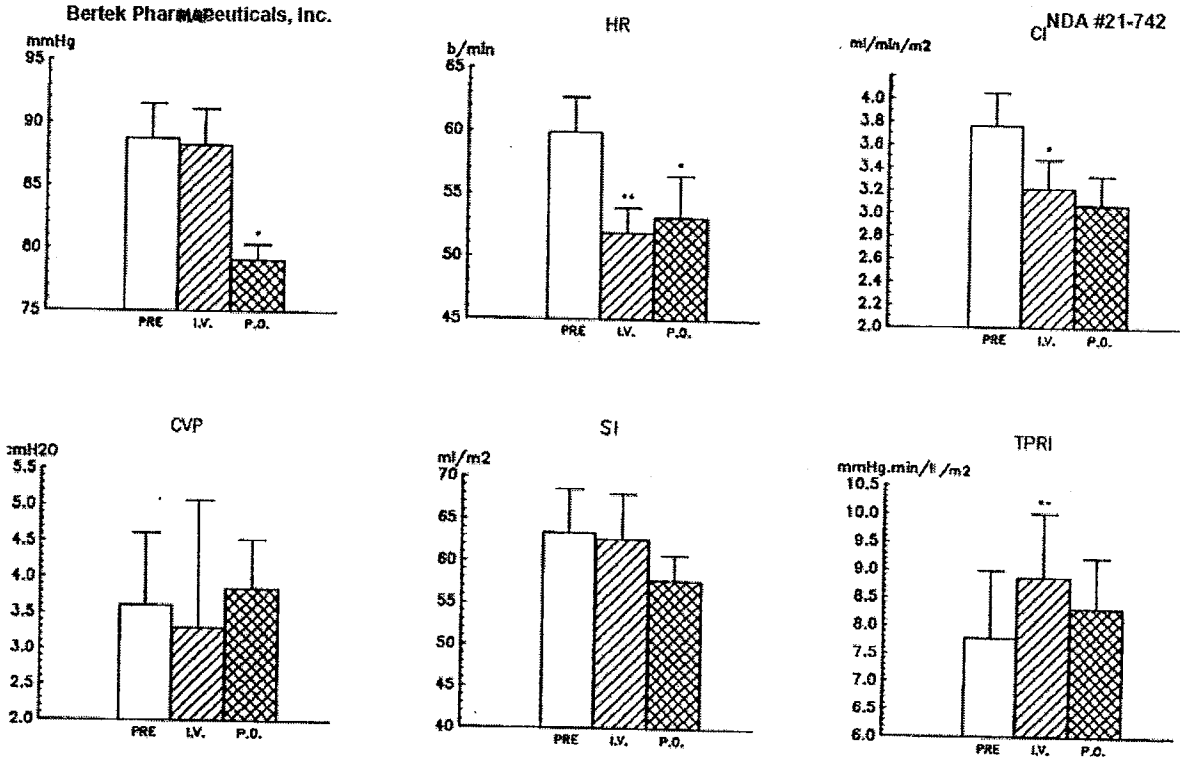
Figure 27. Mean Haemodynamic Data (± SEM) Before Nebivolol and After the Intravenous and Oral Application of the Drug (LMD No. 59987)

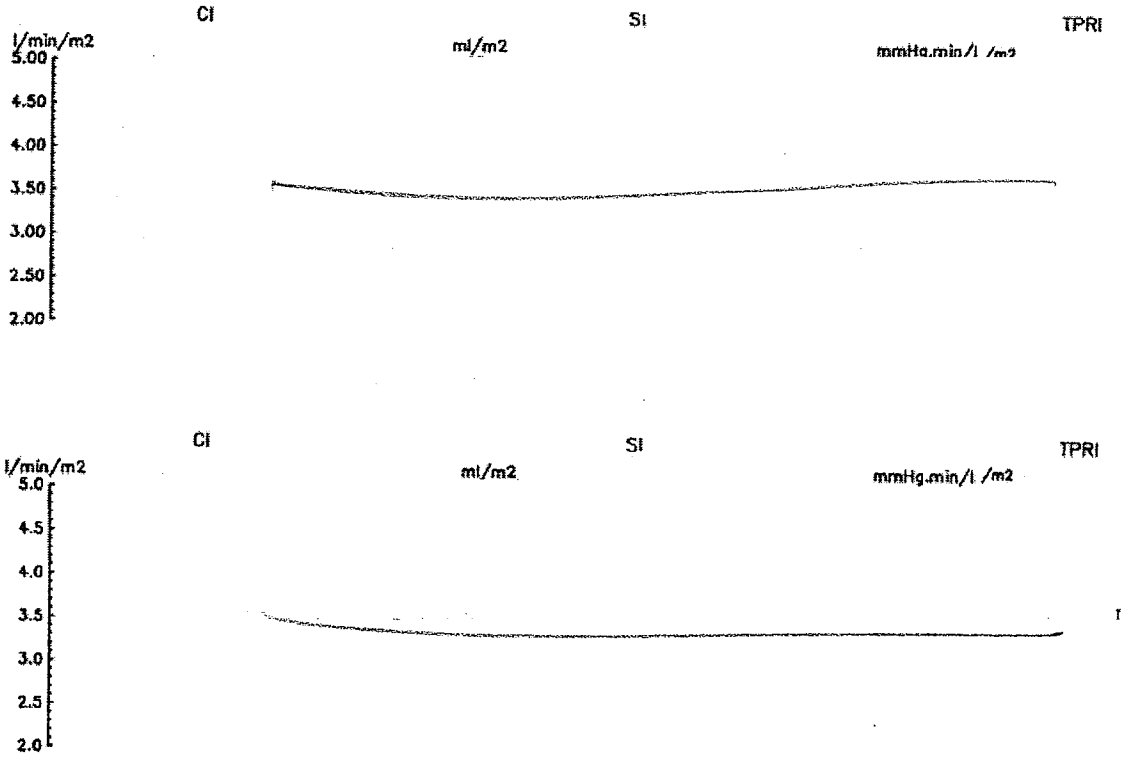


* p<0.05; ** p<0.01 by Wilcoxon m.p.s.r test, two-tailed probability versus pre.

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

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

Figure 28. Individual Changes in Haemodynamics After Intravenous and Oral Application of Nebivolol (LMD No. 59987)



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

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

IV Nebivolol significantly decreased cardiac index and significantly increased TPRI.

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

1.25 LMD No. 64808. Study ID: BEL-19. ("Effect of Nebivolol 10 mg and 20 mg versus Placebo on Heart Rate, Blood Pressure, Systolic Time Intervals and Side Effects. A Double-Blind Placebo-Controlled Cross-Over Study in Healthy Volunteers. Clinical Research Report NEB-BEL-19") (January 1989) (Reviewer: Maryann Gordon, M.D.)

Objective: The effect of a single oral intake of 10 and 20 mg of nebivolol on heart rate, blood pressure, ECG, systolic time intervals and general well-being was investigated in a double-blind placebo-controlled cross-over study in 12 volunteers.

Methods: In a double-blind fashion and in random sequence, 12 healthy volunteers were given a single oral dose of nebivolol 10 mg, nebivolol 20 mg, or placebo, with a wash-out period of at least 1 week between 2 sessions. Arterial blood pressure and heart rate measurements before and 6 hours after drug intake were carried out after a rest of 10 minutes in supine position, after a rest of 2 minutes in sitting position, and after a rest of 2 minutes in standing position. ECG and systolic time intervals, before and 6 hours after drug intake, were measured after a rest of 10 minutes in supine position.

Results: The effects of nebivolol and placebo on heart rate in supine, sitting, and standing position and blood pressure in standing position 6 hours after intake are shown in Table 26 and Figure 29. Heart rate decreased with both doses in all positions. Blood pressure decreased significantly only in the standing position. There was no difference in systolic time intervals between either dose of drug and placebo, as shown in Figure 30. In Table 27, there were more reported adverse events with 20 mg (5 reports) compared to 10 mg (2 reports). None appeared to be serious or unexpected.

Table 26. Effect of a Single Oral Intake of Placebo, Nebivolol 10 mg and Nebivolol 20 mg on Heart Rate, Blood Pressure, ECG- and Systolic Time Intervals in 12 Healthy Volunteers (BEL-19)

		Placebo			Nebivolol 10 mg			Nebivolol 20 mg		
		0 hour	6 hour	p_1	0 hour	6 hour	p_1	0 hour	6 hour	p_1
supine	HR (b/min)	65±2.8	65±2.3	n.s.	68±2.4	58±2.4**	0.001	69±3.6	58±2.8**	0.001
	SBP (mmHg)	124±2.0	126±3.1	n.s.	123±3.9	126±3.5	n.s.	126±2.7	122±3.4	n.s.
	DBP (mmHg)	74±1.3	76±1.8	n.s.	75±1.8	77±2.2	n.s.	78±1.3*	74±1.7	0.02
sitting	HR (b/min)	75±4.3	74±2.3	n.s.	78±2.6	68±2.0*	0.01	78±2.9	65±2.6*	0.0004
	SBP (mmHg)	129±2.7	130±3.9	n.s.	131±3.1	126±4.8	n.s.	129±2.9	123±3.3	n.s.
	DBP (mmHg)	80±1.5	81±2.2	n.s.	81±1.2	78±2.2	n.s.	78±1.8	74±1.7*	n.s.
standing	HR (b/min)	81±3.0	77±2.8	0.05	83±2.6	69±1.6*	0.0004	81±3.3	68±2.0*	0.0004
	SBP (mmHg)	131±2.4	136±4.1	n.s.	130±2.9	126±3.1*	n.s.	130±3.4	125±3.8**	n.s.
	DBP (mmHg)	82±1.3	84±2.5	n.s.	82±1.9	77±1.6*	0.01	82±1.7	77±2.0**	0.02
E.C.G.	PQ (msec)	160±8.3	160±7.8	n.s.	159±7.3	160±6.7	n.s.	157±7.3	156±7.8	n.s.
	QRS (msec)	79±2.9	78±2.4	n.s.	80±2.8	81±2.6	n.s.	82±2.4	81±1.9	n.s.
	QT (msec)	372±5.8	368±5.5	n.s.	365±4.7	383±6.4**	0.004	362±9.3	381±9.8	0.009
	QT_c (msec)	385±6.2	381±4.9	n.s.	388±5.7	375±7.9	0.01	382±6.4	376±6.5	n.s.
	QT_m (msec)	381±3.6	376±3.8	n.s.	379±4.0	380±6.1	n.s.	376±5.7	381±5.1	n.s.
S.T.I.	QS_{2c} (msec)	398±4.1	386±2.6	0.001	396±3.3	387±2.7	0.02	395±3.1	388±2.5	0.01
	$LVET_c$ (msec)	302±2.2	298±2.5	n.s.	301±3.0	298±1.9	n.s.	304±3.0	300±2.4	n.s.
	PEP_c (msec)	96±2.3	88±3.0	0.01	95±1.5	89±2.2	n.s.	91±2.0	88±2.5	n.s.
	$PEP_c/LVET_c$	0.32±0.007	0.30±0.012	n.s.	0.32±0.007	0.30±0.008	n.s.	0.30±0.008	0.29±0.010	n.s.
					← no significant differences →					

p_1 = Wilcoxon m.p.s.r. test, 2-tailed probability versus 0-hour values
*p≤0.05, **p≤0.01 Wilcoxon m.p.s.r. test, 2-tailed probability versus placebo

(Reproduced from Sponsor, BEL-19, Table 3, page 9)

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Figure 29. Mean Values (± SEM) of Heart Rate and Blood Pressure 6 Hours After a Single Oral Intake of Placebo, 10 mg, and 20 mg of Nebivolol in 12 Healthy Volunteers in a Randomized Cross-Over Study (BEL-19)

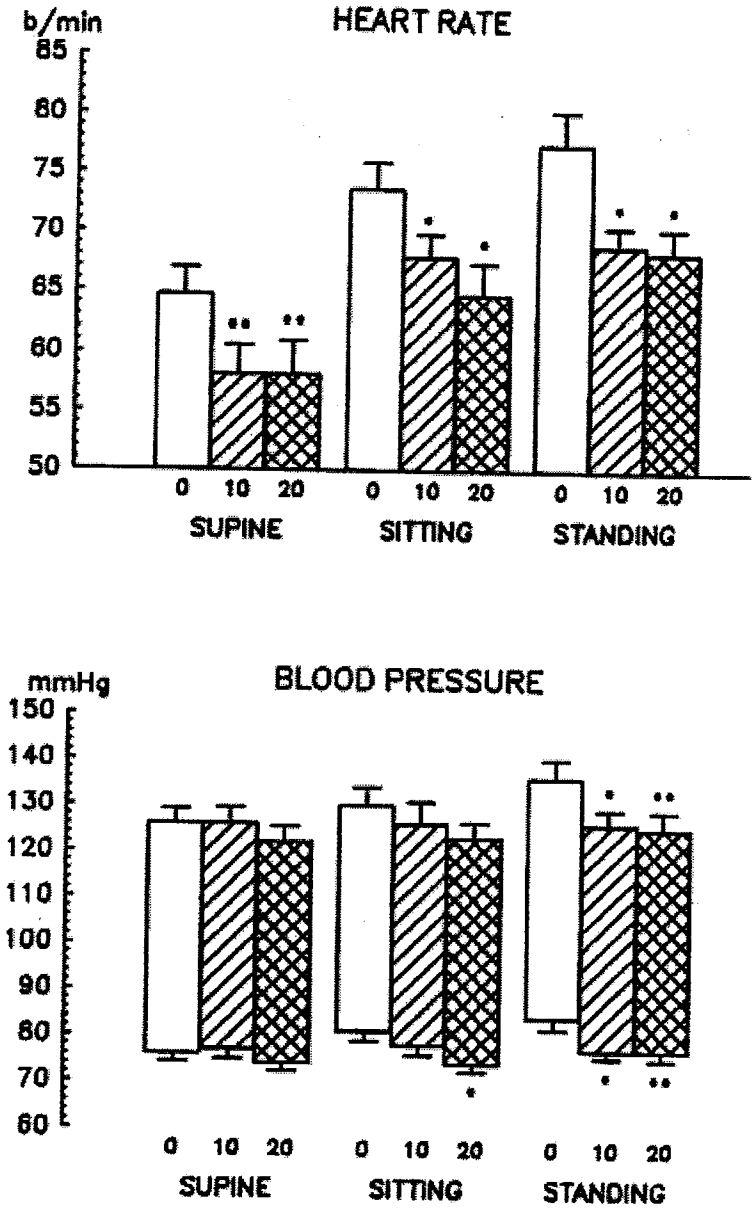

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Figure 30. Mean Values (± SEM) of Systolic Time Intervals 6 Hours After a Single Oral Intake of Placebo, 10 mg and 20 mg of Nebivolol in 12 Healthy Volunteers in a Randomized Cross-Over Study (BEL-19)

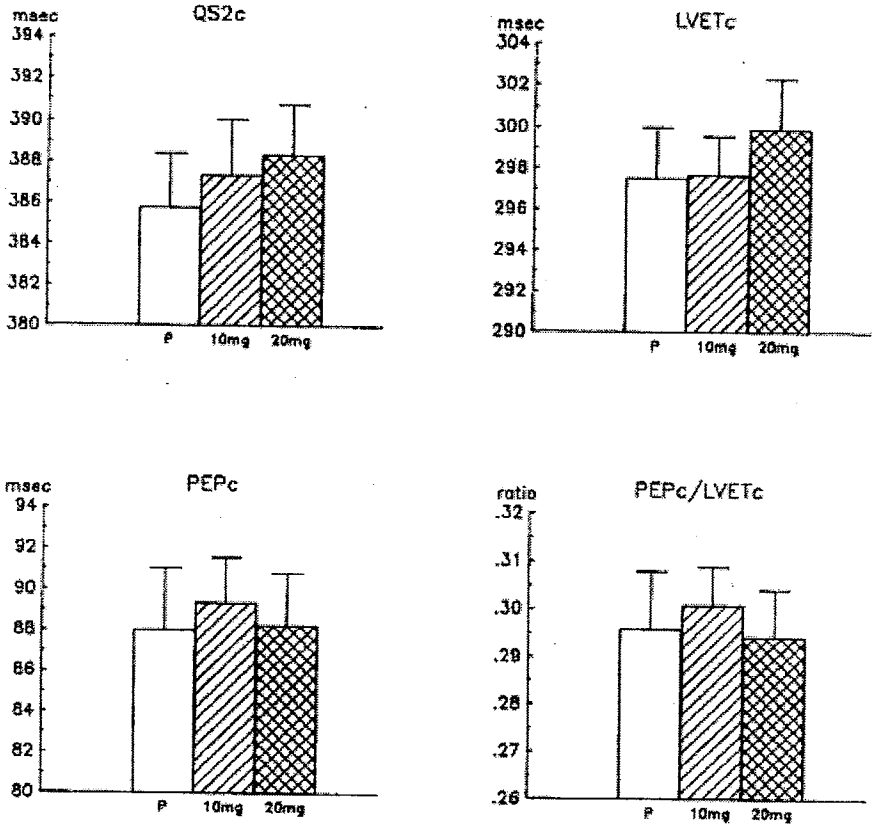

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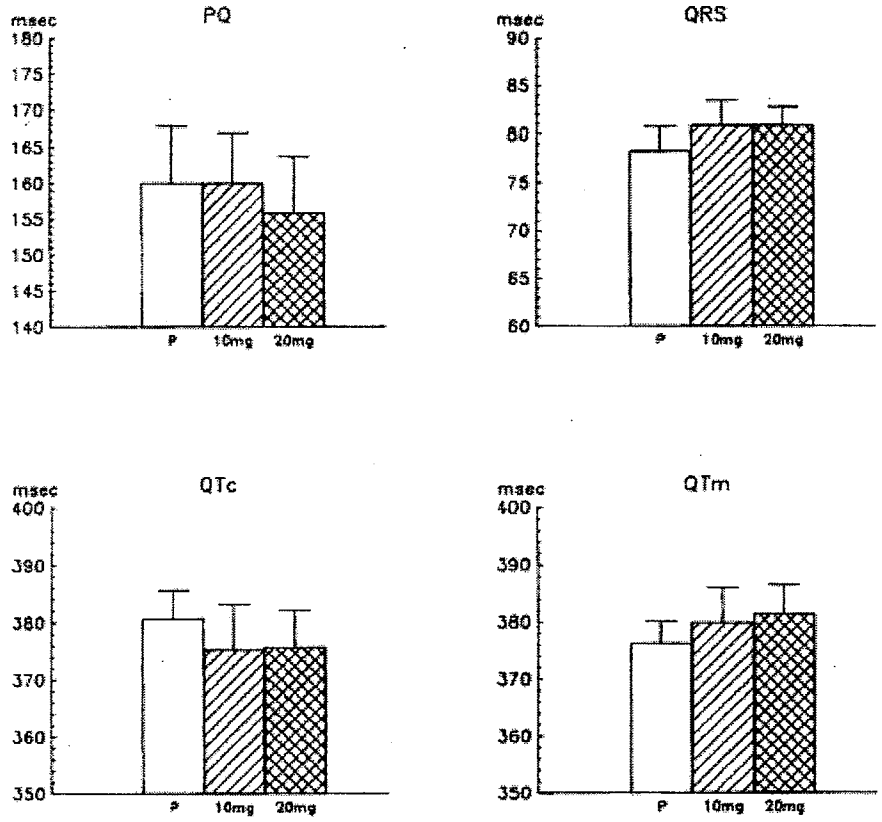
Table 27. Side-Effects of 12 Volunteers at 3 Hours, 6 Hours, and 24 Hours after Intake of a Single Dose of Placebo, Nebivolol 10 mg, and Nebivolol 20 mg (BEL-19)

treatment	complaint	hours after drug	n
nebivolol 10 mg	sleepy	6	1
	slow reactivity	24	1
	No. of patients		2
nebivolol 20 mg	hot flushes	6	1
	hungry	3/6	1
	back pain	24	1
	abdominal cramps	3	1
	headache	3/6/24	1
	No. of patients		5

(Reproduced from Sponsor, BEL-19, Table 5, page 11)

The effect of study drug on ECG Parameters is shown in Figure 31.

Figure 31. Mean Values (± SEM) of ECG-Intervals 6 Hours After a Single Oral Intake of Placebo, 10 mg and 20 mg of Nebivolol in 12 Healthy Volunteers in a Randomized Cross-Over Study (QTc = Bazett's Correction) (BEL-19)



(Reproduced from Sponsor, BEL-19, Figure 2, page 13)

1.26 LMD No. 65661. BEL-17. ("Phase I Study: Effect of Nebivolol on Dopamine Related Phenomena. Part II: Haemodynamic Effects. Clinical Research Report NEB-BEL-17. February 1989") (Reviewer: Maryann Gordon, M.D.)

Objective: Heart rate, blood pressure, and ECG- and systolic time intervals were investigated before and after a 1 week placebo-controlled double-blind cross-over treatment with nebivolol 5 mg once daily in 10 healthy volunteers.

Methods: Ten normal volunteers were randomly assigned to double-blind cross-over treatment with a 5 mg nebivolol tablet or a placebo tablet once daily for 1 week with a wash-out period of 1 week between the two sessions. On the control day and 24 hours after the last dosing of each session, an intravenous injection of 10 mg metoclopramide was administered over a 5-minute period. Heart rate, blood pressure, and ECG- and systolic time intervals were determined on these days, each time after a rest of 15 minutes in supine position.

Results: Only hemodynamic results are shown here. After nebivolol intake, heart rate and blood pressure were significantly decreased. Additionally; the ratio PEPc/LVETc significantly decreased as a result of a shortening of PEPc and a lengthening of LVETc.

Table 28. Effect of a 1-Week Double-Blind Placebo-Controlled Cross-Over Treatment with Nebivolol 5 mg O.D. on Heart Rate, Blood Pressure, ECG-, and Systolic Time Intervals in 10 Healthy Volunteers (BEL-17)

	Placebo			nebivolol			
	pre	post		pre	post		
	Mean±SEM	Mean±SEM	p1	Mean±SEM	Mean±SEM	p1	p2
HR b/min	66±2.8	63±2.1	n.s.	63±3.0	55±2.1	0.008	n.s.
SBP mmHg	130±2.8	132±3.1	n.s.	134±3.7	126±3.0	0.02	0.02
DBP mmHg	80±1.7	82±2.0	n.s.	82±2.0	78±1.6	0.05	0.05
PQ msec	167±7.6	165±7.3	n.s.	164±7.8	166±6.2	n.s.	n.s.
QRS msec	96±3.4	97±2.6	n.s.	97±4.2	97±4.2	n.s.	n.s.
QT msec	373±6.2	379±6.0	n.s.	368±7.4	386±5.6	0.02	n.s.
QT_C msec	390±4.1	386±3.9	n.s.	376±5.5	367±4.0	n.s.	n.s.
QT_m msec	384±3.0	383±3.7	n.s.	374±4.6	377±3.3	n.s.	n.s.
QS_{2C} msec	395±5.9	399±4.4	n.s.	401±3.1	403±3.8	n.s.	n.s.
$LVET_C$ msec	297±4.6	298±5.4	n.s.	300±2.2	308±4.2	0.04	n.s.
PEP_C msec	98±4.1	100±4.9	n.s.	101±3.0	95±2.6	0.04	0.02
$PEP_C/LVET_C$	0.33±0.016	0.34±0.022	n.s.	0.34±0.012	0.31±0.011	0.02	0.04

p1 : Wilcoxon m.p.s.r. test, 2-tailed probability versus pre-values
p2 : Wilcoxon m.p.s.r. test, 2-tailed probability on differences post-pre versus placebo-values

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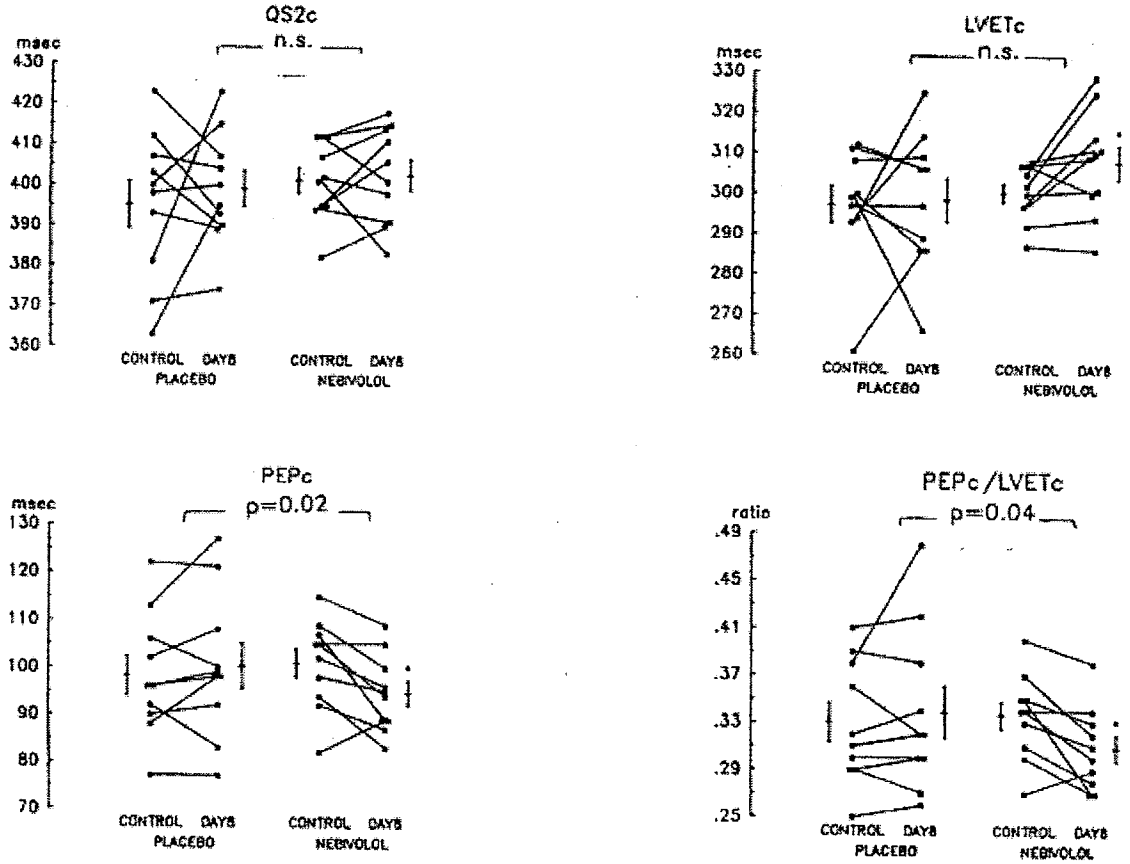
Figure 32. Effect of a 1-Week Double-Blind Placebo-Controlled Cross-Over Treatment with Nebivolol 5 mg O.D. on Systolic Time Intervals in 10 Healthy Volunteers



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1.27 LMD No. 65662. BEL-32. ("Cardiac Haemodynamic Effects of *d*-, *l*-, *dl*-Nebivolol and Atenolol During a 7-Day Double-Blind Cross-Over Study in Healthy Volunteers. Clinical Research Report NEB-BEL-32. March 1989") (Reviewer: Maryann Gordon, M.D.)

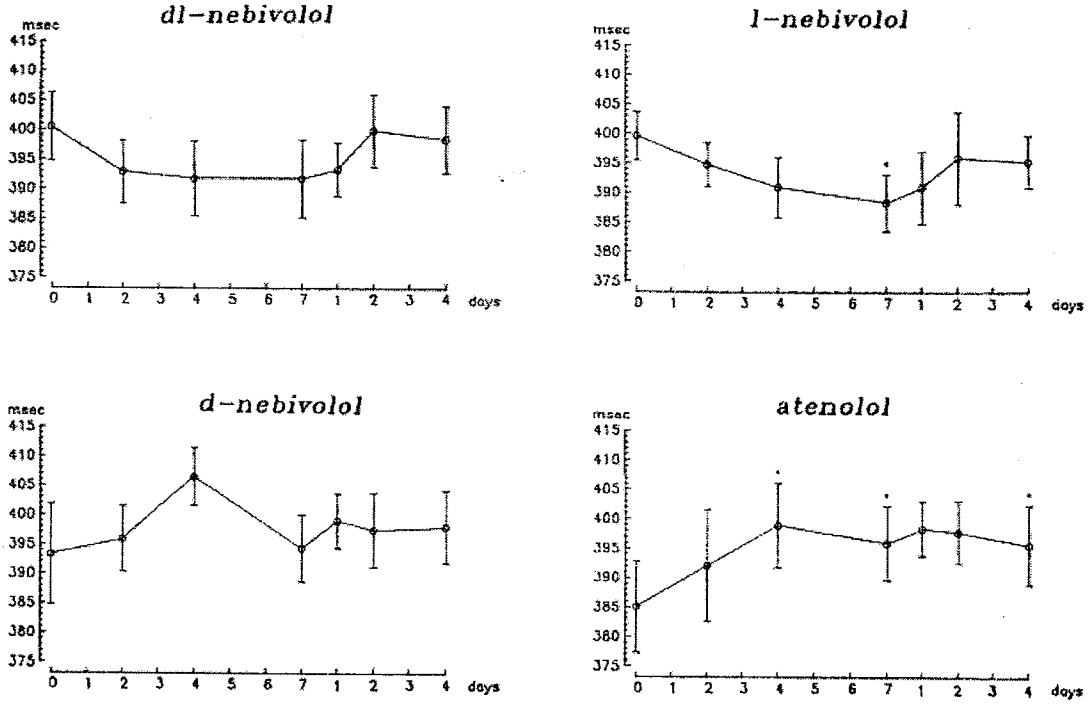
Objective: Heart rate, blood pressure, and ECG- and systolic time intervals were investigated before, during, and after a 7-day double-blind cross-over treatment with *dl*-nebivolol 5 mg o.d., *l*-nebivolol 2.5 mg o.d., *d*-nebivolol 2.5 mg o.d., and atenolol 100 mg o.d. in 7 healthy volunteers.

Methods: Seven healthy volunteers (2 female, 5 male) took part in this study. They were randomly assigned to treatment with *dl*-nebivolol 5 mg o.d., *l*-nebivolol 2.5 mg o.d., *d*-nebivolol 2.5 mg o.d. or atenolol 100 mg o.d. following a double-blind cross-over design, with a one-week interval between the different study phases. On a control day, day 2, 4, and 7 of treatment, and day 1, 2, and 4 after discontinuation of treatment, heart rate, blood pressure, and systolic time intervals were measured. ECG-intervals were measured

on a control day and on the last day of treatment. Measurements were always done in the morning at a fixed hour on a control day and before each daily intake of the study medication (trough values). Also, on a control day, on day 2, 4, and 7 during treatment, and on day 1, 2, and 4 after discontinuation of treatment, an isometric handgrip test was performed. All assessments were done at a fixed hour in the morning and 24 hours after the last intake of each test.

Results: The effects of *l*-nebivolol on QS2c (Figure 33) and PEPc (Figure 34) were similar to those of *dl*-nebivolol while *d*-nebivolol was more similar to the effect of atenolol. The results for PEPc/LVETc are shown in Figure 35.

Figure 33. QS2c Before, During, and After a 7-Day Treatment with dl-Nebivolol 5 mg O.D., l-Nebivolol 2.5 mg O.D., d-Nebivolol 2.5 mg O.D., and Atenolol 100 mg O.D. in 7 Healthy Volunteers (BEL-32)



* p ≤ 0.05 Wilcoxon m.p.s.r. test, 2-tailed probability versus day 0

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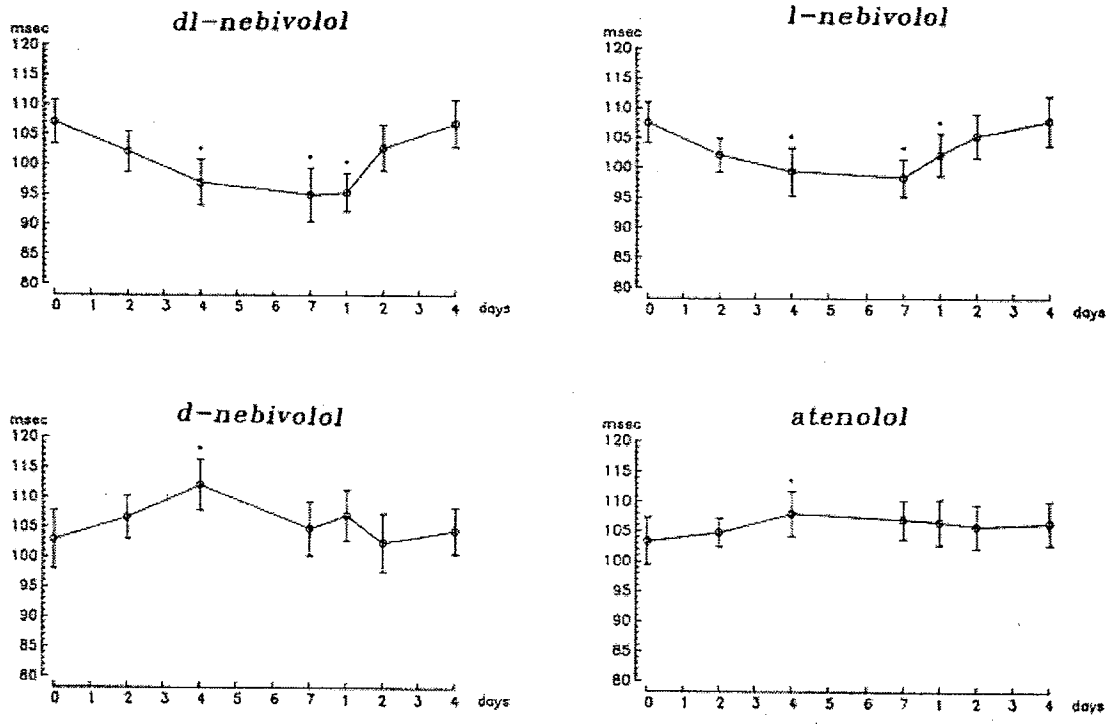
Figure 34. PEPc Before, During, and After a 7-Day Treatment with *dl*-Nebivolol 5 mg O.D., *l*-Nebivolol 2.5 mg O.D., *d*-Nebivolol 2.5 mg O.D. and Atenolol 100 mg O.D. in 7 Healthy Volunteers (BEL-32)



* $p \leq 0.05$ Wilcoxon m.p.s.r. test, 2-tailed probability versus day 0

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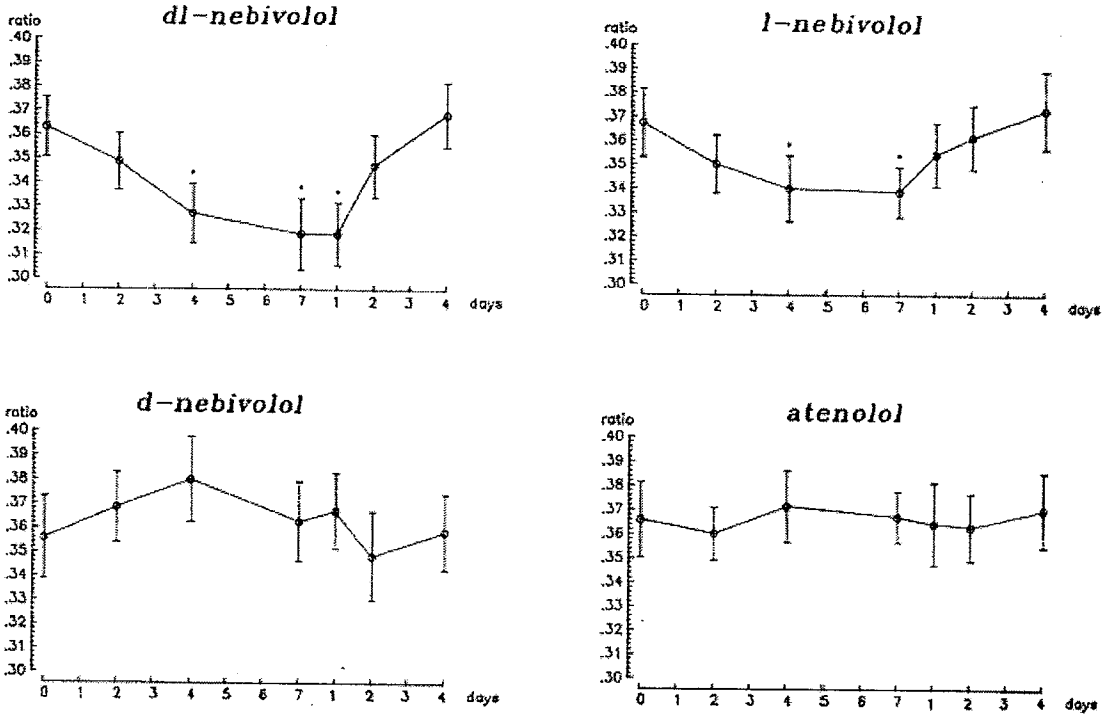
Figure 35. PEPc/LVETc Ratio Before, During, and After a 7-Day Treatment with *dl*-Nebivolol 5 mg o.d., *l*-Nebivolol 2.5 mg O.D., *d*-Nebivolol 2.5 mg O.D., and Atenolol 100 mg O.D. in 7 Healthy Volunteers (BEL-32)



* $p \leq 0.05$ Wilcoxon m.p.s.r. test, 2-tailed probability versus day 0

(Reproduced from Sponsor, BEL-32, Figure 4, page 12)

Heart rate increase was less after the 3-minute isometric handgrip in both *dl*-nebivolol and atenolol compared to *l*-nebivolol. The effect on systolic blood pressure was similar across treatment groups.

LMD No. 65659. Study ID BEL-32. ("Effects of Isometric Handgrip on Blood Pressure and Heart Rate During a 7-Day Double-Blind Cross-Over Treatment with *dl*-, *d*-, and *l*-Nebivolol and Atenolol in Healthy Volunteers. Clinical Research Report NEB-BEL-32, January 1989") (Trial Period: February 2, 1988 – October 10, 1988) (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the effect of a 3-minute isometric handgrip test on heart rate and systolic blood pressure in 7 volunteers before, during, and after 7 days of treatment with dl-nebivolol 5 mg o.d., l-nebivolol 2.5 mg o.d., d-nebivolol 2.5 mg o.d., and atenolol 100 mg o.d.

Methods: Seven healthy volunteers (2 female, 5 male), ages 28 to 50 years, participated in this study. Subjects were randomly assigned to double-blind treatment with *dl*-nebivolol 5 mg o.d., *l*-nebivolol 2.5 mg o.d., *d*-nebivolol 2.5 mg o.d., or atenolol 100 mg o.d. for 7 days. On a control day, on day 2, 4, and 7 during treatment, and on day 1, 2, and 4 after discontinuation of treatment, an isometric handgrip test was performed.

Investigators performed assessments at a fixed hour in the morning and 24 hours after the last intake of study drug.

Results: Seven volunteers completed the study. No volunteers discontinued the study prematurely. The effect of handgrip on systolic blood pressure was not influenced by any of the 4 treatment sessions. Increase of heart rate after 3 minutes of handgrip was significantly reduced after 7 days of treatment with dl-nebivolol and after atenolol 100 mg but not after d- and l-nebivolol. Table 29, Table 30, Table 31, and Table 32 describe the efficacy results for systolic blood pressure, diastolic blood pressure, and heart rate.

Table 29. Systolic Blood Pressure During a 3-Minute Isometric Handgrip Test on a Control Day and After 7 Days of Treatment with *dl*-Nebivolol, *l*-Nebivolol, *d*-Nebivolol and Atenolol in 7 Healthy Volunteers

HANDGRIP POWER TEST		dl-nebivolol 5mg		l-nebivolol 2.5mg		d-nebivolol 2.5mg		atenolol 100mg	
		Mean±SEM	p	Mean±SEM	p	Mean±SEM	p	Mean±SEM	p
Control day	0 min	122±4.3	--	121±3.8	--	126±1.4	--	121±3.9	--
	1 min	127±4.0	--	131±4.0	--	133±1.9	--	128±3.0	--
	2 min	136±4.2	--	143±5.4	--	142±2.0	--	139±3.9	--
	3 min	148±4.7	--	147±2.3	--	147±3.2	--	147±4.8	--
Day 2	0 min	116±3.1	n.s.	123±2.8	n.s.	116±4.6	0.08	114±4.8	0.08
	1 min	121±3.0	n.s.	132±1.6	n.s.	125±3.8	0.03	119±3.8	0.03
	2 min	132±4.5	0.03	139±1.3	n.s.	134±3.3	0.03	134±3.1	0.08
	3 min	141±4.8	0.05	148±4.0	n.s.	145±4.5	n.s.	140±3.4	n.s.
Day 4	0 min	115±2.4	n.s.	120±2.4	n.s.	114±2.2	0.02	113±5.6	0.08
	1 min	123±2.3	n.s.	128±2.6	n.s.	122±2.0	0.02	123±3.9	0.03
	2 min	132±3.0	0.08	139±3.9	n.s.	132±1.8	0.02	133±3.3	0.03
	3 min	142±3.6	n.s.	150±2.9	n.s.	146±2.3*	n.s.	143±5.2	n.s.
Day 7	0 min	113±2.5	0.08	123±3.1	n.s.	114±2.8	0.02	116±3.7	n.s.
	1 min	123±2.1	n.s.	128±1.8	n.s.	124±2.9	n.s.	124±3.2	0.08
	2 min	137±2.5	n.s.	138±2.5	n.s.	132±3.1	0.04	131±3.6	0.05
	3 min	144±5.1	n.s.	148±2.3	n.s.	141±3.3	0.03	144±5.7	n.s.
Day 1 post	0 min	116±2.8	n.s.	125±4.4	n.s.	117±3.1	0.02	114±3.8	0.03
	1 min	123±3.6	n.s.	134±4.0	n.s.	123±3.2	0.03	122±4.0	0.03
	2 min	135±2.6	n.s.	140±3.0	n.s.	134±4.1	n.s.	131±3.4	0.08
	3 min	140±5.2	0.02	150±3.9	n.s.	142±4.7	n.s.	139±3.1	0.03
Day 2 post	0 min	113±4.1	0.06	123±4.8	n.s.	118±4.6	0.08	117±2.9	n.s.
	1 min	123±3.3	n.s.	128±3.0	n.s.	128±3.3	n.s.	126±2.6	n.s.
	2 min	132±3.9	n.s.	137±2.6	n.s.	135±4.5	n.s.	135±3.4	n.s.
	3 min	147±3.2	n.s.	150±4.0	n.s.	145±5.6*	n.s.	147±3.7	n.s.
Day 4 post	0 min	116±3.1	0.08	124±3.0	n.s.	124±3.8	n.s.	122±2.8	n.s.
	1 min	123±2.7	n.s.	127±2.6	n.s.	126±2.5	0.02	128±2.3	n.s.
	2 min	135±3.4	n.s.	138±2.9	n.s.	134±3.0	0.04	140±3.4	n.s.
	3 min	143±4.6	n.s.	146±3.7	n.s.	143±2.8	0.02	146±4.0	n.s.

* $p \leq 0.05$ by Wilcoxon m.p.s.r. test on differences with 0 min values versus control values.
p-value : 2-tailed probability by Wilcoxon m.p.s.r. test versus control day values.

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Table 30. Diastolic Blood Pressure During a 3-Minute Isometric Handgrip Test on a Control Day and After 7 Days of Treatment with *dl*-Nebivolol, *l*-Nebivolol, *d*-Nebivolol and Atenolol in 7 Healthy Volunteers

COLD PRESSURE TEST		dl-nebivolol 5mg		l-nebivolol 2.5mg		d-nebivolol 2.5mg		atenolol 100mg	
		Mean±SEM	p	Mean±SEM	p	Mean±SEM	p	Mean±SEM	p
Control day	0 min	81±2.7	--	82±1.2	--	85±1.4	--	84±2.6	--
	1 min	88±2.5	--	90±2.2	--	88±1.9	--	87±2.4	--
	2 min	90±2.1	--	91±2.6	--	91±2.9	--	89±2.3	--
	3 min	88±2.5	--	92±1.8	--	90±2.7	--	86±3.3	--
Day 2	0 min	76±2.4	0.06	82±1.6	n.s.	79±2.3	0.03	77±2.4	0.02
	1 min	84±2.2	n.s.	83±1.2	0.05	86±1.3	n.s.	81±2.2	0.04
	2 min	89±2.2	n.s.	88±1.9	n.s.	92±2.5	n.s.	84±2.5	0.03
	3 min	86±2.0*	n.s.	89±2.0	n.s.	88±1.5	n.s.	83±2.7	n.s.
Day 4	0 min	76±2.2	0.03	81±1.7	n.s.	77±2.1	0.02	77±3.3	0.02
	1 min	82±1.5	0.05	84±1.4	n.s.	83±1.4	0.02	81±1.8	0.03
	2 min	84±1.9	0.04	89±2.2	n.s.	84±2.1	0.03	84±2.7	0.08
	3 min	83±2.5	n.s.	87±1.8	0.08	82±2.3	0.03	82±2.3	n.s.
Day 7	0 min	77±1.8	0.08	82±1.9	n.s.	79±2.3	0.04	78±1.8	0.02
	1 min	81±1.4	0.09	85±2.0	n.s.	81±1.7	0.02	81±2.0	n.s.
	2 min	83±2.0	0.03	89±1.7	n.s.	85±1.5	n.s.	85±2.4	n.s.
	3 min	82±1.9	n.s.	90±1.8	n.s.	84±1.7	0.03	83±2.3	n.s.
Day 1 post	0 min	76±2.1	0.02	85±1.9	0.08	76±1.5	0.02	77±1.9	0.02
	1 min	82±1.6	0.03	90±1.5	n.s.	83±2.4	0.03	83±2.1	n.s.
	2 min	86±1.7	0.03	93±1.8	n.s.	84±2.0	0.09	83±2.1	0.06
	3 min	87±2.0	n.s.	91±1.6*	n.s.	82±1.6	0.02	82±1.6	n.s.
Day 2 post	0 min	78±2.7	n.s.	82±1.5	n.s.	78±2.5	0.02	80±2.9	0.03
	1 min	84±2.6	n.s.	85±2.9	n.s.	80±2.5	0.02	85±3.4	n.s.
	2 min	85±1.8	0.03	86±3.5	n.s.	82±3.4	0.08	86±3.3	n.s.
	3 min	85±2.4	n.s.	86±2.8	0.08	81±3.6	0.03	83±2.8	n.s.
Day 4 post	0 min	78±2.7	n.s.	82±1.7	n.s.	80±2.8	n.s.	79±3.0	0.06
	1 min	83±1.6	n.s.	83±2.2	n.s.	84±2.6	n.s.	85±1.7	n.s.
	2 min	84±1.8	0.04	85±1.9*	0.04	86±1.6	n.s.	86±2.8	n.s.
	3 min	87±2.5	n.s.	85±2.1*	0.06	84±1.5	n.s.	86±2.7	n.s.

* $p \leq 0.05$ by Wilcoxon m.p.s.r. test on differences with 0 min values versus control values.
p-value : 2-tailed probability by Wilcoxon m.p.s.r. test versus control day values.

(Reproduced from Sponsor, BEL-32, Second Study, Table 2, page 7)

Table 31. Heart Rate During a 3-Minute Isometric Handgrip Test on a Control Day and After 7 Days of Treatment with *dl*-nebivolol, *l*-Nebivolol, *d*-Nebivolol and Atenolol in 7 Healthy Volunteers

HANDGRIP POWER TEST		dl-nebivolol 5mg		l-nebivolol 2.5mg		d-nebivolol 2.5mg		atenolol 100mg	
		Mean±SEM	p	Mean±SEM	p	Mean±SEM	p	Mean±SEM	p
Control day	0 min	76±3.5	--	74±4.1	--	76±2.0	--	75±4.1	--
	1 min	79±4.1	--	80±3.9	--	81±2.7	--	82±4.0	--
	2 min	83±4.0	--	79±2.6	--	81±3.1	--	83±3.6	--
	3 min	83±4.6	--	79±3.6	--	82±2.7	--	84±3.4	--
Day 2	0 min	66±3.6	0.02	73±3.6	n.s.	65±4.9	0.08	66±3.7	0.03
	1 min	71±4.4	0.03	80±2.4	n.s.	71±5.3	0.05	70±3.1	0.02
	2 min	70±2.8	0.02	79±2.8	n.s.	71±4.6	n.s.	70±2.9	0.02
	3 min	72±3.2	0.02	81±2.2	n.s.	73±4.3	0.09	72±4.0	0.02
Day 4	0 min	66±3.0	0.02	74±2.3	n.s.	67±4.2	0.06	65±4.9	0.02
	1 min	68±3.4	0.03	78±3.3	n.s.	71±4.9	0.03	66±4.7	0.02
	2 min	70±3.5	0.02	77±2.9	n.s.	71±3.5	0.02	67±3.9	0.02
	3 min	73±4.0	0.02	79±2.6	n.s.	75±5.3	n.s.	71±4.3	0.02
Day 7	0 min	70±2.2	0.08	73±2.8	n.s.	69±5.2	n.s.	65±4.4	0.02
	1 min	72±4.7	0.08	80±2.3	n.s.	77±5.8	n.s.	70±3.8	0.02
	2 min	75±4.5	0.03	79±1.4	n.s.	77±5.5	n.s.	70±3.7	0.02
	3 min	74±4.6	0.02	80±2.9	n.s.	77±6.1	n.s.	69±3.9*	0.02
Day 1 post	0 min	68±5.0	0.08	79±4.3	n.s.	67±3.4	0.03	63±3.4	0.02
	1 min	72±4.3	n.s.	82±4.8	n.s.	68±3.2	0.02	68±3.9	0.02
	2 min	71±4.0	0.02	82±4.5	n.s.	70±3.2	0.02	68±3.1	0.02
	3 min	68±4.6*	0.02	82±4.8	n.s.	67±4.0	0.03	68±2.6	0.02
Day 2 post	0 min	67±3.0	0.02	73±3.0	n.s.	68±4.5	n.s.	68±4.2	0.02
	1 min	70±4.1	0.03	81±3.0	n.s.	73±4.2	0.02	71±4.9	0.02
	2 min	71±3.6	0.02	81±3.0	n.s.	72±3.6	0.03	73±3.9	0.02
	3 min	70±5.1	0.02	79±4.9	n.s.	74±4.5	0.08	77±4.2	0.02
Day 4 post	0 min	66±4.4	0.02	77±3.9	n.s.	72±5.0	n.s.	74±4.3	n.s.
	1 min	74±5.2	n.s.	77±4.2	n.s.	74±4.1	0.06	80±4.1	n.s.
	2 min	76±5.5	0.02	79±4.2	n.s.	77±5.1	n.s.	82±5.5	n.s.
	3 min	76±6.8	0.08	79±3.6	n.s.	76±5.8	n.s.	84±5.6	n.s.

* $p \leq 0.05$ by Wilcoxon m.p.s.r. test on differences with 0 min values versus control values.
p-value : 2-tailed probability by Wilcoxon m.p.s.r. test versus control day values.

(Reproduced from Sponsor,BEL-32, Second Study, Table 3, page 8)

Table 32. Efficacy Results (BEL-32, Study 2)

Results (Control day / Day 7)

	dl-nebivolol	l-nebivolol	d-nebivolol	atenolol
HR (b/min)	74 / 66*	73 / 73	73 / 69 (day 1 post: 64*)	77 / 63*
SBP (mmHg)	122 / 113	121 / 123	126 / 114*	121 / 116 (day 1 post: 114*)
DBP (mmHg)	78 / 72 (day 1 post: 73*)	78 / 79	79 / 73*	76 / 74 (day 1 post: 73*)
QS2c (ms)	400 / 392	400 / 388*	393 / 394	385 / 396*
PEPc (ms)	107 / 95*	107 / 98*	103 / 105 (day 4: 112*)	103 / 107 (day 4: 108*)
LVETc (ms)	293 / 297	292 / 290	290 / 290	282 / 290
PEPc/ LVETc	0.36 / 0.32*	0.37 / 0.34*	0.36 / 0.36	0.37 / 0.37
PQ, ms	149 / 153	150 / 151	146 / 149	143 / 151
QRS, ms	94 / 94	93/ 90	93 / 93	90 / 93
QT, ms	359 / 374	360 / 360	363 / 367	350 / 376
QTc, ms	396 / 391	396 / 396	400 / 390	395 / 383
QTm, ms	382 / 385	383 / 383	385 / 382	380 / 381

3 min Handgrip test

Increase HR, b/min	7.6 / 3.7 (day 1 post: 0.3*)	4.7 / 7.1	6.1 / 7.9	9.0 / 3.9*
Increase SBP, mmHg	26 / 31	26 / 25	22 / 26	26 / 27
Increase DBP, mmHg	19 / 19	17 / 18	17 / 17	19 / 18

Asterisks refer to differences with control day values
*Levels of significance * $p \leq 0.05$*

(Reproduced from Sponsor, BEL-32, Study 2, page 3)

Conclusions: The increase of heart rate after 3 minutes of handgrip was significantly reduced after treatment with dl-nebivolol and after treatment with atenolol. Increase of systolic blood pressure was not influenced in any of the treatment sessions.

1.28 LMD No. 68085. Study ID BEL-21. ("Phase I Study: Comparison of the Subacute Haemodynamic Effects of *l*-nebivolol versus A Combination of *l*-Nebivolol and Atenolol in Healthy Volunteers. Clinical Research Report NEB-BEL-21. March 1989") (Reviewer: Maryann Gordon, M.D.)

Objective: To compare the subacute haemodynamic effect of *l*-nebivolol versus a combination of *l*-nebivolol and atenolol in healthy volunteers.

Methods: Sixteen healthy volunteers were subdivided in 2 groups of 8 after stratification for control values of systolic time intervals. In a double-blind way, one group received 2.5 mg o.d. of *l*-nebivolol for 3 weeks, followed by a single-blind placebo wash-out of 1 week. The other group of 8 subjects received 100 mg o.d. of atenolol for 3 weeks, from the second week on associated with 2.5 mg o.d. of *l*-nebivolol and also followed by a placebo wash-out period of 1 week. Heart rate, blood pressure, and ECG- and systolic time intervals were measured serially before and during the study period.

In a double-blind experiment heart rate, blood pressure, and ECG- and systolic time intervals were measured serially before, during, and after a 3-week treatment period with *l*-nebivolol 2.5 mg o.d. in a first group of 8 volunteers and with atenolol 100 mg o.d. associated during the last 2 weeks with *l*-nebivolol 2.5 mg o.d. in a second group of 8 volunteers.

Results: Heart rate and blood pressure were not influenced by *l*-nebivolol intake but significantly decreased after atenolol intake, and this decrease remained so after additional administration of *l*-nebivolol.

After *l*-nebivolol administration, a significant but transient decrease of the ratio PEP/LVET was observed, whereas such a decrease in the second study group was only seen after addition of *l*-nebivolol to atenolol treatment. These decreases were entirely due to a shortening of PEP values. In both study groups, effects on LVETc, QS2c, and ECG-intervals were minimal.

Table 33. Systemic Blood Pressure and Heart Rate Before, During, and After a Treatment with *l*-Nebivolol 2.5 mg O.D. and a Combination of Atenolol 100 mg O.D. and *l*-Nebivolol 2.5 mg O.D. in 16 Healthy Volunteers (BEL-21)

Table 2: Systemic blood pressure and heart rate before, during and after treatment with l-nebivolol 2.5 mg o.d. and a combination of atenolol 100 mg o.d. and l-nebivolol 2.5 mg o.d. in 16 healthy volunteers.

Study group	Study day	SBP (mmHg) Mean±SEM	SBP p-value* vs day 0	SBP p-value* vs day 7	DBP (mmHg) Mean±SEM	DBP p-value vs day 0	DBP p-value vs day 7	HR (b/min) Mean±SEM	HR p-value vs day 0	HR p-value vs day 7
I	0	127±2.5	--	--	81±1.6	--	--	75±2.2	--	--
(n=8)	1	128±5.0	n.s.	--	80±2.5	n.s.	--	70±4.5	n.s.	--
	2	127±2.7	n.s.	--	80±1.7	n.s.	--	67±4.7	0.07	--
	4	128±3.4	n.s.	--	81±1.7	n.s.	--	73±5.2	n.s.	--
	7	131±3.4	n.s.	--	81±1.5	n.s.	--	72±5.2	n.s.	--
	8	127±2.5	n.s.	--	79±1.6	n.s.	--	68±3.5	0.08	--
	9	130±2.4	n.s.	--	81±1.6	n.s.	--	67±4.8	n.s.	--
	11	128±2.6	n.s.	--	80±1.4	n.s.	--	68±3.9	0.04	--
	14	137±2.2	0.04	--	86±1.4	n.s.	--	74±5.9	n.s.	--
	15	131±4.5	n.s.	--	81±2.5	n.s.	--	71±5.4	n.s.	--
	16	132±5.2	n.s.	--	83±2.8	n.s.	--	71±4.3	n.s.	--
	18	135±2.5	n.s.	--	83±1.3	n.s.	--	72±5.4	n.s.	--
	21	132±5.0	n.s.	--	83±2.8	n.s.	--	74±4.4	n.s.	--
	22	127±3.2	n.s.	--	80±2.0	n.s.	--	64±3.6	0.008	--
	23	132±3.2	n.s.	--	82±1.7	n.s.	--	68±3.4	0.04	--
	25	126±2.1	n.s.	--	78±1.1	n.s.	--	70±6.1	n.s.	--
	28	132±3.4	n.s.	--	82±1.6	n.s.	--	71±5.6	n.s.	--
II	0	134±5.6	--	--	82±3.1	--	--	68±3.8	--	--
(n=8)	1	117±5.2	0.008	--	72±2.8	0.008	--	59±3.6	0.008	--
	2	116±5.2	0.008	--	71±2.9	0.008	--	55±1.8	0.02	--
	4	121±4.8	0.02	--	74±2.4	0.008	--	56±2.4	0.02	--
	7	113±4.9	0.008	--	68±2.4	0.008	--	59±2.3	0.07	--
	8	118±5.2	0.008	0.05	72±2.5	0.008	0.05	56±1.6	0.02	n.s.
	9	119±5.2	0.02	0.05	72±2.7	0.02	0.07	57±2.4	n.s.	n.s.
	11	119±4.1	0.008	0.02	73±2.4	0.02	0.05	61±2.9	n.s.	n.s.
	14	116±4.2	0.03	n.s.	72±2.0	0.02	0.06	57±1.6	0.05	n.s.
	15	121±5.9	0.02	0.02	75±2.9	0.02	0.008	58±1.6	0.05	n.s.
	16	119±6.1	0.02	n.s.	74±2.6	0.02	0.008	59±2.4	0.08	n.s.
	18	116±4.8	0.008	n.s.	72±2.6	0.02	0.02	58±2.7	0.02	n.s.
	21	117±4.4	0.02	n.s.	72±2.5	0.02	0.08	57±2.4	0.03	n.s.
	22	122±6.0	0.07	0.03	75±3.1	0.07	0.03	61±2.6	n.s.	n.s.
	23	122±5.4	0.03	0.02	76±3.3	0.08	0.02	67±2.7	n.s.	0.08
	25	126±5.4	n.s.	0.008	79±3.0	n.s.	0.008	66±2.8	n.s.	n.s.
	28	129±5.2	n.s.	0.008	79±2.4	n.s.	0.008	67±2.7	n.s.	0.05

Group I : l-nebivolol 2.5 mg o.d. for 3 weeks, followed by a 1 week wash-out
Group II: atenolol 100 mg o.d. for 3 weeks, from 2nd week on associated with l-nebivolol 2.5 mg o.d., followed by a 1 week wash-out
* Wilcoxon m.p.s.r. test, 2-tailed probability.

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Table 34. Systolic Time Intervals Before, During, and After a Treatment with *l*-Nebivolol 2.5 mg O.D. and a Combination of Atenolol 100 mg O.D. and *l*-Nebivolol 2.5 mg O.D. in 16 Healthy Volunteers

Table 4 : Systolic time intervals before, during and after a treatment with l-nebivolol 2.5 mg o.d. and a combination of atenolol 100 mg o.d. and l-nebivolol 2.5 mg o.d. in 16 healthy volunteers.

		PEP (msec)			$LVET_c$ (msec)			QS_{2c} (msec)			PEP/LVET		
Study group	Study day	Mean±SEM	p-value* vs day 0	p-value* vs day 7	Mean±SEM	p-value vs day 0	p-value vs day 7	Mean±SEM	p-value vs day 0	p-value vs day 7	Mean±SEM	p-value vs day 0	p-value vs day 7
I	0	108±4.2	--	--	289±5.3	--	--	397±7.9	--	--	0.374±0.012	--	--
(n=8)	1	107±3.8	n.s.	--	289±6.0	n.s.	--	396±7.8	n.s.	--	0.368±0.013	n.s.	--
	2	104±3.9	0.05	--	296±6.6	0.08	--	397±7.1	n.s.	--	0.346±0.014	0.02	--
	4	99±4.2	0.008	--	292±4.9	n.s.	--	391±5.6	n.s.	--	0.341±0.014	0.008	--
	7	108±5.6	n.s.	--	289±4.4	n.s.	--	397±7.0	n.s.	--	0.373±0.011	n.s.	--
	8	108±4.3	n.s.	--	288±3.8	n.s.	--	397±5.3	n.s.	--	0.372±0.013	n.s.	--
	9	111±3.3	n.s.	--	291±5.5	n.s.	--	399±6.0	n.s.	--	0.376±0.012	n.s.	--
	11	111±3.7	n.s.	--	286±3.1	n.s.	--	394±4.5	n.s.	--	0.380±0.012	n.s.	--
	14	107±3.7	n.s.	--	288±4.6	n.s.	--	395±5.7	n.s.	--	0.372±0.010	n.s.	--
	15	109±4.5	n.s.	--	289±3.3	n.s.	--	397±3.4	n.s.	--	0.376±0.014	n.s.	--
	16	110±4.5	n.s.	--	288±5.3	n.s.	--	397±7.0	n.s.	--	0.378±0.011	n.s.	--
	18	109±4.2	n.s.	--	289±5.4	n.s.	--	398±6.9	n.s.	--	0.378±0.011	n.s.	--
	21	107±4.0	n.s.	--	290±4.9	n.s.	--	398±5.3	n.s.	--	0.375±0.013	n.s.	--
	22	112±3.3	n.s.	--	292±4.5	n.s.	--	402±5.5	n.s.	--	0.377±0.010	n.s.	--
	23	112±4.0	n.s.	--	291±5.9	n.s.	--	400±7.4	n.s.	--	0.378±0.011	n.s.	--
	25	112±4.1	n.s.	--	286±1.7	n.s.	--	395±3.0	n.s.	--	0.385±0.011	n.s.	--
	28	112±5.0	n.s.	--	294±4.2	n.s.	--	405±5.3	n.s.	--	0.381±0.013	n.s.	--
II	0	108±2.4	--	--	294±7.9	--	--	401±7.0	--	--	0.361±0.013	--	--
(n=8)	1	111±3.3	n.s.	--	292±6.7	n.s.	--	397±6.7	n.s.	--	0.360±0.015	n.s.	--
	2	112±3.3	0.07	--	293±7.3	n.s.	--	397±7.3	n.s.	--	0.359±0.013	n.s.	--
	4	113±3.9	n.s.	--	293±7.0	n.s.	--	398±7.3	n.s.	--	0.364±0.015	n.s.	--
	7	114±3.2	0.05	--	297±6.4	n.s.	--	405±6.7	n.s.	--	0.365±0.012	n.s.	--
	8	106±4.2	n.s.	0.008	295±6.3	n.s.	n.s.	393±7.7	0.03	0.02	0.337±0.015	0.08	0.008
	9	106±3.1	n.s.	0.008	296±6.0	n.s.	n.s.	394±6.8	0.02	n.s.	0.336±0.011	0.04	0.008
	11	110±3.3	n.s.	n.s.	295±4.3	n.s.	n.s.	398±5.1	n.s.	n.s.	0.352±0.009	n.s.	0.04
	14	110±3.9	n.s.	n.s.	294±5.7	n.s.	n.s.	397±6.6	n.s.	n.s.	0.355±0.011	n.s.	0.05
	15	112±3.0	0.08	n.s.	299±6.1	n.s.	n.s.	404±6.8	n.s.	n.s.	0.355±0.010	n.s.	0.02
	16	113±4.3	n.s.	n.s.	296±7.1	n.s.	n.s.	402±7.2	n.s.	n.s.	0.360±0.014	n.s.	n.s.
	18	113±3.0	n.s.	n.s.	296±5.2	n.s.	n.s.	400±5.3	n.s.	n.s.	0.355±0.012	n.s.	0.08
	21	112±3.0	n.s.	n.s.	299±7.0	0.07	n.s.	403±7.9	n.s.	n.s.	0.351±0.010	n.s.	0.008
	22	112±4.1	n.s.	n.s.	297±7.1	n.s.	n.s.	403±8.6	n.s.	n.s.	0.357±0.011	n.s.	0.04
	23	111±4.4	n.s.	n.s.	300±7.8	0.02	n.s.	409±8.7	0.02	n.s.	0.365±0.013	n.s.	n.s.
	25	111±2.8	n.s.	0.08	297±6.9	n.s.	n.s.	404±7.4	n.s.	n.s.	0.364±0.011	n.s.	n.s.
	28	109±4.3	n.s.	0.04	290±7.1	0.03	0.04	396±7.3	0.02	0.03	0.367±0.016	n.s.	n.s.

Group I : l-nebivolol 2.5 mg o.d. for 3 weeks, followed by a 1 week wash-out
Group II: atenolol 100 mg o.d. for 3 weeks, from 2nd week on associated with l-nebivolol 2.5 mg o.d., followed by a 1 week wash-out
* Wilcoxon m.p.s.r. test, 2-tailed probability.

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Table 35. ECG-Intervals Before, During, and After a Treatment with *l*-Nebivolol 2.5 mg O.D. and a Combination of Atenolol 100 mg O.D. and *l*-Nebivolol 2.5 mg O.D. in 16 Healthy Volunteers

Study group	Study day	PQ (msec) Mean±SEM	p-value* vs day 0	p-value* vs day 7	QRS (msec) Mean±SEM	p-value vs day 0	p-value vs day 7	QT (msec) Mean±SEM	p-value vs day 0	p-value vs day 7	QT_c (msec) Mean±SEM	p-value vs day 0	p-value vs day 7	QT_m (msec) Mean±SEM	p-value vs day 0	p-value vs day 7
I	0	144±6.5	--	--	93±3.1	--	--	374±7	--	--	403±11	--	--	393±6	--	--
(n=8)	1	148±5.3	n.s.	--	91±3.0	n.s.	--	375±7	n.s.	--	402±12	n.s.	--	393±5	n.s.	--
	2	146±5.0	n.s.	--	91±2.3	n.s.	--	376±7	n.s.	--	397±13	n.s.	--	390±6	n.s.	--
	4	146±6.5	n.s.	--	93±2.5	n.s.	--	374±8	n.s.	--	406±11	n.s.	--	396±6	n.s.	--
	7	145±6.5	n.s.	--	93±2.5	n.s.	--	373±10	n.s.	--	406±12	n.s.	--	396±7	n.s.	--
	8	148±5.6	n.s.	--	94±2.6	n.s.	--	375±7	n.s.	--	402±10	n.s.	--	392±6	n.s.	--
	9	149±5.8	n.s.	--	94±2.6	n.s.	--	376±7	n.s.	--	402±11	n.s.	--	392±6	n.s.	--
	11	146±6.0	n.s.	--	94±2.6	n.s.	--	375±7	n.s.	--	391±11	n.s.	--	386±6	n.s.	--
	14	144±5.6	n.s.	--	94±2.6	n.s.	--	374±8	n.s.	--	403±11	n.s.	--	393±6	n.s.	--
	15	145±6.5	n.s.	--	93±2.5	n.s.	--	374±8	n.s.	--	402±11	n.s.	--	393±7	n.s.	--
	16	144±6.8	n.s.	--	93±2.5	n.s.	--	370±6	n.s.	--	393±11	0.02	--	385±6	0.05	--
	18	144±6.5	n.s.	--	94±1.8	n.s.	--	370±9	n.s.	--	398±11	n.s.	--	390±6	n.s.	--
	21	148±5.6	n.s.	--	94±2.6	n.s.	--	366±8	n.s.	--	405±7	n.s.	--	392±4	n.s.	--
	22	150±5.7	n.s.	--	91±2.3	n.s.	--	376±7	n.s.	--	396±10	n.s.	--	389±7	n.s.	--
	23	146±5.6	n.s.	--	91±2.3	n.s.	--	374±9	n.s.	--	391±10	0.02	--	386±6	0.07	--
	25	148±5.6	n.s.	--	91±2.3	n.s.	--	370±11	n.s.	--	386±11	0.008	--	382±8	0.02	--
	28	146±6.0	n.s.	--	93±2.5	n.s.	--	365±9	n.s.	--	394±12	0.08	--	385±7	0.04	--
II	0	155±10.7	--	--	95±4.2	--	--	370±8	--	--	393±11	--	--	384±9	--	--
(n=8)	1	151±9.7	n.s.	--	95±3.3	n.s.	--	385±9	0.02	--	377±8	0.008	--	381±8	n.s.	--
	2	150±9.3	n.s.	--	95±3.3	n.s.	--	393±10	0.02	--	379±8	0.02	--	386±8	n.s.	--
	4	154±9.2	n.s.	--	96±4.2	n.s.	--	388±9	0.03	--	374±10	0.08	--	381±9	n.s.	--
	7	158±9.4	n.s.	--	96±3.2	n.s.	--	383±8	0.08	--	377±12	0.008	--	379±10	n.s.	--
	8	153±7.0	n.s.	n.s.	94±3.8	n.s.	n.s.	390±8	0.008	n.s.	377±12	0.04	n.s.	383±10	n.s.	n.s.
	9	149±7.4	n.s.	0.06	96±2.6	n.s.	n.s.	390±7	0.02	0.09	378±7	n.s.	n.s.	384±6	n.s.	n.s.
	11	156±8.9	n.s.	n.s.	96±4.2	n.s.	n.s.	386±8	0.03	n.s.	380±10	n.s.	n.s.	383±8	n.s.	n.s.
	14	153±7.3	n.s.	n.s.	95±3.8	n.s.	n.s.	385±9	0.08	n.s.	378±10	n.s.	n.s.	382±8	n.s.	n.s.
	15	155±8.0	n.s.	n.s.	95±3.8	n.s.	n.s.	381±9	n.s.	n.s.	377±9	n.s.	n.s.	379±9	n.s.	n.s.
	16	155±8.5	n.s.	n.s.	95±3.8	n.s.	n.s.	381±9	n.s.	n.s.	370±6	0.02	n.s.	376±6	n.s.	n.s.
	18	150±7.8	n.s.	n.s.	96±3.2	n.s.	n.s.	391±8	0.02	0.09	372±10	0.02	n.s.	381±8	n.s.	n.s.
	21	151±7.7	n.s.	n.s.	98±4.1	n.s.	n.s.	390±9	0.03	n.s.	374±8	0.02	n.s.	382±8	n.s.	n.s.
	22	149±7.2	n.s.	0.06	95±3.8	n.s.	n.s.	388±9	0.02	n.s.	383±9	n.s.	n.s.	387±6	n.s.	n.s.
	23	146±7.1	n.s.	0.03	95±3.8	n.s.	n.s.	378±9	n.s.	n.s.	402±9	n.s.	0.02	394±7	n.s.	0.05
	25	151±7.7	n.s.	n.s.	98±4.1	n.s.	n.s.	379±7	n.s.	n.s.	395±9	n.s.	0.04	388±6	n.s.	n.s.
	28	151±9.3	n.s.	n.s.	96±4.6	n.s.	n.s.	371±10	n.s.	0.08	389±7	n.s.	n.s.	383±6	n.s.	n.s.

Group I : l-nebivolol 2.5 mg o.d. for 3 weeks, followed by a 1 week wash-out

Group II: atenolol 100 mg o.d. for 3 weeks, from 2nd week on associated with l-nebivolol 2.5 mg o.d., followed by a 1 week wash-out

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

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Appears This Way
On Original

1.29 LMD No. 108085. Study ID: NED-7. ("Invasive Hemodynamics of Nebivolol in Hypertensive Patients. Synoptic Clinical Research Report NEB-NED-7. April 1994") (Reviewer: Maryann Gordon, M.D.)

Objective: Hypertension/hemodynamic effects 3 hours after last intake of nebivolol 5 mg once daily for 4 weeks.

Design: Double blind, randomized placebo controlled, cross over. Eleven subjects with essential mild to moderate hypertension (diastolic blood pressure 90-115 mmHg) were studied. Two patients withdrew and are not included in the results.

Results:
There were lower blood pressure and heart rate in the nebivolol group compared to placebo. CO, SV, TPR, and CVP, however, were similar between drug and placebo. See Table 36 and Figure 36.

Table 36. Results (NED-7), Mean Values (SEM)

Mean values (SEM)	Placebo (n= 9)	Nebivolol (n =9)
MAP, mmHg	122 (4)	111 (3)*
HR, bpm	70 (4)	59 (3)*
CO, l/min	6.29 (0.36)	5.70 (0.21)
SV, ml	91 (6)	97 (4)
TPR, mmHg.min/l	19.85 (1.19)	19.70 (0.81)
CVP, cm H_2O	3.6 (0.6)	3.7 (0.6)

Levels of significance at $p < 0.01$:*
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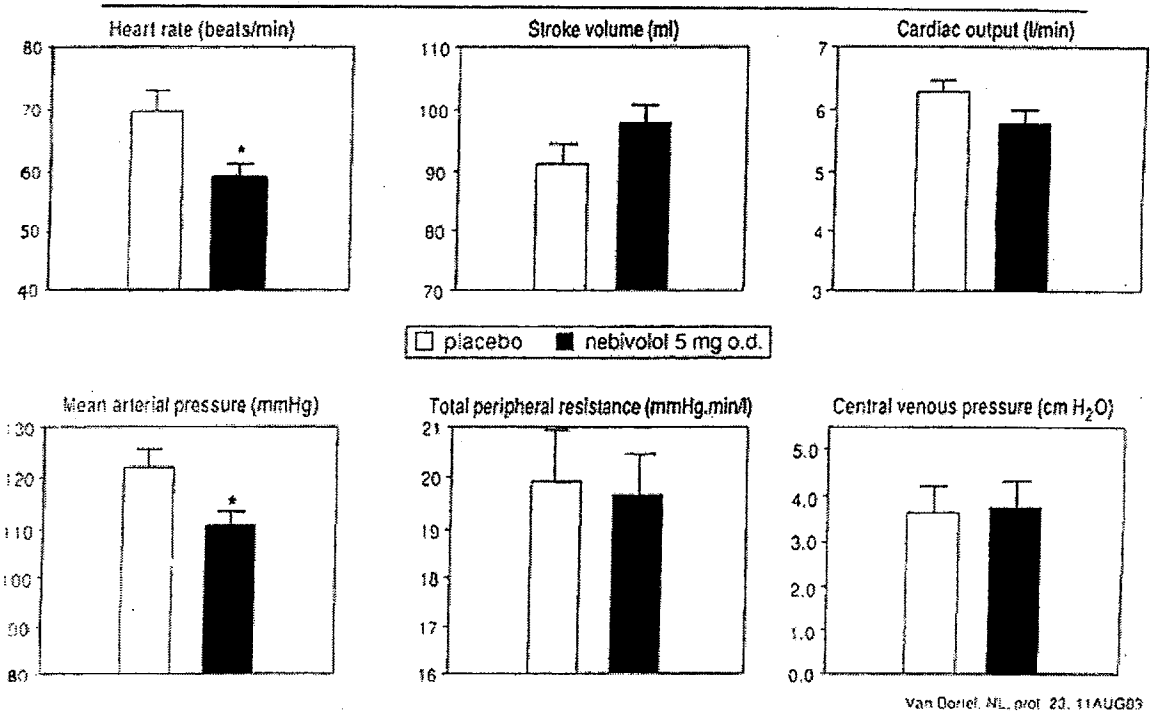
Figure 36. Haemodynamic Effects of Nebivolol in Hypertensive Patients (Dye Dilution Technique, 2 x 4 Weeks Cross-Over with Placebo) (n = 9) (NED-7)



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LMD No. 106560. Study ID NED-7. Invasive Hemodynamics of Nebivolol in Hypertensive Patients.

Same report as above.

1.30 LMD No. 107433. Study ID: USA-2. ("Evaluation of left Ventricular Function Assessed with Doppler Echocardiography and Radionuclide Ventriculography in Hypertensive Patients after Chronic Treatment with Nebivolol and Atenolol. Clinical Research Report NEB-USA-2, April 1994") (Reviewer: Maryann Gordon, M.D.)

Objectives: to study the mechanism of blood pressure reduction with nebivolol versus atenolol and to evaluate the influence of treatment with nebivolol versus atenolol in cardiac performance.

Methods: Twenty hypertensive patients (mean sitting diastolic blood pressure between 95 and 114 mmHg) were randomized in a four-way cross-over trial with nebivolol 2.5 mg and 5 mg, atenolol, and placebo, to assess cardiac performance and the mechanism of

blood pressure reduction. There was a four-week placebo run-in period and a wash-out period of one week between treatment phases which lasted three weeks.

Blood pressure, radionuclide ventriculography, and Doppler echocardiography were assessed at the end of each treatment phase. Seven patients dropped out before trial completion: four during the placebo phase, one with atenolol, one with nebivolol 5 mg, and one during the washout period after nebivolol 2.5 mg.

Results:

Table 37. Radionuclide Ventriculography Efficacy Results (USA-2)

Mean values	Neb 2.5	Neb 5	Atenolol	Placebo
Left ventricular peak ejection rate, Hz				
Load 0 watt	-1.97	-2.07	-1.94*	-2.17
25 watt	-2.51	-2.51*	-2.45	-2.62
75 watt	-2.78*	-2.94*	-2.91*	-3.43
Left ventricular peak filling rate, Hz				
25 watt	2.71*	2.99	2.51*	3.00
75 watt	3.18*	3.44	3.46*	3.74
Heart rate, bpm				
0 watt	61.1°*	59.4*	56.9*	67.8
25 watt	90.1 *	90.2°*	84.0*	97.1
75 watt	108.0*	103.5*	102.6*	116.5
Systolic blood pressure, mmHg				
25 watt	153.0	156.8	150.7*	156.4
50 watt	156.9*	163.8°	157.5*	165.7
75 watt	171.5	170.3	170.9*	177.3
Diastolic blood pressure, mmHg				
0 watt	94.3	94.4	91.8*	98.3
25 watt	99.6	99.7	93.3*	103.4
50 watt	101.0	101.5	95.9*	105.3
75 watt	104.1°	99.5*	98.9*	107.5

***significant difference compared to placebo**
°significant difference compared to atenolol
(Reproduced from Sponsor, USA-2, page vii)

Table 38. Cardiac Doppler-Echocardiography Results (USA-2)

Mean values	Neb 2.5	Neb 5	Atenolol	Placebo
Left ventricular internal dimension:				
• **end-diastolic, cm**	4.95°	5.12	5.14*	5.05
Cycle length, s	1.034*	0.985*	1.047*	0.901
Diastolic blood pressure, mm Hg	94.6*	91.8*	91.4	99.4
Heart rate, bpm	58.5*	62.1*	58.3*	69.5
Left ventricular ejection time, ms	0.314°	0.299°	0.346*	0.303
Early mitral peak flow velocity, $m.s^{-1}$	65.60	74.80*	69.26	65.23
Atrial peak/early peak velocity	0.920*	0.897*	0.825*	1.018

***significant difference compared to placebo**
°significant difference compared to atenolol
(Reproduced from Sponsor, USA-2, page vii)

1.31 LMD No. 54549. Study ID: BEL-30. ("Hemodynamic Effects of a Single Oral Administration of R65824 (Nebivolol), a New Selective Beta-1-Adrenoreceptor Blocking Agent in Human Volunteers as Compared to the Effects of Atenolol, Pindolol and Propranolol") (Source: Clinical Research Report NEB-BEL-30, September, 1985 and Study Publication[1]. No protocol was submitted.) (Reviewer: Shari Targum, M.D.)

Objective: evaluate acute effects of nebivolol, compared to atenolol, propranolol, and pindolol, on systemic and cardiac hemodynamics in healthy volunteers.

Study summary: This was an open-label, active-controlled, single-dose crossover study in healthy adult males and females. All subjects underwent a complete evaluation on a control day and at 6 different days after a single oral dose of R 65824 5 mg, R 65824 10 mg, propranolol 80 mg, pindolol 15 mg, pindolol 30 mg and atenolol 100 mg. Subjects received test drugs in random sequence and one week apart for each drug. Each volunteer took study medication at the same time of day and all measurements were performed at exactly the same time of day, both during control and after intake of test drug. No medication was allowed 48 hours prior to testing. Evaluations consisted of the following: 1) Systolic and diastolic blood pressures (BP) at rest were measured before drug intake and at 3 and 6 hours post-dose. BP measurements used the subject's left arm and were done by the same observer with the subject in supine position after a 10 minute rest. 2) In addition, subjects underwent a 9-minute exercise treadmill test. It is noted that the protocol used a "modified Bruce" with the following speeds/elevations: 2.5 mph/10% incline (3 min), 3.4 mph/12% incline, 4.2 mph/14% incline. No diastolic BPs were taken during treadmill testing.

[1] **De Cree J. et. al. Haemodynamic Effects in Man During Exercise of a Single Dose of Narbivolol (R67555), a New Beta-1-Adrenoceptor Blocking Agent: A comparative Study With Atenolol, Pindolol, and Propranolol. Drug Development Research 8: 109-117 (1986).**

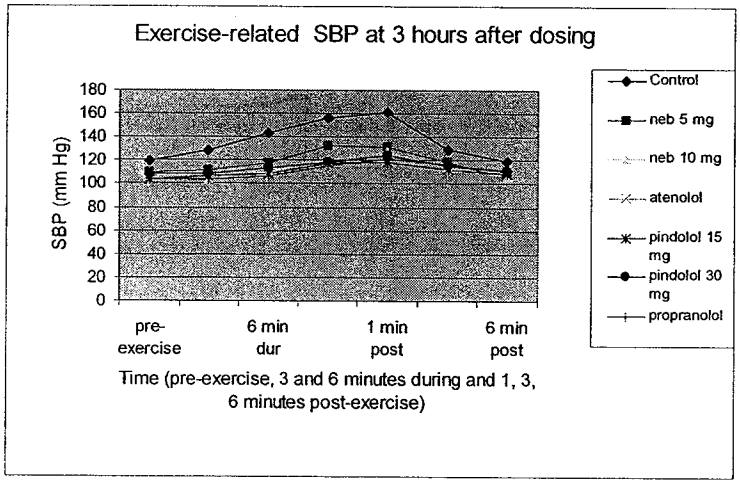
3) Systolic time intervals were measured from simultaneous recordings of a peripheral ECG lead (**Reviewer**: it is not known if any lead was prespecified), phonocardiograms, and carotid pulse wave. At least 5 consecutive cardiac cycles were analyzed and averaged for the following parameters: QS_2 (total electromechanical systole), LVET (left ventricular ejection time), and PEP (pre-ejection period). LVET and PEP were corrected for heart rate according to a regression equation: LVET = -1.112 HR + 370.22 and PEP = -0.32357 HR + 125.25. PEPc/LVETc was used as an index of left ventricular (LV) performance. The difference between LVETc before exercise and 30 seconds after end exercise was calculated and expressed as LVETc post-pre-exercise.

Reviewer: No primary endpoint was identified in the study report.

Results: Two females and 6 males, mean age 34 (range 27-47 years) and mean weight 63 (range 54-76) kg participated in this study. There were no dropouts.

Exercise-related SBP and HR are expressed graphically: for SBP at 3 hours, all active study drug values during exercise were different from control (via Wilcoxon matched pairs signed-ranks test, 2-tailed probability; $p \leq 0.05$).

Figure 37. Mean Exercise-Related SBP on a Control Day and at 3 Hours Post Dosing (BEL-30)



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