1.58 LMD No. 113227. Study ID BEL-55. ("The Effects of a One Week Administration of Nebivolol 5 mg o.d. on the Endocrine System and on Lipid Peroxidation in Healthy Male Volunteers. Clinical Research Report NEB-BEL-55. January 1996") (Trial Dates: March 27, 1995 – May 10, 1995). (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the influence of an 8-day oral administration of 5 mg nebivolol on the pituitary-adrenal-testicular endocrine system under basal conditions and after stimulation with ACTH in 8 healthy men. Additionally, the sponsor explored the effect of a 5 mg daily administration of nebivolol for one week on the ex-vivo Cu^{2+} induced LDL oxidation.

Methods: Healthy caucasian male volunteers, $\geq$ 18 and $\leq$ 60 years of age, participated in this double-blind, placebo-controlled cross-over study. Patients participated in 2 consecutive sessions which were separated by at least a one week washout period. In each session, subjects received either nebivolol 5 mg or placebo orally for 8 consecutive days. The trial was performed in accordance with the Declaration of Helsinki. Investigators performed a physical examination and screening laboratory safety profile at screening. On Day 1, serum was obtained for LDL-ox (Cu^{2+} induced oxidation of LDL). On Day 8, a 24 hour urine was collected, as well as serum for basal endocrinology (cortisol, aldosterone, 17-OH progesterone, progesterone, ACTH, estradiol, testosterone, sex hormone binding globulin (SHGB), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), androstenedione, and dihydroepiandrosterone (DHEA)), LDL-ox (Cu^{2+} induced oxidation of LDL), and plasma levels. An ACTH stimulation test was also performed at this time point. At thirty minutes, 1 hour, and 2 hours after IV ACTH (0.25 mg), venous blood samples were obtained for determinations of cortisol, aldosterone, 17-OH, and progesterone.

Results: 8 men with a median age of 43.5 years participated in this trial. On Day 8, 2 hours following nebivolol or placebo intake, there were no significant differences in basal hormonal levels between placebo and nebivolol, except for aldosterone levels. Aldosterone levels were lower but not significantly ($p = 0.057$) lower after nebivolol than after placebo treatment, as shown in Table 85. There was no significant period effect in any parameters, although FSH was lower in the second period (not statistically significant). There was a significant carry-over effect ($p = 0.0571$) for estradiol levels.

After IV injection of ACTH, hormone levels were comparable between treatments. There was a significant carry-over effect for aldosterone levels ($p = 0.057$ considering weighted average, $p = 0.029$ considering % AUC). These results are shown in Figure 87.

Twenty-four hour urine collection did not demonstrate any significant difference in aldosterone and cortisol levels, and there was no carry-over or period effect.

Although this was studied only in 2 volunteers, there was no nebivolol effect on LDL-oxidation.

Only two volunteers reported adverse events. One volunteer had a headache after intake of placebo, and 1 patient experienced flu-like symptoms following nebivolol intake. There were no drop-outs.

Sponsor's Conclusions:

1. Nebivolol did not significantly influence basal hormone levels after 8 days of therapy with nebivolol 5 mg daily.
2. Nebivolol did not significantly influence urinary excretion of cortisol and aldosterone.
3. Nebivolol did not influence the adrenal responsiveness after stimulation with ACTH.

Table 85. Hormonal Levels: Statistics (BEL-55)

Display 2: Hormonal levels: statistics

Laboratory test	Placebo					Nebivolol 5mg					Treat-ment effect	Carry-over effect	Period effect
	n	Mean	95% CI	SE	Median	n	Mean	95% CI	SE	Median			
BLOOD													
17α-OH progesterone(nmol/l)	8	4.6	3.1; 6.1	0.63	4.1	8	5.0	2.7; 7.2	0.95	3.9			
30min. post ACTH	8	9.0	6.7; 11.2	0.96	8.7	8	10.0	7.8; 12.1	0.91	9.8			
1 hr post ACTH	8	8.3	6.7; 9.9	0.66	7.8	8	8.6	6.7; 10.5	0.80	7.8			
2 hrs post ACTH	8	9.9	8.6; 11..2	0.55	9.9	8	9.8	8.1; 11.5	0.71	10.5			
ACTH (pg/ml)	6	14.0	7.7; 20.3	2.44	13.5	8	10.6	5.4; 15.9	2.22	8.7			
Aldosterone (pmol/l)	8	562	497; 628	28	566	8	481	399; 563	35	485	(*)		
30min. post ACTH	8	942	740; 1144	85	997	8	875	724; 1027	64	857			
1 hr post ACTH	8	854	648; 1059	87	958	8	816	691; 940	53	774			
2 hrs post ACTH	8	695	518; 871	75	717	8	712	590; 834	52	735			
Androstenedione (nmol/l)	8	5.5	3.90; 7.15	0.69	5.0	8	5.4	3.59; 7.11	0.75	4.6			
Cortisol (nmol/l)	8	248	203; 292	19	255	8	272	211; 333	26	263			
30min. post ACTH	8	664	593; 735	30	687	8	669	599; 739	30	695			
1 hr post ACTH	8	742	673; 812	30	745	8	758	669; 846	37	752			
2 hrs post ACTH	8	908	787; 1030	51	935	8	916	801; 1030	48	940			
Dihydroepiandrosterone (nmol/l)	8	12.7	10.75; 14.55	0.80	13.0	8	12.1	10.56; 13.64	0.65	12.0			
FSH (U/l)	8	3.4	2.29; 4.48	0.46	3.1	8	3.0	2.36; 3.62	0.27	2.9			(*)
LH (U/l)	8	2.5	0.81; 4.12	0.70	1.7	8	2.0	1.20; 2.78	0.34	1.9			
Oestradiol (pmol/l)	8	52	31; 73	8.79	52	8	53	37; 73	7.72	62		(*)	
Progesterone (nmol/l)	8	1.3	0.95; 1.55	0.13	1.2	8	1.4	1.02; 1.77	0.16	1.4			
30min. post ACTH	8	3.0	2.51; 3.51	0.21	3.3	8	3.4	2.78; 4.07	0.27	3.3			
1 hr post ACTH	8	3.5	2.93; 4.05	0.24	3.5	8	3.5	2.85; 4.10	0.26	3.5			
2 hrs post ACTH	8	4.1	3.16; 5.04	0.40	4.0	8	4.3	3.89; 4.79	0.19	4.6			
Prolactin (ng/ml)	8	3.0	1.65; 4.30	0.56	2.2	8	3.9	2.07; 5.73	0.78	3.5			
SHBG (nmol/l)	8	25.6	17.3; 34	3.54	24.0	8	27.9	16.9; 38.9	4.66	26.5			
Testosterone (nmol/l)	8	16.6	11.2; 21.9	2.27	15.0	8	15.8	9.78; 21.85	2.55	14.0			
URINE													
Aldosterone (nmol/mg crea)	8	0.010	0.007; 0.013	0.001	0.011	7	0.010	0.009; 0.012	0.001	0.011			
Cortisol (nmol/mg crea)	8	0.28	0.21; 0.35	0.03	0.26	8	0.26	0.20; 0.33	0.03	0.24			

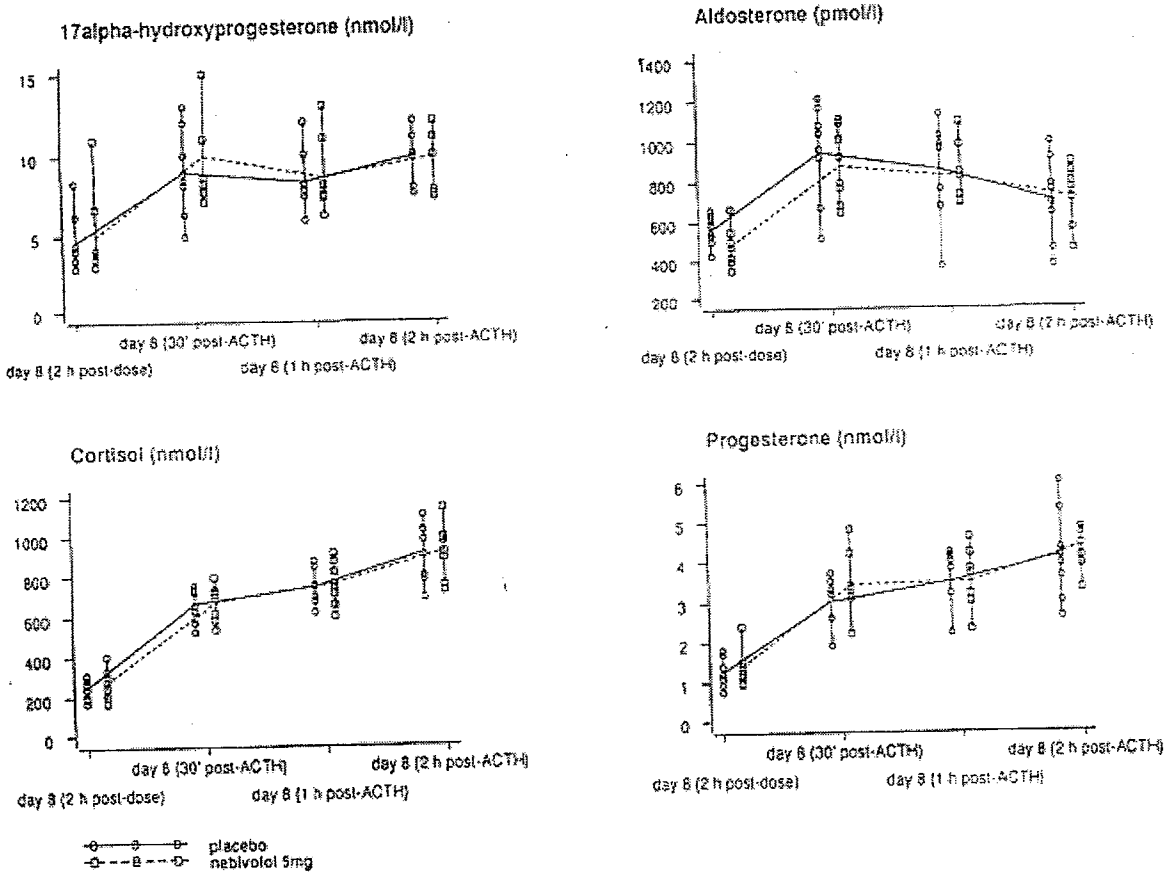
(*)0.05<p<0.1 two-tailed probability by Mann-Whitney U-test (Rank analysis)

21

(Reproduced from Sponsor, Display 2, BEL-55, page 21)

Appears This Way
On Original

Figure 87. Graphical presentation: Individual and Mean Serum Hormonal Levels (Basal and After ACTH Stimulation) (BEL-55)



(Reproduced from Sponsor, BEL-55, Display 3, page 22)

1.59 LMD No. 106748. Study ID ITA-5. ("Efficacy and Tolerance of Nebivolol Compared to Atenolol in Non-Insulin Dependent Diabetics with Essential Hypertension. Clinical Research Report NEB-ITA-5. October 1994") (Trial Period: January 22, 1993 – January 27, 1994) (Reviewer: Karen A. Hicks, M.D.)

Objective: To compare the effects of nebivolol and atenolol on blood pressure, heart rate, glucose and lipid metabolism, and haematological biochemical and clinical tolerance in hypertensive patients with non-insulin-dependent diabetes mellitus.

Methods: This was a randomized, single centre, double-blind parallel, active control study in hypertensive, non-insulin dependent male and female diabetic patients, ranging from 18 to 70 years in age. The trial was performed in accordance with the Declaration of Helsinki. Patients underwent a 4-week period of single-blind treatment with placebo. Existing medication was discontinued during the first 2 weeks of placebo treatment. If

eligible, patients then received either nebivolol 5 mg or atenolol 50 mg once daily for 24 weeks in a randomized, double-blind fashion.

Study assessments were performed as shown in Table 86.

Table 86. Study Assessments (ITA-5)

Assessments	Study Week						
	Placebo run-in		Double-blind treatment				
	-4	-2	0	2	6	12	24
• Efficacy							
- blood pressure	x	x	x	x	x	x	x
• Metabolic studies							
- euglycaemic clamp test			x			x	x
- 24-h urinary excretion tests			x				x
- plasma glucose	x		x	x	x	x	x
- serum lipids			x			x	x
- glycosylated haemoglobin	x		x		x	x	x
• Safety							
- heart rate	x	x	x	x	x	x	x
- body weight	x		x		x	x	x
- ECG	x		x		x	x	x
• Adverse Events	x	x	x	x	x	x	x
• Clinical laboratory parameters	x		x			x	x

(Reproduced from Sponsor, ITA-5, page 6)

The aim was to enroll 30 patients into the trial. Patients were examined at the first visit and at the end of the 4 week run-in period (Week 0). Patients returned for study visits at Weeks 2, 6, 12, and 24, at which time safety and efficacy was evaluated. Investigators made assessments at trough plasma levels (i.e. approximately 24 hours after the previous dose of study drug) after patients fasted overnight.

The euglycaemic hyperinsulinaemic clamp technique was performed 24 to 48 hours after the glucose tolerance test to measure tissue sensitivity to exogenous insulin at the end of the placebo run-in (Week 0) and at the completion of treatment (Week 24).

Intravenous glucose tolerance tests were performed at Weeks 0, 12, and 24.

Results: A total of 30 patients (15 patients in each group) participated in the study. Twenty-six patients (13 patients in each group) had concomitant illnesses, as shown in Table 87. Ten patients in the nebivolol treatment group and eight patients in the atenolol treatment group received concomitant medication during the study, as seen in Table 88. Thirteen patients were treated for diabetes with dietary measures only.

Table 87. Co-Existing Disease (ITA-5)

	Nebivolol 5 mg (n=15)	Atenolol 50 mg (n=15)	All Patients (n=30)
diabetic retinopathy (1st degree)	3	0	3
gall stones	2	1	3
gastritis	1	1	2
hypertensive retinopathy (1st degree)	5	5	10
hypertensive retinopathy (2nd degree)	3	1	4
hyperuricaemia	0	1	1
inguinal hernia	0	1	1
previous appendectomy	5	8	13
previous cholecystectomy	2	2	4
previous hysterectomy	2	5	7
previous tonsillectomy	1	1	2
varicose veins	1	1	2
Total patients with co-existing disease	**13**	**13**	**26**

(Reproduced from Sponsor, ITA-5, Display 2, page 33)

Table 88. Concomitant Medication (ITA-5)

	Nebivolol 5 mg (n=15)	Atenolol 50 mg (n=15)
Antigout		
allopurinol		1
Total		1
Diuretics		
indapamide		1
Total		1
H_2-receptor antagonists		
ranitidine	1	
Total	1	
Hypoglycaemics		
glibenclamide	5	4
Glibomet®	2	
Gliquidone	1	
metformin		1
phenformin	1	
tolbutamide	2	3
Total	10	7
Total patients with concomitant medication	**10**	**8**

(Reproduced from Sponsor, ITA-5, Display 3, page 34)

Compliance ranged from 99 to 110% in the nebivolol group and from 90 to 110% in the atenolol group. All 30 patients completed the study.

Nebivolol and atenolol demonstrated comparable reductions in supine and standing diastolic and systolic blood pressure. Blood pressure reductions in each group were evident by 2 weeks.

Table 89. Blood Pressures from Baseline (ITA-5)

	Blood pressure changes from baseline (mm Hg)								
	Nebivolol (n=15)			Atenolol (n=15)			P-value		
	Wk 0	Wk 2	Wk 24	Wk 0	Wk 2	Wk 24	Wk 0	Wk 2	Wk 24
Supine									
DBP	103.2	-12.9	-17.9	103.3	-11.7	-18.8	ns	ns	ns
SBP	164.9	-19.2	-25.7	165.9	-18.5	-28.7	ns	ns	ns
Standing									
DBP	105.7	-13.2	-18.0	105.5	-11.9	-18.7	ns	ns	ns
SBP	162.3	-19.6	-25.6	161.9	-18.3	-27.7	ns	ns	ns

ns p>0.05 Mann-Whitney *U* test

(Reproduced from Sponsor, ITA-5, page 24)

Table 90. Efficacy Study Results (ITA-5)

Baseline characteristics - patient disposition	nebivolol 5 mg	atenolol 50 mg
Number of patients entered (M/F) Age: median (min-max), yrs	8/7 61 (46-69)	6/9 58 (43-67)
Drop-outs	0	0

Effectiveness (n = number of patients with data)	nebivolol 5 mg (n = 15)	atenolol 50 mg (n = 15)
Primary parameters		
• mean blood pressure (End run-in/Week 24)		
- supine DBP, mm Hg	103.2/ 85.3	103.3/ 84.5
- standing DBP, mm Hg	105.7/ 87.7	105.5/ 86.8
- supine SBP, mm Hg	164.9/139.2	165.9/137.2
- standing SBP, mm Hg	162.3/136.7	161.9/134.1
• Metabolic studies (End run-in/Week 24), mean		
- total body glucose utilization, mg	20444/19896	21072/21260
- average glucose infusion rate, mg/kg/min	4.8/4.8	5.5/5.7
- Haemoglobin A1c	7.15/7.16	7.58/7.54
- HDL, mg/dl	45.8/47.0	48.5/50.1
- LDL, mg/dl	145.1/140.5	147.2/139.5
- total cholesterol, mg/dl	222.9/219.0	227.0/221.2
- triglycerides, mg/dl	159.6/157.7	156.3/158.0
- 24-h urinary glucose, g/l	0.0/0.0	0.1/0.1
- 24-h urinary albumin, mg/l	32.8/19/9	13.2/7.9
- 24-h urinary C-peptide, ng/ml	27.5/26.9	29.1/29.3

There were no statistically significant intergroup differences

(Reproduced from Sponsor, ITA-5, page 7)

Laboratory Safety Variables

There were no significant changes in blood chemistry or haematology, as shown in Table 91.

Table 91. Blood Count/Blood Chemistry/Urinalysis: Descriptive Statistics and Changes During Treatment (ITA-5)

Study group:nebivolol

Laboratory test	Unit	N	DBPG : start Mean	Sem	Median	DBPG : week 24 Mean	Sem	Median	(a)	?	Below B	Below W	Below A	Below M	Within B	Within W	Within A	Within M	Above B	Above W	Above A	Above M	N
(b)											=	-	--	?	+	=	-	?	++	+	=	?	
(c)																							
Biochemistry																							
Potassium	mmol/l	15	4.21	0.06	4.20	4.25	0.05	4.20								15							15
Sodium	mmol/l	15	142	0.76	141	142	0.70	141								15							15
Total protein	g/l	15	70.8	0.90	70.0	70.5	0.80	70.0								15							15
Albumin	%	15	57.6	0.88	58.9	57.8	0.84	59.3				1				14							15
Glucose	mmol/l	15	7.50	0.16	7.38	7.48	0.15	7.44													15		15
Total cholesterol	mmol/l	15	5.76	0.23	5.56	5.66	0.20	5.59								12					3		15
Triglycerides	mmol/l	15	1.82	0.10	1.92	1.80	0.09	1.84								7	2				6		15
HDL	g/l	15	0.46	0.02	0.46	0.47	0.02	0.49								2				3	10		15
LDL	g/l	15	1.45	0.09	1.41	1.40	0.08	1.34								15							15
Total bilirubin	micmol/l	15	10.2	0.78	8.72	10.2	0.64	10.3								15							15
Alkaline phosphatase	U/l	14	92.1	2.72	91.0	89.0	2.20	88.5								14		1					15
GGT	U/l	15	14.5	1.73	12.0	14.6	1.28	14.0				1			1	13							15
AST	U/l	15	19.8	2.21	19.0	20.5	1.92	19.0								15							15
ALT	U/l	15	14.3	1.54	14.0	14.3	1.17	15.0								15							15
Creatinine	micmol/l	15	89.0	3.81	88.4	94.3	2.39	97.2								15							15
Urea	mmol/l	15	4.46	0.32	4.00	4.57	0.29	4.16								15							15
Uric acid	micmol/l	15	355	9.49	351	340	8.84	345								15							15
Haematology																							
Haemoglobin	g/l	15	148	2.83	148	148	2.66	150								15							15
RBC	tera/l	15	4.75	0.13	4.91	4.72	0.12	4.86				3				12							15
Haematocrit	vol-%	14	42.7	0.58	42.6	42.6	0.55	42.6								14		1					15
WBC	giga/l	15	5.98	0.26	5.80	5.93	0.23	5.80				1				14							15
Segm neutrophils	%	15	62.9	0.97	64.0	62.9	0.97	63.0								15							15
Lymphocytes	%	15	33.6	0.80	32.0	34.3	0.93	34.0								15							15
Monocytes	%	15	1.47	0.22	2.00	1.00	0.17	1.00								15							15
Eosinophils	%	15	1.40	0.19	2.00	1.20	0.20	1.00								15							15
Basophils	%	15	0.53	0.17	0.00	0.60	0.13	1.00								14	1						15
Platelet count	giga/l	15	276	11.8	289	276	11.1	290								14						1	15
Urine																							
pH*		13	6.05	0.12	6.00	6.05	0.07	6.00		1						13		1					15
Protein	Code	15	1.13	0.09	1.00	1.07	0.07	1.00								13	1					1	15
Glucose*	Code	15	1.00	0.00	1.00	1.00	0.00	1.00								15							15
RBC*	Code	15	1.00	0.00	1.00	1.00	0.00	1.00								15							15

The means, standard errors and medians at the specified times of sampling are calculated for the same patients (paired data), after conversion of the units, generally into the SI unit. Descriptive statistics are not given for enzyme assays or for leucocyte differential count (in giga/l) because no generally applicable converting factor is available.

[a] No. of values below, within, and above normal range at end point (determined by reference to the range of normal values of each particular laboratory)

[b] No. of values below (B), within (W), and above (A) the normal range, or missing (M), at baseline

[c] Shifts of values from one class (B, W, A) to another (- or --: decrease; + or ++: increase; =: no change; ?: not known)

(Reproduced from Sponsor, ITA-5, Display 10, pages 45 and 46)

Appears This Way
On Original

Study group:atenolol

Laboratory test	Unit	N	DBPG : start Mean	Sem	Median	DBPG : week 24 Mean	Sem	Median	(a) (b) (c)	?	Below B =	W −	A −−	M ?	Within B +	W =	A −	M ?	Above B ++	W +	A =	M ?	N
Biochemistry																							
Potassium	mmol/l	15	4.14	0.05	4.10	4.20	0.04	4.20								15							15
Sodium	mmol/l	15	142	0.91	140	142	0.71	141								15							15
Total protein	g/l	15	70.5	0.93	71.0	70.5	0.67	70.0								15							15
Albumin	%	15	57.9	0.88	58.7	58.3	0.83	59.0			1					14							15
Glucose	mmol/l	15	7.77	0.21	7.66	7.62	0.21	7.55									1				14		15
Total cholesterol	mmol/l	15	5.97	0.29	5.66	5.72	0.26	5.48								10					5		15
Triglycerides	mmol/l	15	1.79	0.10	1.76	1.91	0.09	1.73								9	1				5		15
HDL	g/l	15	0.49	0.02	0.49	0.50	0.02	0.50								3					12		15
LDL	g/l	15	1.47	0.14	1.26	1.40	0.13	1.30								15							15
Total bilirubin	micmol/l	15	11.3	0.85	10.9	11.1	0.84	11.3								15							15
Alkaline phosphatase	U/l	15	88.4	4.28	93.0	88.1	3.04	90.0								15							15
GGT	U/l	15	15.0	1.94	13.0	15.2	1.40	14.0							4	11							15
AST	U/l	15	17.9	1.93	18.0	18.8	1.95	18.0								15							15
ALT	U/l	15	14.5	1.56	12.0	14.5	1.61	12.0								15							15
Creatinine	micmol/l	15	97.2	3.23	97.2	96.7	3.39	97.2								15							15
Urea	mmol/l	15	5.17	0.31	5.00	5.08	0.23	5.00								15							15
Uric acid	micmol/l	15	355	11.5	363	344	9.34	345								15							15
Haematology																							
Haemoglobin	g/l	15	142	2.90	139	143	2.83	140							2	13							15
RBC	tera/l	15	4.64	0.12	4.75	4.63	0.12	4.71			4					11							15
Haematocrit	vol-%	15	42.0	0.67	41.5	42.0	0.64	41.3			1					14							15
WBC	giga/l	15	6.15	0.26	5.80	5.85	0.19	5.90				1				14							15
Segm neutrophils	%	15	60.7	0.67	61.0	61.1	0.61	60.0								15							15
Lymphocytes	%	15	35.5	0.60	35.0	35.4	0.67	36.0								15							15
Monocytes	%	15	1.67	0.25	1.00	1.13	0.17	1.00								15							15
Eosinophils	%	15	1.33	0.19	1.00	1.67	0.21	2.00								15							15
Basophils	%	15	0.73	0.12	1.00	0.67	0.13	1.00								15							15
Platelet count	giga/l	15	253	15.0	226	255	14.5	230								14					1		15
Urine																							
pH*		14	6.05	0.15	6.00	5.96	0.09	6.00								13	1	1					15
Protein	Code	15	1.00	0.00	1.00	1.00	0.00	1.00								15							15
Glucose*	Code	15	1.13	0.09	1.00	1.13	0.09	1.00								12	1			1	1		15
RBC*	Code	15	1.00	0.00	1.00	1.00	0.00	1.00								15							15

The means, standard errors and medians at the specified times of sampling are calculated for the same patients (paired data), after conversion of the units, generally into the SI unit. Descriptive statistics are not given for enzyme assays or for leucocyte differential count (in giga/l) because no generally applicable converting factor is available.

* No. of values below, within, and above normal range at end point (determined by reference to the range of normal values of each particular laboratory)

* No. of values below (B), within (W), and above (A) the normal range, or missing (M), at baseline

* Shifts of values from one class (B, W, A) to another (- or - -: decrease; + or + +: increase; =: no change; ?: not known)

(Reproduced from Sponsor, Display 10, pages 45 and 46)

Heart Rate

In the nebivolol treatment group, supine heart rate decreased by a mean of 10.4 and 14.4 bpm at Weeks 2 and 24, compared with 11.1 and 13.3 bpm for atenolol. Reductions in standing heart rate were comparable for both nebivolol and atenolol treatment groups. Heart rate reductions are shown in Table 92 and Table 93.

Table 92. Supine Heart Rate (ITA-5)

Group	Phase	Interval	N	MEAN	SEM	(95% CI-mean)	P-value*
		Supine heart rate (beats/min)					
nebivolol	Run-in	start	15	82.3	2.41	(77.11; 87.43)	
		week 2	15	79.7	2.43	(74.52; 84.94)	
		week 4	15	81.1	2.12	(76.52; 85.61)	
	Treatment	week 2	15	70.7	1.83	(66.75; 74.59)	
		week 6	15	68.7	1.72	(64.98; 72.36)	
		week 12	15	69.7	1.65	(66.18; 73.28)	
		week 24	15	66.7	1.95	(62.49; 70.85)	
atenolol	Run-in	start	15	80.9	2.54	(75.48; 86.39)	
		week 2	15	78.5	2.56	(73.04; 84.03)	
		week 4	15	80.4	3.02	(73.91; 86.89)	0.4040
	Treatment	week 2	15	69.3	2.56	(63.85; 74.82)	0.5193
		week 6	15	68.7	2.36	(63.60; 73.74)	0.6569
		week 12	15	68.0	2.07	(63.57; 72.43)	0.8313
		week 24	15	67.1	2.26	(62.22; 71.91)	0.4356

* Mann-Whitney U test for between treatment differences in changes from end of run-in
Note: Heart rate reductions from end of run-in to Week 24 were highly significant within each treatment group (P <0.001) Friedman test

(Reproduced from Sponsor, ITA-5, Display 11, page 47)

Table 93. Standing Heart Rate (ITA-5)

Group	Phase	Interval	N	MEAN	SEM	(95% CI-mean)	P-value[a]
		Standing heart rate (beats/min)					
nebivolol	Run-in	start	15	86.3	2.49	(80.92; 91.61)	
		week 2	15	83.7	2.28	(78.84; 88.63)	
		week 4	15	85.9	2.48	(80.55; 91.19)	
	Treatment	week 2	15	73.6	2.09	(69.13; 78.07)	
		week 6	15	70.5	1.93	(66.40; 74.67)	
		week 12	15	73.2	1.71	(69.53; 76.87)	
		week 24	15	70.3	1.83	(66.34; 74.19)	
atenolol	Run-in	start	15	84.9	2.62	(79.30; 90.56)	
		week 2	15	82.8	2.65	(77.12; 88.48)	
		week 4	15	84.1	2.98	(77.75; 90.52)	0.3132
	Treatment	week 2	15	72.1	2.62	(66.51; 77.76)	0.9666
		week 6	15	72.1	2.46	(66.86; 77.40)	0.0513
		week 12	15	71.9	2.18	(67.20; 76.54)	0.6902
		week 24	15	70.8	2.35	(65.76; 75.84)	0.2952

[a] Mann-Whitney U test for between treatment differences in changes from end of run-in
Note: Heart rate reductions from end of run-in to Week 24 were highly significant within each treatment group (P <0.001) Friedman test

(Reproduced from Sponsor, ITA-5, Display 11, page 48)

Adverse Events

Regarding safety, there were no drop-outs and no deaths in this study.

Table 94. Safety Results: ITA-5

Safety (n = number of patients with data)	nebivolol 5 mg (n = 15)	atenolol 50 mg (n = 15)
Adverse events (AE)		
• abdominal pain	1	1
• nightmares	1	
• headache	1	
• asthenia		1
Total number of patients assessed	15	15
No. (%) with one or more AE	3	2
No. (%) with one or more severe AE	0	0
No. (%) with one or more serious AE	0	0
No. (%) treatment stopped due to AE	0	0
Clinical laboratory parameters	no consistent or clinically important changes	

(Reproduced from Sponsor, ITA-5, page 8)

Conclusions: Nebivolol and atenolol had similar efficacy in reducing blood pressure in this group of patients. Neither nebivolol nor atenolol adversely affected carbohydrate metabolism in terms of insulin sensitivity, whole body glucose utilization, haemoglobin A_{1c} levels, or 24-h excretion of glucose or C-peptide. During the 6 months of treatment, there were no significant changes in total cholesterol, LDL, HDL, triglycerides, and body weight. Patients tolerated both nebivolol and atenolol, and both agents reduced heart rate between 10 and 14 beats/minute. Three nebivolol and two atenolol patients experienced

adverse events. Nebivolol was not associated with the development of significant abnormalities in haematology or clinical biochemistry variables. No significant ECG changes were reported, but individual ECGs were not available for review.

1.60 LMD No. 125153. Study ID CAN-7. ("Clinical Evaluation of the Effects of Nebivolol vs. Atenolol on Plasma Lipid Profile and Carbohydrate Metabolism in Normometabolic Patients with Mild-to-Moderate Hypertension. Clinical Research Report NEB-CAN-7. October 1997") (Trial Dates: October 6, 1993 – August 16, 1995) (Reviewer: Karen A. Hicks, M.D.)

Objective: Primary objectives were to compare the effects of nebivolol 5 mg daily with atenolol 50 mg daily on lipids, lipoproteins, and variables related to carbohydrate metabolism in normometabolic subjects with mild to moderate essential hypertension. Secondary objectives were to compare the effects of nebivolol with atenolol on hormone profile and blood pressure.

Methods: This was a double-blind, randomized, two-centre, active-controlled, prospective, parallel study in male and female normometabolic subjects, ages 18-70 years, with mild to moderate essential hypertension. Patients underwent a four week, single-blind placebo wash-out phase and a twelve week double-blind treatment phase during which they received either nebivolol 5 mg or atenolol 50 mg daily. Investigators performed various assessments as shown in Table 95.

Table 95. Assessments (CAN-7)

Assessments	Phase I: Wash-out			Phase II: Active Treatment			
Visit	1	2	3	4	5	6	7
Week	-4	-2	0	2	4	8	12
Demographic data							
- informed consent	x						
- medical history	x						
- physical examination	x						
- chest X-ray	x						
Clinic Blood Pressure	x	x	x	x	x	x	x
ECG	x						x
Lipid Profile		x	x				x
Oral Glucose Tolerance Test			x				x
Laboratory	x		x		x		x
- hormone analysis			x				x
Adverse Events		x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x

(Reproduced from Sponsor, CAN-7, page 9)

The trial was performed in accordance with the Declaration of Helsinki.

Results: A total of 72 patients entered the trial and 39 patients were randomized. Thirty-three patients were screening failures and were discontinued before randomization. After

randomization, one patient experienced an adverse event and one patient had a protocol violation. Both of these patients were prematurely discontinued from the study. A total of 17 males and 20 females (21 nebivolol, 16 atenolol) were evaluable. The average age was 53.8 for the nebivolol treatment group and 55.6 for the atenolol treatment group.

During double-blind treatment 13 atenolol patients (81%) and 18 nebivolol patients (86%) used concomitant medications. Acetaminophen and aspirin were the most commonly used medications. Three patients on atenolol and one patient on nebivolol took L-thyroxine. Three patients in the atenolol treatment group and one patient in the nebivolol treatment group took estrogen replacement therapy.

Total Apolipoprotein A-1 and C-III, Apolipoprotein A- and C-containing Lipoparticles
The efficacy results are summarized in Table 96. There were no statistically significant differences in lipid and apolipoprotein parameters between the nebivolol and atenolol groups following three months of active treatment.

Table 96. Efficacy Results (CAN-7)

Effectiveness (n = number of evaluable patients)	nebivolol	atenolol
Primary parameters mean at baseline/week 12		
Lipids (mMol/L)	(n=17)	(n=13)
- Total cholesterol	5.00/4.77	4.58/4.47
- LDL C	3.45/3.10	2.59/2.87
- HDL C	1.05/1.00 *	1.06/1.00
- HDL_3 C	0.40/0.37	0.39/0.37
- HDL_2 C	0.69/0.63	0.71/0.65
- VLDL C	0.49/0.48	0.52/0.59
- LDL/HDL C	3.40/3.01	2.86/3.11
- Total TG	1.49/1.46	1.47/1.71
- HDL TG	0.24/0.25	0.25/0.25
- VLDL TG	0.94/0.97	0.97/1.16
Apolipoproteins (g/l)	(n=17)	(n=13)
- Apolipoprotein B (Total)	0.96/0.95	0.86/0.87
- Apolipoprotein B (LDL)	0.87/0.87	0.76/0.77
- Apolipoprotein B (VLDL)	0.09/0.07	0.09/0.10
- Apolipoprotein A-I (HDL)	1.24/1.15 *	1.23/1.15 *
- LDL C/LDL B	3.97/3.61	3.94/3.78
- Lp (a)	0.19/0.17	0.25/0.24
Apolipoproteins (mg/dL)	(n=8)	(n=6)
- Apo A-I plasma	125/120	132/121
- Apo C-III plasma (WP)	10.10/9.81	9.51/11.32
Lipoprotein particles (mg/dL)	(n=8)	(n=6)
- LP A-I plasma	30.20/29.90	35.20/31.90
- LP A-I: A II plasma	94.80/90.50	96.80/89.50
- Apo C-III heparin supernate (HS)	6.60/6.28	6.68/7.08
- Apo C-III heparin precipitate (HP)	2.52/2.72	2.40/3.22
- Apo C- III ratio (HS/HP)	2.62/2.47	3.07/2.39
Metabolic parameters	(n=21)	(n=16)
- Glucose (mMol/L)	5.22/5.29	5.09/5.57 *
- AUC glucose 0-2 hr	1034/1043	929/964
- Insulin (MU/L)	54.25/61.35	62.00/56.56
- AUC insulin 0-2 hr	57012/61867	53815/56109
- C-peptide (ug/L)	1.94/2.02	2.23/2.28
- AUC C-peptide 0-2 hr	943/894	955/974

Secondary parameters mean at baseline/week 12	(n=21)	(n=16)
Clinic BP		
- Sitting DBP (mm Hg)	98/90 * *	99/88 *
- Sitting SBP (mm Hg)	150/141	160/145 *
- Standing DBP (mm Hg)	98/91 *	99/89 *
- Standing SBP (mm Hg)	150/138 *	157/141
Sitting Heart Rate	72/65 *	73/63 *
Standing Heart Rate	77/68 *	78/64 *

Asterisks refer to differences from baseline. Level of significance: * p 0.05

(Reproduced from Sponsor, CAN-7, pages 11 and 12)

Oral Glucose Tolerance Test (OGTT) Parameters

Atenolol significantly increased ($p < 0.05$) serum glucose from baseline (5.09 ± 0.72 mmol/L) to the end of treatment (5.57 ± 0.86 mmol/L). Nebivolol did not significantly affect glucose. There were no other within treatment group differences for insulin and C peptide levels, as shown in Table 101.

Table 97. Mean Serum Glucose, Insulin, and C-Peptide Observed Before and After 3 Months of Nebivolol or Atenolol Treatment Following an oral Glucose Tolerance Test (OGTT) (CAN-7)

Parameter	Baseline* (n = 37) Nebivolol (n = 21)	Atenolol (n = 16)	After 3 months of Nebivolol Treatment (n = 21)	P^b within group	Atenolol Treatment (n = 16)	P^b within group	P* between group
Glucose (mmol/L)	5.22 ± 0.45	5.09 ± 0.72	5.29 ± 0.51	NS	5.57 ± 0.86	0.0368	NS
AUC glucose 0-2h (h x mmol/L)	1034 ± 201	929 ± 200	1 043 ± 225	NS	964 ± 217	NS	NS
Insulin mU/L	54.25 ± 26.72	62.0 ± 43.04	61.35 ± 32.90	NS	56.56 ± 32.19	NS	NS
AUC insulin 0-2h (h x mU/L)	57012 ± 26173	53815 ± 33067	61867 ± 41212	NS	56109 ± 42061	NS	NS
C-peptide (µg/L)	1.94 ± 0.62	2.23 ± 1.33	2.02 ± 0.94	NS	2.28 ± 1.39	NS	NS
AUC C-peptide 0-2h (h x µg/L)	943 ± 280	955 ± 362	894 ± 352	NS	974 ± 413	NS	NS

* Baseline value taken as covariate
Results expressed as mean ± SD
NS: p > 0.05
^a ANCOVA
^b Repeated measures ANOVA

(Reproduced from Sponsor, CAN-7, Display 5, page 57)

Blood Pressure

Both nebivolol and atenolol significantly reduced sitting diastolic blood pressure from baseline to Week 12. The reduction in diastolic blood pressure was apparent at two weeks. Nebivolol did not significantly decrease sitting systolic blood pressure from baseline to end of study. At Week 12, atenolol significantly reduced sitting systolic blood pressure from baseline to end of study, but there was no statistically significant difference between treatment groups at this time point. The blood pressure results are shown in Table 98 and Table 99.

Table 98. Mean Sitting Systolic and Diastolic Blood Pressure Before and After 2, 4, 8, and 12 Weeks of Nebivolol or Atenolol Treatment (CAN-7)

Clinic Blood Pressure (mmHg)	Nebivolol (n = 21)				Atenolol (n = 16)				P[a] between Group
Sitting Systolic BP (Mean of 3 readings)	Baseline	150 ± 17	Decrease[c]	P[b] within group	Baseline	160 ± 19	Decrease[c]	P[b] within group	
	Week 2	141 ± 16	-9 ± 11.8	NS	Week 2	146 ± 16	-10 ± 13.9	NS	NS
	Week 4	144 ± 15	-6 ± 15.0	NS	Week 4	144 ± 18	-13 ± 14.6	NS	NS
	Week 8	147 ± 16	-3 ± 10.2	NS	Week 8	142 ± 18	-15 ± 12.4	NS	< 0.01
	Week 12	141 ±15	-9 ± 15.4	NS	Week 12	145 ± 22	-16 ± 13.3	***	NS
Sitting Diastolic BP (mean of 3 readings)	Baseline	98 ± 6.7			Baseline	99 ± 5.0			
	Week 2	88 ± 8.5	-10 ± 7.0	***	Week 2	89 ± 5.2	-9 ± 4.0	***	NS
	Week 4	92 ± 8.9	-7 ± 6.9	***	Week 4	88 ± 7.7	-10 ± 6.7	***	NS
	Week 8	92 ± 7.8	-6 ± 6.3	***	Week 8	88 ± 7.9	-10 ± 6.7	***	NS
	Week 12	90 ± 8.6	-8 ± 7.4	***	Week 12	88 ± 6.2	-10 ± 5.8	***	NS

[a] ANOVA including the procedure of Dunnett
*** Statistically significant (p 0.05) reduction vs baseline
[c] Decrease = 2, 4, 8 and 12 week values - baseline
[b] ANCOVA NS: non significant at p 0.05 between treatments
Mean ± SD

(Reproduced from Sponsor, CAN-7, Display 6, page 58)

Nebivolol significantly decreased standing systolic and diastolic blood pressure from baseline to end of study. Atenolol significantly reduced standing diastolic blood pressure from baseline to end of study but did not have a significant effect on standing systolic blood pressure. There was no significant difference in these parameters between the nebivolol and atenolol treatment groups.

Table 99. Mean Standing Systolic and Diastolic Blood Pressure Before and After 2, 4, 8, and 12 Weeks of Nebivolol or Atenolol Treatment (CAN-7)

Clinic Blood pressure (mmHg)	Nebivolol (n = 21)				Atenolol (n = 16)				P[a] between Group
Standing systolic BP (1 reading)	Baseline	150 ± 16	Decrease[c]	P[b] within group	Baseline	157 ± 19	Decrease[c]	P[b] within group	
	Week 2	137 ± 16	-13 ± 8.9	NS	Week 2	144 ± 18	-11 ± 15.9	NS	NS
	Week 4	141 ± 16	-8 ± 15.0	NS	Week 4	147 ± 21	-9 ± 16.9	NS	NS
	Week 8	146 ± 18	-3 ± 11.0	NS	Week 8	145 ± 23	-10 ± 16.8	NS	NS
	Week 12	138 ±14	-12 ± 11.0	***	Week 12	141 ± 21	-16 ± 16.1	NS	NS
Standing diastolic BP (1 reading)	Baseline	98 ± 6.7			Baseline	99 ± 5.0			
	Week 2	87 ± 9.0	-12 ± 7.9	NS	Week 2	90 ± 7.1	-9 ± 7.4	***	NS
	Week 4	93 ± 10.9	-5 ± 6.4	NS	Week 4	91 ± 8.6	-7 ± 9.5	***	NS
	Week 8	93 ± 9.6	-6 ± 6.8	***	Week 8	90 ± 10.0	-8 ± 9.7	***	NS
	Week 12	91 ± 11.0	-8 ± 7.7	***	Week 12	89 ± 7.0	-10 ± 7.5	***	NS

[a] ANOVA including the procedure of Dunnett
*** Statistically significant (p < 0.05) reduction vs baseline
[c] Decrease = 2, 4, 8 and 12 week values - baseline
[b] ANCOVA - NS: non significant at p < 0.05 between treatments
Mean ± SD

(Reproduced from Sponsor, CAN-7, Display 7, page 59)

Heart Rate

Both nebivolol and atenolol significantly reduced sitting and standing heart rate from baseline to end of study, but there was no statistical significance between treatment groups, as seen in Table 100.

Table 100. Mean Heart Rate Before and After 2, 4, 8, and 12 Weeks of Nebivolol or Atenolol Treatment

Heart Rate (Beat/min)	Nebivolol (n = 21)				Atenolol (n = 16)				P[d] between Group
Sitting	Baseline	72 ± 10	Decrease[c]	P[b] within group	Baseline	73 ± 10	Decrease[c]	P[b] within group	
	Week 2	68 ± 8	-4 ± 9	NS	Week 2	64 ± 6	-8 ± 9	***	NS
	Week 4	67 ± 5	-6 ± 10	NS	Week 4	64 ± 8	-9 ± 7	***	NS
	Week 8	67 ± 9	-6 ± 10	NS	Week 8	65 ± 9	-7 ± 10	***	NS
	Week 12	65 ± 7	-8 ± 9	***	Week 12	63 ± 5	-10 ± 8	***	NS
Standing	Baseline	77 ± 10			Baseline	78 ± 10			
	Week 2	70 ± 9	-6 ± 9	NS	Week 2	68 ± 9	-10 ± 11	***	NS
	Week 4	68 ± 6	-8 ± 9	***	Week 4	68 ± 8	-10 ± 9	***	NS
	Week 8	69 ± 10	-7 ± 8	***	Week 8	67 ± 10	-11 ± 11	***	NS
	Week 12	68 ± 8	-8 ± 8	***	Week 12	64 ± 7	-14 ± 10	***	NS

[b] ANOVA including the procedure of Dunnett
*** Statistically significant ($p < 0.05$) reduction vs baseline
[c] Decrease = 2, 4, 8 and 12 week values - baseline
[d] ANCOVA. NS: non significant at $p < 0.05$ between treatments
Mean ± SD

(Reproduced from Sponsor, CAN-7, Display 8, page 60)

Compliance: Twenty-one patients in the nebivolol group missed fourteen doses during the 12 weeks of active treatment. Sixteen patients in the atenolol group missed seven doses during active treatment.

Safety: Sixteen atenolol and 21 nebivolol patients were included in the safety analysis. Two patients dropped out of the study early. One patient had depression, and the other patient had elevated triglycerides. Twenty-six patients (70%) reported at least one adverse event during the placebo run-in phase. During active treatment, 12 atenolol patients (75%) and 21 nebivolol patients (100%) reported at least one adverse event. Adverse events "definitively" related by the investigators to drug treatment are listed below in Table 101.

Table 101. Adverse Events Definitively Related to Drug Treatment

Atenolol		Nebivolol	
Adverse Event	Pt. #	Adverse Event	Pt. #
anorgasmia	#238	bradycardia	#259
bradycardia	#238	palpitation	#256
fatigue	#203	parasthesia	#243
headache	#260		
libido	#238		
palpitation	#260		
parasthesia	#203		
vertigo	#260		
dizziness	#240		
tremor	#260		

(Reproduced from Sponsor, CAN-7, Display 10, page 62)

Four patients receiving nebivolol reported serious adverse events (#339-headache, #247-bursitis, #233-leg cramp, and #251-migraine). No patients receiving atenolol experienced severe adverse events.

Table 102. Safety Results (CAN-7)

Safety	Placebo (4 weeks)	Nebivolol (12 weeks)	Atenolol (12 weeks)
Adverse events (AE)			
Most frequent AE's (# of pts)			
- Headache	14	11	2
- Vertigo	5	2	3
- Fatigue	6	2	3
Total number of patients assessed	35	21	16
- No. (%) with one or more AE	26 (74.3)	21 (100.0)	12 (75.0)
- No. (%) with one or more severe AE	2 (5.7)	4 (19.0)	0
- No. (%) treatment stopped due to AE		0	1
Body Weight (kg) mean at baseline/week 12		75.1/74.7	75.3/75.6
Hormonal parameters mean at baseline/week 12			
- ACTH (ng/L)			
- ANF-N terminal (pMol/L)		3.02/2.21 *	5.00/2.41 *
- Cortisol (nMol/L)		419/624 *	433/532 *
- Aldosterone (ng/L)		392/335	446/376 *
- No significant changes in ANF-C terminal, PRA, prolactin, T_3, T_4 or TSH		30.33/38.29	29.66/21.18 †
Laboratory parameters			
- No significant changes in hematology, biochemistry or urine parameters were observed		9	7
- Number of patients with important laboratory abnormalities (code 1-5)		4	3
- Number of patients with "code 4" abnormalities			

Asterisks refer to differences from baseline (p 0.05)
† - Refers to treatment difference (p0.05) - No baseline difference observed

(Reproduced from Sponsor, CAN-7, page 12)

Laboratory Parameters

There were no significant changes in haematology, biochemistry, or urinalysis results during active treatment.

In the nebivolol treatment group, 2 patients had significant increases in fasting glucose, 1 patient had a significant increase in BUN, and 1 patient had a significant increase in RBC. In the atenolol treatment group, 2 patients had a significant increase in BUN, and 1 patient had a significant increase in alkaline phosphatase.

Hormonal Parameters

Both nebivolol and atenolol significantly reduced ACTH levels from baseline to end of study, as shown in Table 103. The reductions in ACTH levels were not significantly different between treatment groups. Nebivolol increased aldosterone levels while

atenolol decreased aldosterone levels. The difference in aldosterone levels was statistically significant (p = 0.0302) between treatment groups. Atenolol significantly decreased cortisol levels (p = 0.0391). Both nebivolol and atenolol significantly increased ANF, but there was no statistical significance between treatment groups.

Table 103. Endocrine Profile Summary Values Observed Before and After 3 Months of Nebivolol or Atenolol Treatment

Parameter	Baseline* Nebivolol (n=21)	Baseline* Atenolol (n= 16)	After 3 months of Nebivolol Treatment (n=21)	p[b] within group	After 3 months of Atenolol Treatment (n=16)	p[b] within group	p[a] between group
ACTH (ng/L)	3.02 ± 1.57 (17)	5.00 ± 3.58 (11)	2.21 ± 1.97 (14)	0.0320	2.41 ± 2.68 (10)	0.0381	NS
Aldosterone (ng/L)	30.33 ± 22.76 (17)	29.66 ± 19.56 (12)	38.29 ± 35.60 (14)	NS	21.18 ± 9.21 (8)	NS	0.0302
ANF (C Terminal) (pmol/L)	15.58 ± 12.54 (17)	17.87 ± 12.45 (13)	25.11 ± 40.16 (17)	NS	18.98 ± 9.63 (12)	NS	NS
ANF (N Terminal) (pmol/L)	419 ± 331 (17)	433 ± 312 (13)	624 ± 351 (16)	0.0001	532 ± 179 (12)	0.0007	NS
Cortisol (nmol/L)	392 ± 146 (17)	446 ± 108 (13)	335 ± 162 (16)	NS	376 ± 124 (12)	0.0391	NS
PRA (ng/mL/hr)	0.998 ± 0.882 (15)	0.794 ± 0.642 (12)	1.181 ± 1.401 (13)	NS	1.187 ± 0.937 (8)	NS	NS
Prolactin (µg/L)	8.05 ± 3.41 (17)	7.40 ± 2.38 (13)	8.45 ± 5.84 (16)	NS	8.86 ± 2.96 (12)	NS	NS
T3 (nmol/L)	0.270 ± 0.014 (18)	0.916 ± 1.111 (13)	1.260 ± 0.918 (16)	NS	1.490 ± 1.098 (13)	NS	NS
T4 (ng/L)	25.1 ± 29.2 (16)	36.5 ± 42.4 (13)	23.1 ± 24.7 (16)	NS	36.0 ± 40.7 (12)	NS	NS
TSH (mU/L)	1.69 ± 0.91 (17)	1.43 ± 1.18 (13)	1.61 ± 0.91 (16)	NS	1.58 ± 1.24 (12)	NS	NS

* Baseline value taken as covariate
Results expressed as mean ± SD
NS: p > 0.05
[a] ANCOVA
[b] Repeated measures ANOVA

(Reproduced from Sponsor, Display 16, page 82)

Conclusions: After twelve weeks of treatment, both drugs significantly decreased HDL apolipoprotein A-1 (HDL Apo A-1) (nebivolol $p < 0.02$, atenolol $p < 0.05$) and HDL cholesterol (HDL C) ($p < 0.05$). The ratio of LDL C to HDL C did not change significantly in either the nebivolol or atenolol treatment groups. During treatment with nebivolol and atenolol, there were no significant changes in total cholesterol, HDL2C, HDL3C, LDL C, VLDL C, total triglycerides, HDL, TG, LDL, TG, VLDL TG, total apo B, LDL B, VLDL B (including the ratio LDL C to LDL B), Lp(a) during treatment with both drugs. There was no "between drug" significance in plasma Apo A-1, Apo-C-III, Apo-A-1-, C-III-containing lipoparticles (including the Apo-C-III ratio). Atenolol significantly increased serum glucose following a 2 hour oral glucose tolerance test (OGTT), but there was no statistical significance between atenolol and nebivolol treatment groups. There were no significant differences between nebivolol or atenolol nor within each treatment group regarding insulin or C-peptide concentrations following a 2 hour oral glucose tolerance test (OGTT).

In the nebivolol treatment group, mean clinic trough sitting SBP/DBP significantly decreased from 150/98 at baseline to 141/90 at termination, compared with a decrease from 160/99 mm Hg at baseline to 145/88 mm Hg at termination for atenolol. There were no significant differences in sitting SBP/DBP between treatments. Both atenolol and nebivolol significantly reduced heart rate.

Both nebivolol and atenolol significantly increased ($p < 0.001$) plasma atrial natriuretic factor (ANF) concentrations and significantly decreased ($p < 0.05$) plasma ACTH levels.

Only atenolol significantly decreased ($p < 0.05$) plasma cortisol levels. Adverse events were similar between treatment groups.

Atenolol significantly increased serum glucose levels after three months of treatment following an oral glucose tolerance test. Otherwise, there were no significant changes in haematology, biochemistry, or urinalysis results within or between treatment groups.

In summary, nebivolol produced a statistically significant reduction in HDL C levels from baseline to end of treatment. Atenolol significantly increased serum glucose after three months of treatment following an oral glucose tolerance test. Both nebivolol and atenolol reduced diastolic and systolic BP and heart rate. Other than aldosterone, which was increased in the nebivolol group and decreased in the atenolol group, there were no significant between group differences in the endocrine profile.

1.61 LMD No. 126525. Study ID CAN-8. ("A Prospective Comparison of the Effects of Nebivolol and Atenolol on Glucose, Insulin, and Lipid Metabolism During Long-Term Treatment in Patients with Mild to Moderate Essential Hypertension and Impaired Glucose Intolerance. Clinical Research Report NEB-CAN-8. February 1998"). (Trial Dates: March 29, 1993 – July 5, 1995) (Reviewer: Karen A. Hicks, M.D.)

Objective: To compare the effect of nebivolol and atenolol on insulin sensitivity and insulin response in patients with confirmed mild to moderate essential hypertension and impaired glucose tolerance; also to compare the effect of nebivolol and atenolol on lipid profile, ambulatory and clinic blood pressure, and regional and systemic haemodynamics at rest and during isometric and dynamic exercise.

Methods: This was a double-blind, randomized, single-centre, active-controlled, prospective, two-way, cross-over study to compare the effects of nebivolol (2.5 mg/day to 5 mg/day) and atenolol (50 mg/day to 100 mg/day) on glucose, insulin, and lipid metabolism during long-term therapy. Male or female patients, ages 40-65 years inclusive, with mild to moderate hypertension, underwent a 4-week, single-blind placebo run-in phase and two 16-week, double-blind treatment (nebivolol or atenolol) phases separated by a 4-week single-blind placebo washout. Using sitting trough diastolic blood pressure (DBP) in clinic as a measure of antihypertensive response, investigators titrated each study drug, if necessary, from the initial dose of either nebivolol 2.5 mg/day or atenolol 50 mg/day.

The trial design is shown in Figure 88.

Figure 88. Trial Design (CAN-8)

STUDY PHASE	Phase 1 (run-in)		Phase 2 (active treatment)							Phase 3 (washout)		Phase 4 (active treatment)					
BLINDING	single		double							single		double					
STUDY WEEK	-4	-2	0	2	4	8	12	16		18		20	22	24	28	32	36
VISIT	1	2	3	4	5	6	7	8		9		10	11	12	13	14	15
STUDY MEDICATION	placebo		nebivolol or atenolol							placebo		atenolol or nebivolol					

(Reproduced from Sponsor, CAN-8, page 14)

Study assessments were performed as follows in Table 104:

Table 104. Study Assessments (CAN-8)

STUDY PHASE	PHASE 1 Placebo (run-in)			PHASE 2 Active treatment (atenolol or nebivolol)					PHASE 3 Placebo (washout)		PHASE 4 Active treatment (nebivolol or atenolol)				
BLINDING	Single			Double					Single		Double				
STUDY WEEK	-4	-2	0	2	3	8	12	16	18	20	22	24	28	32	36
VISIT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Screening:															
Informed Consent	X														
Medical History	X														
Demographics	X														
Physical Examination	X														
Efficacy:															
Clinic BP and HR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ambulatory BP and HR			X					X							X
Clamp Study			X					X							X
IVGTT			X					X							X
Lipid Profile			X					X							X
$HgbA_{1c}$			X					X							X
OGTT	X														
Maximal O_2 uptake		X						X							X
Haemodynamic study			X					X							X
Safety:															
Body weight	X		X					X							X
Laboratory tests		X						X							X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Additional:															
Lifestyle check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Med/Disease	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note:

1. Patients prematurely discontinuing during Phase 2 or 4 had to be seen for a final visit for completion of termination assessments (Visits 8 and 15, respectively).
2. Visits were to be scheduled within ±3 days of the visit date as outlined in the protocol. To allow for scheduling of special assessments (ABPM, IVGTT, and the clamp study), visits with metabolic investigations could occur over a 7 day period.
3. Clamp Study = euglycemic-hyperinsulinemic clamp study

(Reproduced from Sponsor, CAN-8, Display 1, page 18)

In the 40-week study, patients were to complete 15 study visits. Maximal oxygen uptake was measured using Sensormedic's Energy Expenditure Unit 2900 while the patient exercised on an electronically controlled ergometer cycle (Monark model 829E).

Results: A total of 28 patients with mild to moderate hypertension and impaired glucose tolerance were enrolled in the study. One patient entered the placebo run-in phase but was discontinued because he did not meet entry criterion (mean daytime diastolic blood

pressure was not ≥ 90 mm Hg). Twenty-seven patients (8 males, 19 females) were randomized, with a median age of 54.3 years. A total of 25 patients completed the trial. Two patients dropped out of the study due to an inadequate response. The final doses in the nebivolol treatment group included 3 patients on 2.5 mg and 23 patients on 5 mg. The final doses in the atenolol treatment group included 6 patients on 50 mg and 20 patients on 100 mg. Of the patients who had their study medication titrated, the average time before the increase was 16 days for nebivolol and 19 days for atenolol.

Euglycemic-Hyperinsulinemic Clamp Study

There was no significant difference in mean insulin concentrations between atenolol and nebivolol or compared with placebo. Atenolol significantly decreased ($p < 0.05$) mean glucose disposal rate by 16%, compared with placebo, but there were no significant differences between atenolol and nebivolol or between nebivolol and placebo, as seen in Table 105.

Table 105. Glucose/Insulin Homeostasis - Euglycemic-Hyperinsulinemic Clamp Test

	Placebo	Atenolol	Nebivolol
Glucose disposal rate (M) (mg/kg/min) n = 25	4.62	3.89*	4.30
Mean insulin concentration (I) (pmol/L) n = 25	672	722	723
Insulin sensitivity index (M/I) n = 25	0.74	0.58**	0.65

* active treatment vs. placebo p<0.05
** active treatment vs. placebo p<0.01

(Reproduced from Sponsor, CAN-8, Display 3, page 53)

There was a carry-over effect ($p = 0.01$) when the insulin sensitivity index was compared by treatment sequence. The first phase of active treatment did not demonstrate any significant differences between treatment groups. When the entire cohort was evaluated, however, atenolol decreased the sensitivity index by 22%, compared with placebo ($p < 0.01$). Nebivolol decreased the sensitivity index by 12%, but it was not significantly different from placebo or atenolol.

Intravenous Glucose Tolerance Test

The "k value" is the glucose disappearance rate and is a measure of glucose tolerance of an individual. Atenolol significantly decreased the k value by 11%, compared with placebo ($p < 0.05$). Nebivolol slightly improved the k value, compared with placebo, but there was no statistical significance. There was a statistically significant difference in k value between atenolol and nebivolol ($p < 0.01$), suggesting atenolol had a greater effect on impairing glucose tolerance.

Table 106. Glucose/Insulin Homeostasis - Intravenous Glucose Tolerance Test (CAN-8)

	Placebo	Atenolol	Nebivolol
Glucose disappearance rate (% / min) n = 25	1.12	1.00***	1.16
Peak insulin response (pmol/L) n = 25	322	350	347
Insulin area (μM·min) n = 25	0.038	0.046	0.042
Glucose area (mM·min) n = 25	1258	1323***	1244
Glucose injected (g) n = 25	36.4	36.8	36.9

* active treatment vs. placebo p<0.05 ** active treatment vs. active treatment p<0.01

(Reproduced from Sponsor, CAN-8, Display 4, page 54)

There was no significant difference between active treatments in the peak insulin response, a reflection of the first phase of insulin response.

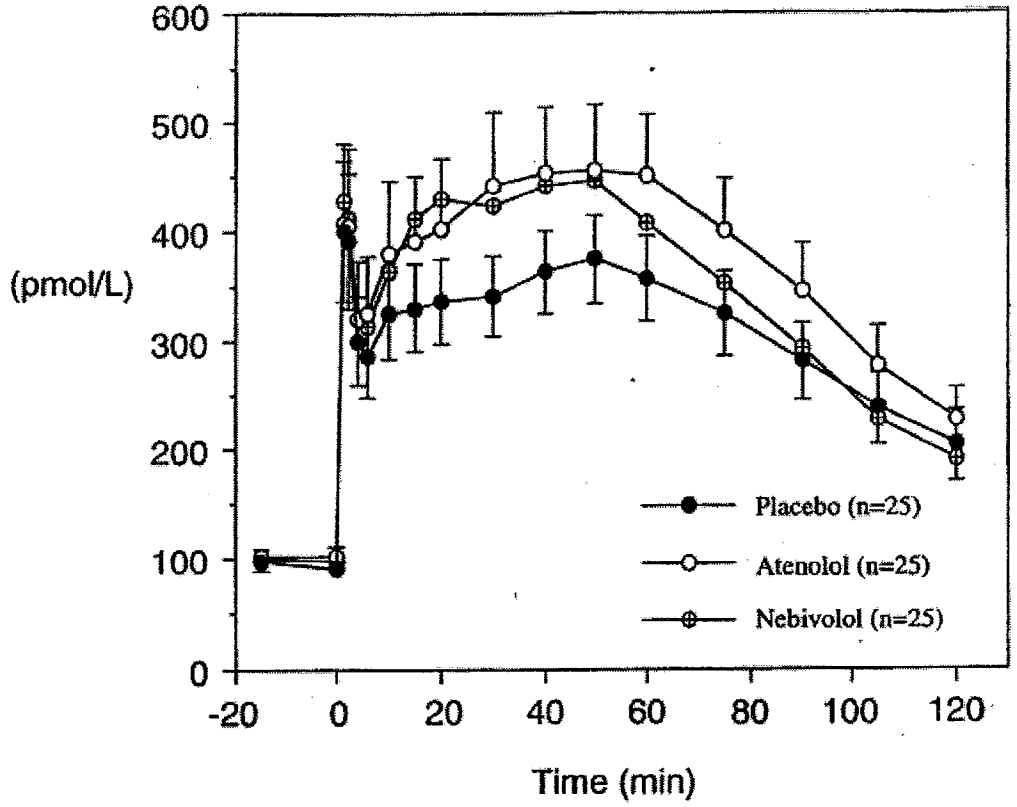
Atenolol significantly increased the glucose area under the curve, another measure of glucose tolerance, by 5% ($p < 0.05$). Nebivolol did not significantly affect this parameter. The difference in glucose area under the curve between active treatments was statistically significant ($p < 0.01$).

Between 40 and 120 minutes of the IVGTT, glucose levels were significantly higher with atenolol than with nebivolol ($p < 0.05$). Between 30 and 120 minutes, glucose levels with atenolol were also statistically significant ($p < 0.05$). Throughout IVGTT testing, nebivolol was not statistically significant from placebo.

At 90 minutes only, the insulin levels between active treatments was statistically significant ($p < 0.05$). Compared with placebo, insulin levels at 90 minutes in the atenolol group were statistically significant ($p < 0.05$) while those in the nebivolol group were not. Insulin levels for the two treatment groups are shown in Figure 89.

Appears This Way
On Original

Figure 89. Glucose/Insulin Homeostasis - Plasma Insulin Levels During IVGTT (CAN-8)



(Reproduced from Sponsor, CAN-8, Display 6, page 56)

Lipid Profile

Patients receiving atenolol had a 6% decrease in HDL ($p < 0.01$), a 5% decrease in apolipoprotein A_1 ($p < 0.01$), a 10% increase in the LDL-cholesterol / HDL-cholesterol ratio ($p < 0.05$), and a 9% decrease in the apolipoprotein A_1 / apolipoprotein B_1 ratio, compared with placebo ($p < 0.01$).

Clinic Blood Pressure

Mean blood pressure readings are shown in Table 107. Atenolol and nebivolol significantly decreased mean sitting and standing blood pressure, compared with placebo. Both active treatments significantly decreased heart rate, compared with placebo.

Table 107. Clinic Blood Pressure and Heart Rate (CAN-8)

	Placebo	Atenolol	Nebivolol
Sitting			
systolic blood pressure (mmHg) n = 25	160	147***	148***
diastolic blood pressure (mmHg) n = 25	101	91***	92***
heart rate (bpm) n = 25	77	66***+	67***
Standing			
systolic blood pressure (mmHg) n = 25	155	144**	145**
diastolic blood pressure (mmHg) n = 25	100	90***	91***
heart rate (bpm) n = 25	80	68***	72***

** active treatment vs. placebo p<0.01
*** active treatment vs. placebo p≤0.001
+ active treatment vs. active treatment p<0.05

(Reproduced from Sponsor, CAN-8, Display 8, page 58)

Ambulatory Blood Pressure

Both atenolol and nebivolol significantly reduced blood pressure and heart rate, as shown in Table 108.

Table 108. Ambulatory Blood Pressure and Heart Rate (CAN-8)

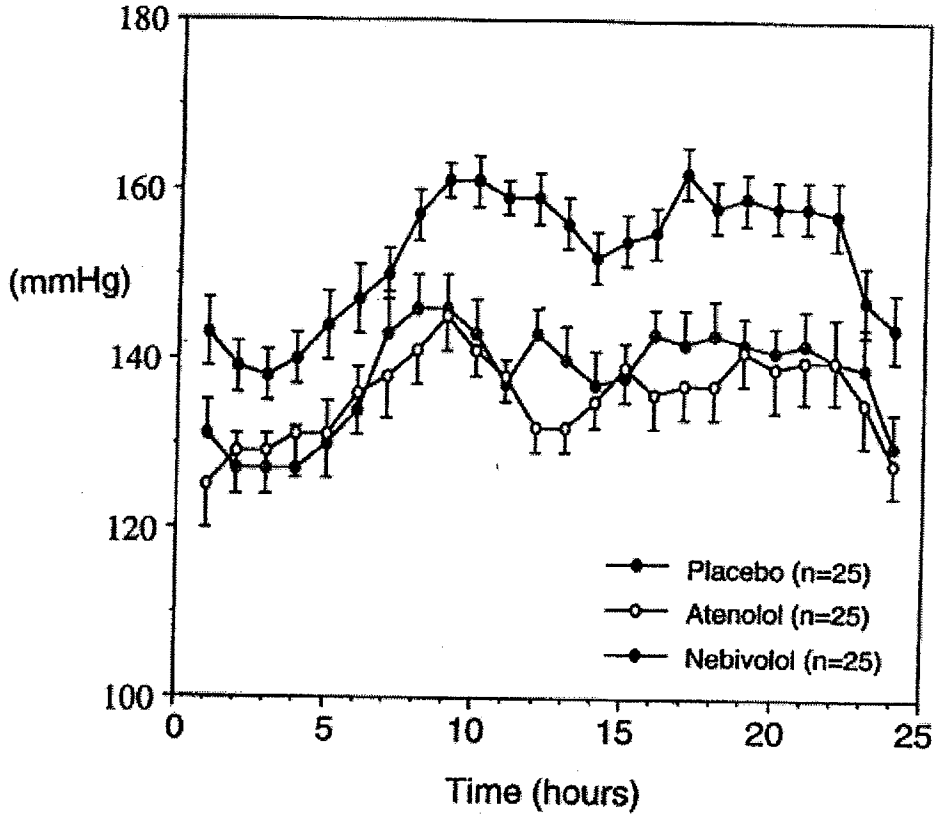
	Placebo	Atenolol	Nebivolol
Mean daytime			
systolic blood pressure (mmHg) n = 25	158	138***	142***
diastolic blood pressure (mmHg) n = 25	94	81***++	84***
heart rate (bpm) n = 25	79	63***++	70***
Mean nighttime			
systolic blood pressure (mmHg) n = 25	144	131***	131***
diastolic blood pressure (mmHg) n = 25	82	73***	75***
heart rate (bpm) n = 25	67	57***+	60***
Mean 24-hour			
systolic blood pressure (mmHg) n = 25	152	136***	138***
diastolic blood pressure (mmHg) n = 25	90	78***+	81***
heart rate (bpm) n = 25	75	61***++	66***

*** active treatment vs. placebo p≤0.001
+ active treatment vs. active treatment p<0.05
++ active treatment vs. active treatment p<0.01
+++ active treatment vs. active treatment p≤0.001

(Reproduced from Sponsor, CAN-8, Display 9, page 59)

Compared to nebivolol, atenolol significantly lowered mean daytime diastolic blood pressure as well as mean daytime, mean nighttime, and mean 24-hour heart rate ($p < 0.01$).

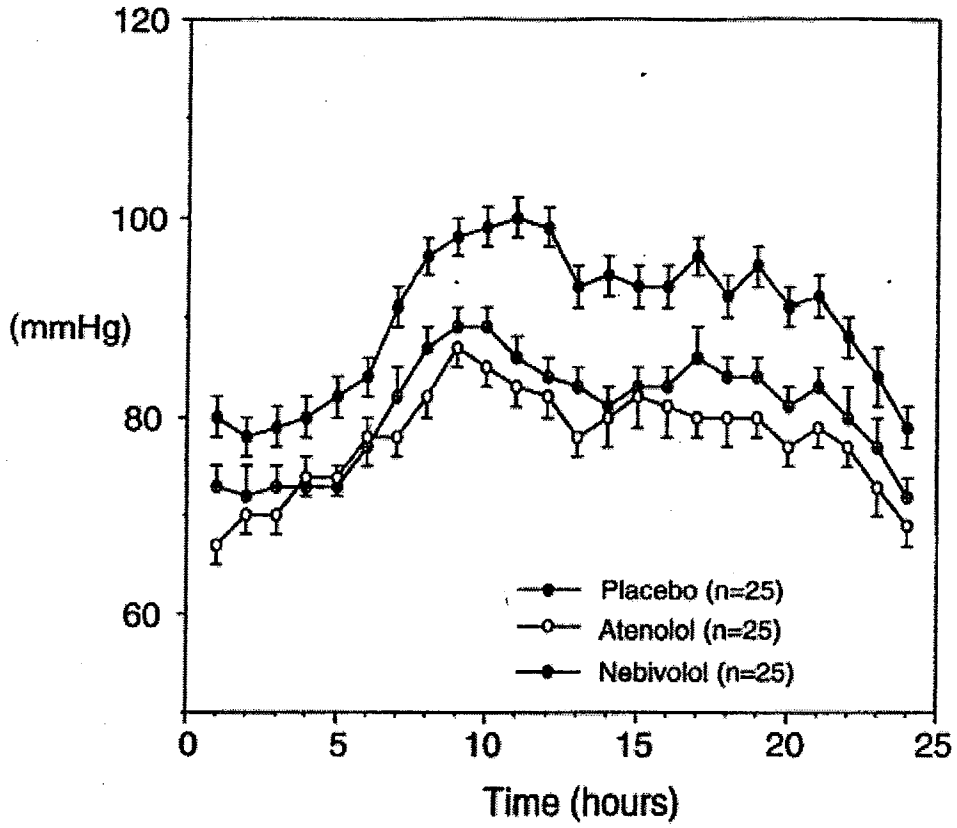
Figure 90. Ambulatory Systolic Blood Pressure Over 24-Hours (CAN-8)



(Reproduced from Sponsor, CAN-8, Display 10, page 60)

Appears This Way
On Original

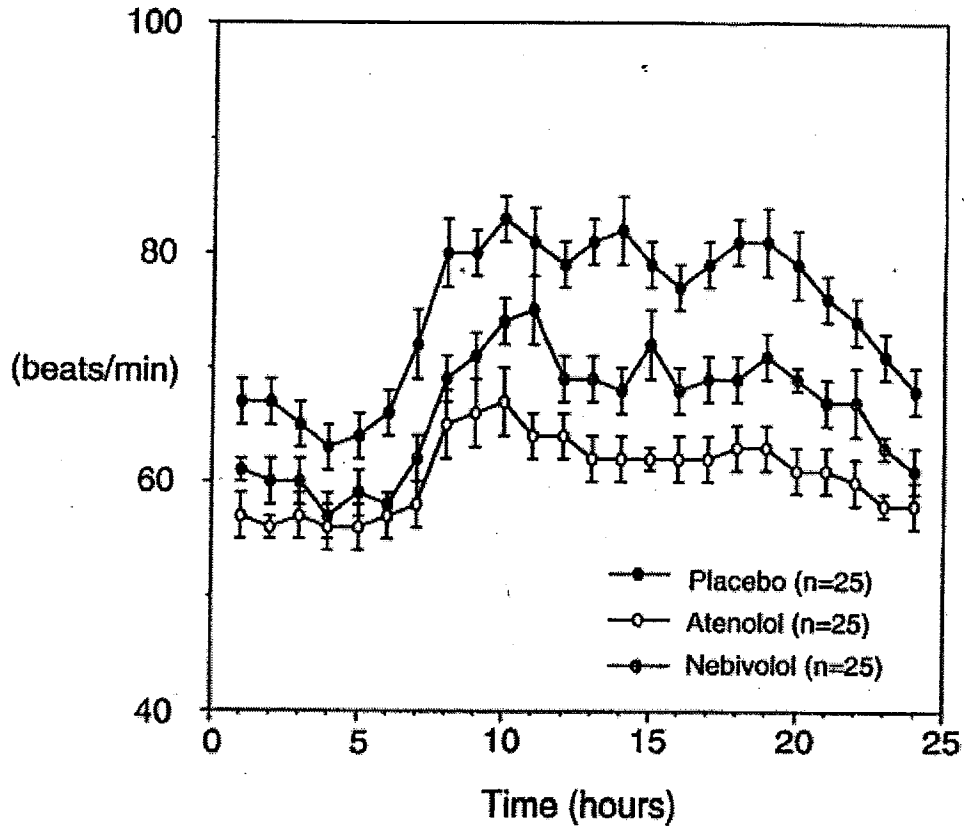
Figure 91. Ambulatory Diastolic Blood Pressure Over 24-Hours (CAN-8)



(Reproduced from Sponsor, CAN-8, Display 11, page 61)

Appears This Way
On Original

Figure 92. Ambulatory Heart Rate Over 24-Hours (CAN-8)



(Reproduced from Sponsor, CAN-8, Display 12, page 62)

Regional and Systemic Haemodynamics

Maximal Oxygen Uptake Test

Investigators performed these measurements at the end of the placebo phase and at the end of treatment with atenolol and nebivolol. The results are summarized in Table 109. There were no significant differences between nebivolol and atenolol in heart rate, systolic blood pressure, diastolic blood pressure, respiratory exchange ratio, oxygen consumption (VO_2), or workload measured at the end of the test.

Table 109. Maximal Oxygen Uptake Test (CAN-8)

	Placebo	Atenolol	Nebivolol
Heart rate (beats / min)			
rest (n = 23)	82	68***	65***
end (n = 23)	153	127***	121***
Systolic blood pressure (mmHg)			
rest (n = 23)	154	145	143*
end (n = 23)	212	190***	190***
Diastolic blood pressure (mmHg)			
rest (n = 23)	89	82**	81**
end (n = 23)	99	92**	94*
Respiratory exchange ratio			
rest (n = 22)	0.84	0.80	0.80
end (n = 22)	1.05	1.06	1.05
Oxygen consumption (L/min)			
rest (n = 22)	0.33	0.33	0.34
end (n = 23)	1.78	1.71	1.55
Oxygen consumption (ml/min/kg)			
rest (n = 22)	4.00	4.00	4.26
end (n = 23)	22.0	20.6	19.7
Workload (watts)			
end (n = 23)	115	109	105

* active treatment vs. placebo $p<0.05$
** active treatment vs. placebo $p<0.01$
*** active treatment vs. placebo $p \leq 0.001$

(Reproduced from Sponsor, CAN-8, Display 13, page 63)

Systemic Haemodynamics – Aerobic Exercise

The results for the 12 parameters measured are listed in Table 110.

Table 110. Systemic Haemodynamics - Aerobic Exercise (CAN-8)

	Placebo	Atenolol	Nebivolol
Heart rate (beats / min)			
rest (n = 24)	81	63***+++	70***
50% VO_{2max} (n = 24)	109	85***+++	96***
Systolic blood pressure (mmHg)			
rest (n = 24)	152	141**	145
50% VO_{2max} (n = 24)	176	155***++	166*
Diastolic blood pressure (mmHg)			
rest (n = 24)	90	80***+	84**
50% VO_{2max} (n = 24)	91	84**	85*
Mean arterial blood pressure (mmHg)			
rest (n = 24)	111	100***	104*
50% VO_{2max} (n = 24)	120	107***+	112***
Respiratory exchange ratio			
rest (n = 24)	0.81	0.82	0.81
50% VO_{2max} (n = 23)	0.85	0.87	0.87
Oxygen consumption (ml/min/kg)			
rest (n = 24)	3.68	4.24	4.16
50% VO_{2max} (n = 23)	11.1	11.8	11.7
Cardiac output (L/min)			
rest (n = 24)	3.91	3.57*	3.63*
50% VO_{2max} (n = 23)	10.33	9.17**	9.80
Cardiac index (L/min/m^2)			
rest (n = 24)	2.11	1.94	2.08
50% VO_{2max} (n = 23)	5.49	5.22	5.53
Stroke volume (ml/beat)			
rest (n = 24)	49	58***+	52
50% VO_{2max} (n = 23)	93	111***	103*
Stroke index (ml/beat/m^2)			
rest (n = 24)	26.5	31.4***++	28.1
50% VO_{2max} (n = 23)	49.7	59.4***+	54.5*
Total peripheral resistance (mmHg/L/min)			
rest (n = 24)	29.6	29.0	30.3
50% VO_{2max} (n = 23)	13.3	12.8	12.9
Conductance (L/min/mmHg)			
rest (n = 24)	0.036	0.036	0.035
50% VO_{2max} (n = 23)	0.086	0.086	0.088

* active treatment vs. placebo p<0.05 + active treatment vs. active treatment p<0.05
** active treatment vs. placebo p<0.01 ++ active treatment vs. active treatment p<0.01
*** active treatment vs. placebo p≤0.001 +++ active treatment vs. active treatment p≤0.001

(Reproduced from Sponsor, CAN-8, Display 14, page 64)

Regional Haemodynamics – Isometric Exercise

Both active drugs significantly decreased heart rate and blood pressure but did not significantly affect forearm blood flow, forearm vascular resistance, and conductance. During the cold pressor test, however, atenolol significantly decreased forearm blood flow by 27%, compared with 22% for nebivolol

Table 111. Regional Haemodynamics - Isometric Exercise (CAN-8)

	Placebo	Atenolol	Nebivolol
Heart rate (beats/min)			
rest (n = 25)	73	59***+++	64***
30% MVC (n = 25)	80	63***+++	70***
post exercise (n = 24)	71	57***+++	62***
cold pressor (n = 25)	76	59***+++	66***
Systolic blood pressure (mmHg)			
rest (n = 25)	147	137**	143
30% MVC (n = 25)	179	174	175
post exercise (n = 24)	150	140**	144
cold pressor (n = 25)	178	167*	173
Diastolic blood pressure (mmHg)			
rest (n = 25)	85	78***	79**
30% MVC (n = 25)	103	99	98
post exercise (n = 24)	87	80***	78***
cold pressor (n = 25)	101	94**	95**
Mean arterial blood pressure (mmHg)			
rest (n = 25)	105	97***	100*
30% MVC (n = 25)	129	124	124
post exercise (n = 24)	107	100***	100**
cold pressor (n = 25)	127	119**	121*
Forearm blood flow (ml/100cc/min)			
rest (n = 25)	3.74	3.60	3.78
30% MVC (n = 25)	4.14	3.49	3.88
post exercise (n = 24)	3.36	3.21	3.24
cold pressor (n = 25)	2.36	1.72**	1.83*
Forearm vascular resistance			
rest (n = 25)	32.82	34.02	32.11
30% MVC (n = 25)	37.94	47.00	42.64
post exercise (n = 24)	36.62	37.74	36.42
cold pressor (n = 25)	73.85	113.56	106.56
Conductance (L/min/mmHg)			
rest (n = 25)	0.036	0.038	0.038
30% MVC (n = 25)	0.032	0.029	0.032
post exercise (n = 24)	0.031	0.033	0.033
cold pressor (n = 25)	0.019	0.015	0.016

* active treatment vs. placebo p<0.05 +++ active treatment vs. active treatment p≤0.001
** active treatment vs. placebo p<0.01
*** active treatment vs. placebo p≤0.001

(Reproduced from Sponsor, CAN-8, Display 15, page 65)

Glycosylated Haemoglobin ($HgbA_{1c}$)

Compared with placebo, both active treatments produced significantly higher $HgbA_{1c}$ levels ($p < 0.05$), although the active treatments were not statistically significant from each other. The mean $HgbA_{1c}$ value for placebo was 0.057 and for both atenolol and nebivolol was 0.060.

Appears This Way
On Original

Overall Efficacy Results

Table 112. Summary of Efficacy Results (CAN-8)

Effectiveness (n = number of patients with data)	Placebo (n = 25)	Atenolol (n = 25)	Nebivolol (n = 25)
Primary parameters			
• clamp study:			
- glucose disposal rate (mg/kg/min)	4.62	3.89*	4.30
- insulin sensitivity index	0.74	0.58**	0.65
• IVGTT:			
- glucose disappearance rate (%/min)	1.12	1.00*$^{++}$	1.16
- peak insulin response (pmol/L)	322	350	347
- glucose area (mM · min)	1258	1323*$^{++}$	1244
- insulin area (μM · min)	0.038	0.046	0.042
Secondary parameters			
• lipid profile			
- total cholesterol (mmol/L)	5.91	5.94	6.00
- triglycerides (mmol/L)	2.56	2.51	2.66
- HDL-cholesterol (mmol/L)	1.25	1.18**	1.21
- LDL-cholesterol (mmol/L)	3.53	3.66	3.59
- VLDL-cholesterol (mmol/L)	0.96	0.97	1.04
- Apolipoprotein A_1 (g/L)	1.44	1.37**	1.41
- total cholesterol / HDL-cholesterol	5.0	5.3	5.2
- LDL-cholesterol / HDL-cholesterol	2.9	3.2*	3.0
- Apo A_1 / Apo B_1	1.24	1.13**	1.17
• clinic and ambulatory blood pressure			
- sitting trough BP (mmHg)	160/101	147/91***	148/92***
- standing trough BP (mmHg)	155/100	144/90**	145/91**
- mean daytime ABP (mmHg)	158/94	138/81***	142/84***
• systemic haemodynamics			
- heart rate (beats/min)			
rest	81	63***$^{+++}$	70***
50% VO_{2max}	109	85***$^{+++}$	96***
- cardiac output (L/min)			
rest	3.91	3.57*	3.63*
50% VO_{2max}	10.33	9.17**	9.80
- stroke volume (ml/beat)			
rest	49	58***$^{+}$	52
50% VO_{2max}	93	111***	103*
- stroke index (ml/beat/m^2)			
rest	26.5	31.4***$^{++}$	28.1
50% VO_{2max}	49.7	59.4***$^{+}$	54.5*
• regional haemodynamics			
- forearm blood flow (ml/100cc/min)			
rest	3.74	3.60	3.78
30% MVC	4.14	3.49	3.88
post exercise	3.36	3.21	3.24
cold pressor	2.36	1.72**	1.83*
• glycosylated haemoglobin			
- $HgbA_{1c}$ (fraction)	0.57	0.60*	0.60*

* refer to differences with placebo and $^{+}$ refers to differences between active treatments
Levels of significance: *($^{+}$) $p < 0.05$; ** ($^{++}$) $p < 0.01$, *** ($^{+++}$) $p \leq 0.001$

(Reproduced from Sponsor, CAN-8, page 9)

Safety

There were a total of 43 adverse events reported by 20 patients, with the most common being headache (13), fatigue (6), dizziness (4), and dyspnea (4). The adverse events are summarized in Table 113. There were no deaths in the study.

Table 113. Adverse Event Summary (CAN-8)

Adverse Event	# Patients	# Reports	# Reports per treatment		
			Placebo	Atenolol	Nebivolol
headache	9	13	4	5	4
fatigue	6	6	0	3	3
dizziness	4	4	0	2	2
dyspnoea	4	4	0	2	2
epistaxis	2	2	1	0	1
heart pounding	2	2	0	0	2
numbness localized	2	2	0	1	1
pruritis	2	2	1	0	1
hypertension aggravated	1	1	0	1	0
libido decreased	1	1	0	1	0
nervousness	1	1	0	0	1
sweating increased	1	1	0	0	1
rigors	1	1	1	0	0
bronchitis	1	1	1	0	0
flatulence	1	1	n/a	n/a	n/a
hypothyroidism	1	1	n/a	n/a	n/a

n/a = treatment phase not available

(Reproduced from Sponsor, CAN-8, Display 16, page 66)

Table 114. Overall Safety Results (CAN-8)

Safety (n = number of patients with data)	Placebo (n =28)	Atenolol (n =27)	Nebivolol (n =27)
Adverse events (AE)	# reports	# reports	# reports
• headache	4	5	4
• fatigue	0	3	3
• dizziness	0	2	2
• dyspnoea	0	2	2
Total number of patients assessed			
No. (%) with one or more AE	6	10	11
No. (%) with one or more severe AE	0	0	0
No. (%) with one or more serious AE	0	0	0
No. (%) treatment stopped due to AE	0	0	0
Clinical laboratory parameters			
No. with code-4 abnormality	0	9	9
(code 4 = baseline value is not pathological and last treatment value is pathological)	no relevant trends or changes in laboratory parameter values were observed within or between treatment groups		

(Reproduced from Sponsor, CAN-8, page 10)

Laboratory Safety Variables

Important laboratory abnormalities are shown in Table 115 and Table 116.

Table 115. Important Laboratory Abnormalities (CAN-8)

		Codes for Important Abnormalities							
		Nebivolol				Atenolol			
		1	2	4	Total	1	2	4	Total
Laboratory Test									
Haematology	Haemoglobin	1	0	0	1	1	0	1	2
	Haematocrit	1	0	1	2	1	0	1	2
	RBC	0	0	0	0	0	0	1	1
	WBC	0	0	0	0	0	0	1	1
	Platelet count	1	0	0	1	1	0	0	1
Biochemistry	Calcium	1	0	0	1	0	0	0	0
	Total bilirubin	1	1	0	2	2	0	0	2
	GGT	1	6	1	12	1	9	1	11
	Urea	1	1	1	3	0	2	0	2
	Creatinine	0	0	1	1	0	0	1	1
	Uric acid	0	0	0	0	0	0	1	1
Urinalysis	Protein	1	0	1	2	1	0	2	3
	Glucose	0	0	1	1	0	0	0	0

(CONTINUED)

Important Abnormality: determined by the occurrence of pathological values.
Codes: 1: Reference value is pathological (high/low), the last value during the observation period is not pathological.
2: Reference value is pathological (high/low), the last value during the observation period is pathological (high/low).
4: Reference value is not pathological, the last value during the observation period is pathological (high/low).
5: Reference value is pathologically high (low), the last value during the observation period is pathologically low (high).
Urinary Codes (protein, glucose, occult blood, ketones, RBC, WBC, casts)
1) normal (negative or within normal range)
2) dubious (slightly above normal range)
3) abnormal (clearly above normal range)

(Reproduced from Sponsor, CAN-8, Display 19, page 76)

Table 116. Important Laboratory Abnormalities (Urinalysis) (CAN-8)

		Codes for Important Abnormalities							
		Nebivolol				Atenolol			
		1	2	4	Total	1	2	4	Total
Laboratory Test									
Urinalysis	Occult blood	0	0	1	1	0	0	0	0
	Ketones	0	0	0	0	0	0	1	1
	RBC	0	0	1	1	0	0	0	0
	WBC	0	0	1	1	1	0	0	1
	Casts	0	2	0	2	0	1	0	1
Total		8	12	11	31	8	12	12	32
No. of patients with pathological values (codes 1, 2, 4, or 5)				20				17	
No. of patients with code 4 / 5				9				8	

Important Abnormality: determined by the occurrence of pathological values.
Codes: 1: Reference value is pathological (high/low), the last value during the observation period is not pathological.
2: Reference value is pathological (high/low), the last value during the observation period is pathological (high/low).
4: Reference value is not pathological, the last value during the observation period is pathological (high/low).
5: Reference value is pathologically high (low), the last value during the observation period is pathologically low (high).
Urinary Codes (protein, glucose, occult blood, ketones, RBC, WBC, casts)
1) normal (negative or within normal range)
2) dubious (slightly above normal range)
3) abnormal (clearly above normal range)

(Reproduced from Sponsor, CAN-8, Display 19, page 77)

Code-4 laboratory abnormalities, meaning the last value during the observation period is pathologically high or low, are shown in Table 117.

Table 117. Individual Data for Code-4 Important Laboratory Abnormalities (CAN-8)

Active Treatment	Laboratory Test	Unit	Pathological Lower and Upper Limit	Patient Number	Value at Baseline	Value at End of Phase
Nebivolol	Haematocrit	%	0.35 - 0.55	113	0.36	0.36
	GGT	U/L	2 - 16	108	16.00	23.00
				124	15.00	21.00
				127	16.00	18.00
	Urea	MMOL/L	1.7 - 8.3	104	5.30	8.50
	Creatinine	UMOL/L	35.4 - 203	109	70.00	6.10
	Protein	code	1	115	1.00	2.00
	Glucose	code	1	102	1.00	2.00
	Occult blood	code	1	103	1.00	2.00
	RBC	code	1	127	1.00	2.00
	WBC	code	1	127	1.00	2.00

Important Abnormality: determined by the occurence of pathological values.
Codes: 4: Reference value is not pathological, the last value during the observation period is pathological (high/low).
5: Reference value is pathologically high (low), the last value during the observation period is pathologically low (high).
Urinary Codes (protein, glucose, occult blood, ketones, RBC, WBC, casts)
1) normal (negative or within normal range)
2) dubious (slightly above normal range)
3) abnormal (clearly above normal range)

Active Treatment	Laboratory Test	Unit	Pathological Lower and Upper Limit	Patient Number	Value at Baseline	Value at End of Phase
Atenolol	Haemoglobin	G/L	115 - 199	113	119.00	107.00
	Haematocrit	%	0.35 - 0.55	113	0.36	0.31
	RBC		3.6 - 6.2	113	3.97	3.55
	WBC	X10E9/L	2.8 - 11.2	105	10.30	11.40
	GGT	U/L	2 - 16	108	16.00	20.00
				114	13.00	22.00
				124	15.00	18.00
	Creatinine	UMOL/L	35.4 - 203	117	91.00	5.70
	Uric acid	UMOL/L	89 - 541	122	510.00	626.00
	Protein	code	1	107	1.00	2.00
				115	1.00	2.00
	Ketones	code	1	122	1.00	2.00

Important Abnormality: determined by the occurence of pathological values.
Codes: 4: Reference value is not pathological, the last value during the observation period is pathological (high/low).
5: Reference value is pathologically high (low), the last value during the observation period is pathologically low (high).
Urinary Codes (protein, glucose, occult blood, ketones, RBC, WBC, casts)
1) normal (negative or within normal range)
2) dubious (slightly above normal range)
3) abnormal (clearly above normal range)

(Reproduced from Sponsor, CAN-8, Display 20, pages 78 and 79)

Conclusions: Atenolol significantly decreased the insulin sensitivity index ($p < 0.01$) by 22% and the glucose disappearance rate ($p < 0.05$) by 11%, compared with nebivolol, which did not significantly affect these parameters when compared to placebo. Atenolol caused a significant 5-10% change in several of the lipid profile parameters while nebivolol had no significant changes compared with placebo. There were no statistically significant differences in the lipid profile between active treatments.

Both atenolol and nebivolol reduced mean sitting trough blood pressure (placebo 160/101 mm Hg, atenolol 147/91 mm Hg, and nebivolol 148/92 mm Hg) and mean daytime

ambulatory blood pressure ($p \leq 0.001$). Both active treatments reduced heart rate, but atenolol had a greater effect on heart rate than nebivolol ($p \leq 0.001$).

Adverse events between atenolol (10 patients) and nebivolol (11 patients) were comparable. Six patients receiving placebo reported adverse events. Overall, nebivolol did not result in any treatment related changes in blood chemistry, haematology, or urinalysis.

1.62 LMD No. 107425. Study ID N/A. ("A Study to Assess the Effects of Nebivolol on Sedation and Psychomotor Performance") (Reviewer: Karen A. Hicks, M.D.)

Objective: To examine the sedative effects of nebivolol 2.5 mg and 5 mg, propranolol 80 mg, and placebo.

Methods: This was a randomized, double-blind, placebo-controlled four-way cross-over study in 17 healthy volunteers. Each volunteer participated in 4 study days, with a minimum washout of two weeks between study days. Each study day consisted of a 24-hour stay at the sleep laboratory preceded by a baseline night before each study day. Subjects spent a total of 4 days and 8 nights in the sleep laboratory. Subjects reported to the sleep lab at 2100h for the baseline sleep night. Subjects were trained in all of the psychomotor tests prior to study initiation. Patients underwent the Digit Symbol Substitution Test (DSST), Critical Flicker Fusion Threshold (CFFT), Choice Reaction Time, Broadbent Attention Test, Visual Analogue Scales (VAS), Bakan Vigilance Test, Letter Search Test, Spielberger's State Anxiety Test, Thayer's Activation-DeActivation Check List, Multiple Sleep Latency Test (MSLT), and Dream Questionnaire.

Results: A total of 16 patients began the study. One patient was withdrawn on Study Day 1, but the reason was not specified by the investigator. This patient was replaced by another patient. The mean age of the healthy volunteers was 27 years. Nine women and five men participated in the study.

The Multiple Sleep Latency Test is the most direct test of sedation used in this study. The MSLT measures the time it takes a subject to become sleepy in non-stimulating conditions. Although diurnal variation was present, there was no major drug effect or drug time interaction. Four hours after drug intake, however, propranolol seemed to make subjects drowsy more quickly.

According to Eriksen and Eriksen (1974), "normally distracting stimuli impair performance in choice reaction if they arrive within one degree from the stimulus but not if they are further away." Nebivolol 5 mg showed faster reaction times in the "near" condition, compared to placebo, in the Broadbent Attention Task ($p < 0.01$). The results of the BAT are shown in Table 118.

Table 118. Broadbent Attention

BROADBENT ATTENTION

Means (n=16)

	Near	Far
NEBIVOLOL 2.5mg	410.0	387.6
NEBIVOLOL 5mg	409.6	384.9
PROPRANOLOL 80mg	413.7	397.0
PLACEBO	426.0	388.2

(Reproduced from Sponsor, Table 5, page 18)

Nebivolol decreased performance on the Digit Symbol Substitution Task.

Safety: No safety results (blood pressure, heart rate, ECG monitoring, adverse events) were presented in this report.

Conclusions: There were no major sedative effects noted. Nebivolol favorably affected spatial attention, compared to propranolol.

1.63 LMD No. 107425. Study ID GBR-14. ("A Study of the Possible Pharmacokinetic and Psychomotor Interactions of Alcohol and Nebivolol in Healthy Volunteers. Clinical Research Report NEB-GBR-14. March 1994") (Trial Period: January 1, 1990 – June 30, 1990) (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the possible psychomotor and pharmacokinetic interactions of nebivolol 5 mg and alcohol (proposed dose 0.7 g/kg, actual dose 0.23 g/kg) given orally.

Methods: This was a randomized, double-blind, placebo-controlled, 4-way cross-over study in 16 healthy male and female patients, ages 18 to 45 years. Nebivolol 5 mg or its matching placebo, and alcohol or matching placebo were administered according to a pre-determined randomization scheme on each of four study days. The study days were each separated by one week. After abstaining from alcohol for 24 hours, subjects reported to the study center at 2100 hours on the first night of the study period. Electrodes for sleep measurements were attached and overnight recordings made. The following morning, subjects underwent indwelling catheter placement into a forearm vein

for blood sampling. Subjects underwent multiple Sleep Latency Tests and other Performance Tests pre-dose and 2, 4, 6, 8, and 24 hours post-dose on each study day. Performance Tests included Multiple Sleep Latency Test (MSLT), Digit Symbol Substitution Test (DSST), Critical Flicker Fusion Threshold (CFF), Choice Reaction Time (CRT), Broadbent Attention Test, Visual Analogue Scales (VAS), Bakan Vigilance Test, Spielberger's State Anxiety Test, and Thayer's Activation-Deactivation Checklist. Subjects provided blood samples pre-dose and up to 24 hours post dose (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 hours) for plasma concentrations of d-nebivolol plus hydroxylated metabolites, l-nebivolol plus hydroxylated metabolites, hematology, and chemistry. Investigators recorded vital signs and adverse events.

The randomization scheme is described in Table 119 below:

Table 119. Randomization Scheme (GBR-14)

An oral 5 mg tablet of nebivolol followed by placebo to match alcohol
An oral 5 mg tablet of nebivolol followed by alcohol
Placebo to match the nebivolol 5 mg tablet followed by placebo to match alcohol
Placebo to match the nebivolol 5 mg tablet followed by alcohol

(Reproduced from Sponsor, GBR-14, page 12)

Subjects received nebivolol or its matching placebo first, followed 60 minutes later by alcohol or its matching placebo. Investigators recorded overnight sleep measurements the night prior to and night following dosing.

Investigators performed the following assessments:

Table 120. Assessments (GBR-14)

Assessments	V1	V2	V3	V4
Medical Examination	✓			
Overnight sleep measurements	✓	✓	✓	✓
Psychomotor performance tests: 0,2,4,6,8,24 hr	✓	✓	✓	✓
Digit symbol substitution test				
Critical flicker fusion threshold				
Choice reaction time				
Broadbent attention test				
Visual analogue scale				
Balkan vigilance test				
Spielberger's state anxiety test				
Thayer's activation -deactivation checklist				
Multiple sleep latency test				
Blood pressure/Heart rate: 0,1,2,4,6,8,24hr	✓	✓	✓	✓
ECG: 0 + 24hr	✓	✓	✓	✓
Blood samples (Nebivolol & alcohol levels): 0,0.5,1,1.5,2,2.5,3,3.5,4,6,8,12,24hr	✓	✓	✓	✓
. Adverse Events	✓	✓	✓	✓
. Clinical laboratory parameters	✓	-	-	-

(Reproduced from Sponsor, GBR-14, page 2)

Results: Sixteen volunteers initially entered the study, but one volunteer discontinued the study after attending only two study visits, because she did not want to undergo any further blood sampling. Another volunteer replaced this subject. A total of 17 subjects, therefore, participated in the study, including 9 females and 8 males with a mean age of 27.3 years.

Multiple Sleep Latency Time (MSLT)

No treatment effects were observed, although ANOVA found a statistically significant period effect ($p < 0.001$). According to the sponsor, "the latency time measured pre-dose (at baseline) was longer than that measured at 2, 4, 6, 8, or 24 hours post-dose. At 24 hours, the latency time was longer than that at 2, 4, 6, or 8 hours, and MSLTs measured at 2 and 8 hours were longer than those at either 4 or 6 hours."

Table 121. Summary Statistics - Multiple Sleep Latency Tests (GBR-14)

		N	Mean	St. Dev	Min	Max
Treatment	Time					
NEB+ALC	Pre-drug	16	17.94	9.79	7.33	50.33
	2 hours	16	9.46	5.43	3.67	20.33
	4 hours	16	6.69	4.75	1.67	17.67
	6 hours	15	6.73	2.72	3.00	12.67
	8 hours	16	10.94	6.92	1.67	20.33
	24 hours	16	13.77	7.14	3.00	20.33
NEB+PLAC	Pre-drug	16	18.29	3.05	11.67	20.67
	2 hours	16	8.42	5.37	2.00	20.33
	4 hours	16	7.73	5.95	1.33	20.00
	6 hours	16	10.00	6.16	4.00	20.67
	8 hours	16	8.94	6.31	1.00	20.67
	24 hours	16	14.21	6.21	4.00	20.33
PLAC+ALC	Pre-drug	16	16.73	5.51	4.33	21.00
	2 hours	16	9.10	6.10	2.00	21.00
	4 hours	16	7.65	5.79	2.33	21.00
	6 hours	16	6.73	5.93	1.00	20.67
	8 hours	16	10.65	6.39	3.33	21.00
	24 hours	16	15.25	5.35	4.00	21.00
PLAC	Pre-drug	16	14.23	6.36	2.33	20.33
	2 hours	16	9.44	6.06	2.33	20.33
	4 hours	16	6.98	5.05	2.33	20.00
	6 hours	16	7.58	5.65	1.67	20.33
	8 hours	16	9.22	6.09	1.00	20.00
	24 hours	16	12.96	6.49	3.00	20.33

(Reproduced form Sponsor, GBR-14, Table 4, page 37)

Pharmacokinetic Results

Summary statistics for pharmacokinetic results from all subjects are shown in Table 122.

Table 122. Summary Statistics (GBR-14)

Nebivolol	Treatment	C_{max} Mean ± (SD) ng/ml	T_{max} Mean ± (SD) h	AUC_{0-12h} Mean ± (SD) ng.h/ml	AUC_{0-24h} Mean ± (SD) ng.h/ml
Unchanged	NEB+ALC	1.53 (1.86)	2.1 (1.3)	9.71 (16.09)	21.0 (34.5)
d-nebivolol		6.47 (1.45)	3.4 (0.9)	40.5 (9.3)	59.0 (10.0)
l-nebivolol		11.2 (4.4)	3.5 (0.9)	65.3 (24.6)	86.8 (25.1)
Unchanged	NEB	1.49 (1.63)	2.2 (1.3)	10.2 (16.1)	20.5 (33.2)
d-nebivolol		6.09 (1.67)	3.5 (1.0)	38.5 (10.3)	56.0 (11.8)
l-nebivolol		10.0 (4.4)	3.6 (1.0)	58.0 (21.2)	75.6 (19.6)

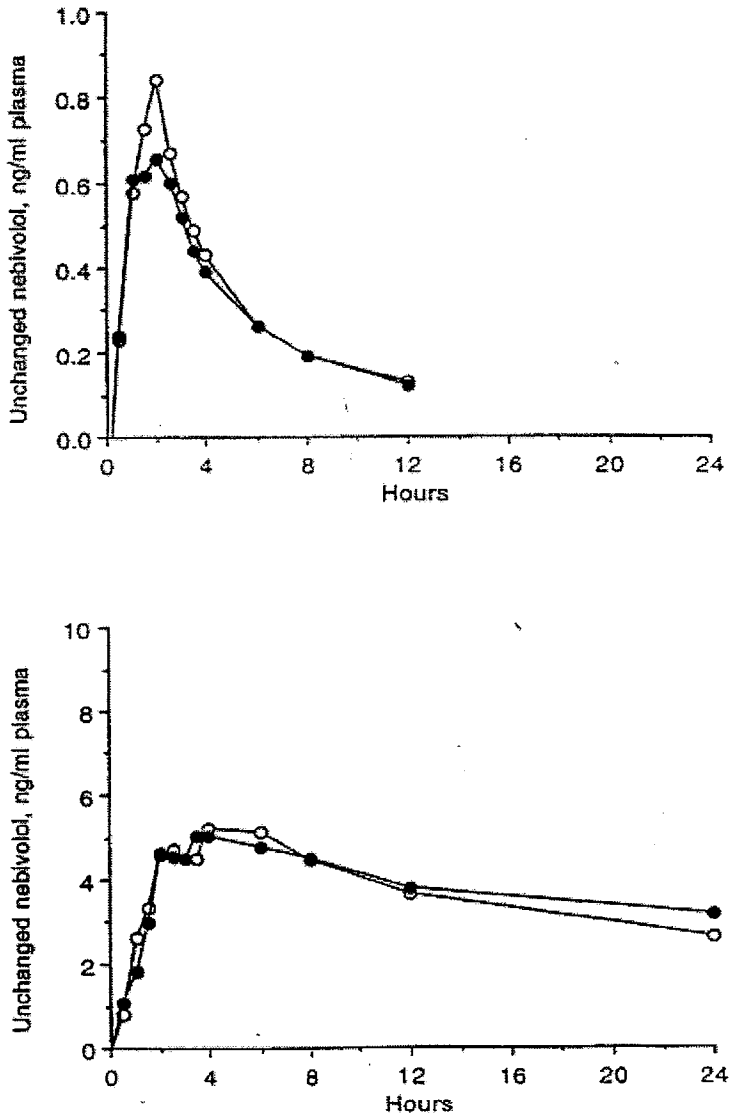
(Reproduced from Sponsor, GBR-14, page 24)

By ANOVA, plasma concentrations and pharmacokinetic parameters of unchanged nebivolol on co-administration of alcohol were not significantly different from those after intake of nebivolol alone.

Figure 93, Figure 94, and Figure 95 show the linear mean plasma concentration-time plot after single oral intake of 5 mg nebivolol alone or in combination with 0.23 g/kg alcohol in extensive and poor metabolizers.

Figure 93. Linear Mean Plasma Concentration-Time Plot after Single Oral Intake of 5 mg Nebivolol Alone or in Combination with 0.23 g/kg Alcohol in 14 Extensive Metabolizers (Upper Graph) and Two Poor Metabolizers (Lower Graph) (GBR-14)

Figure 1: Linear mean plasma concentration-time plot after single oral intake of 5 mg nebivolol alone (○) or in combination with 0.23 g/kg alcohol (●) given to fourteen extensive metabolisers (upper graph) and two poor metaboliser (lower graph).

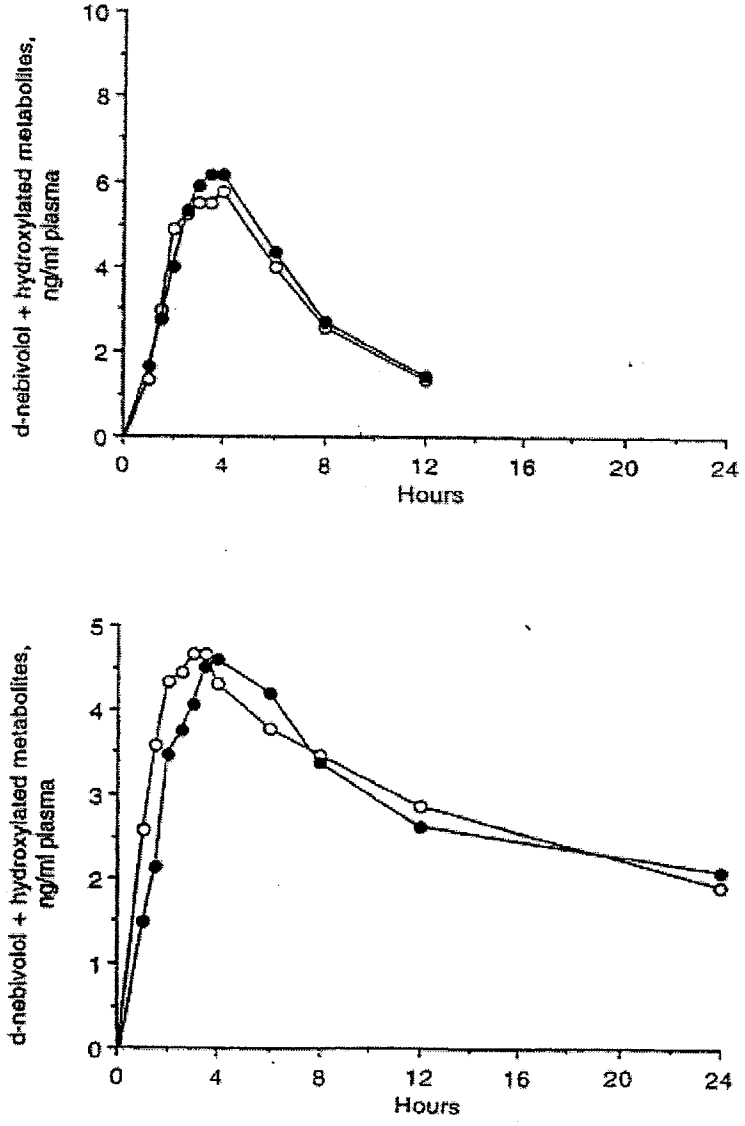


(Reproduced from Sponsor, GBR-14, Figure 1, page 88)

Appears This Way
On Original

Figure 94. Linear Mean Plasma Concentration-Time Plot after Single Oral Intake of 5 mg Nebivolol Alone or in Combination with 0.23 g/kg Alcohol Given to Fourteen Extensive Metabolizers (Upper Graph) and Two Poor Metabolizers (Lower Graph) (GBR-14)

Figure 2: Linear mean plasma concentration-time plot after single oral intake of 5 mg nebivolol alone (○) or in combination with 0.23 g/kg alcohol (●) given to fourteen extensive metabolisers (upper graph) and two poor metaboliser (lower graph).

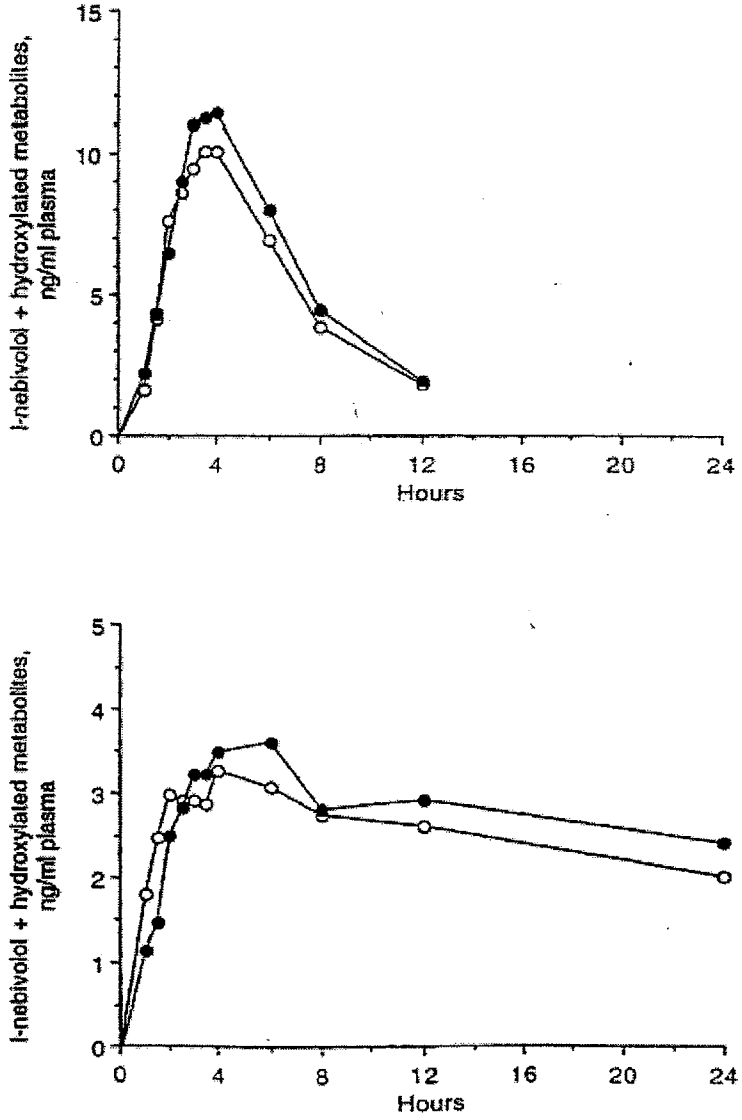


(Reproduced from Sponsor, GBR-14, Figure 2, page 89)

Appears This Way
On Original

Figure 95. Linear Mean Plasma Concentration-Time Plot after Single Oral Intake of 5 mg Nebivolol Alone or in Combination with 0.23 g/kg Alcohol Given to Fourteen Extensive Metabolizers (Upper Graph) and Two Poor Metabolizers (Lower Graph)

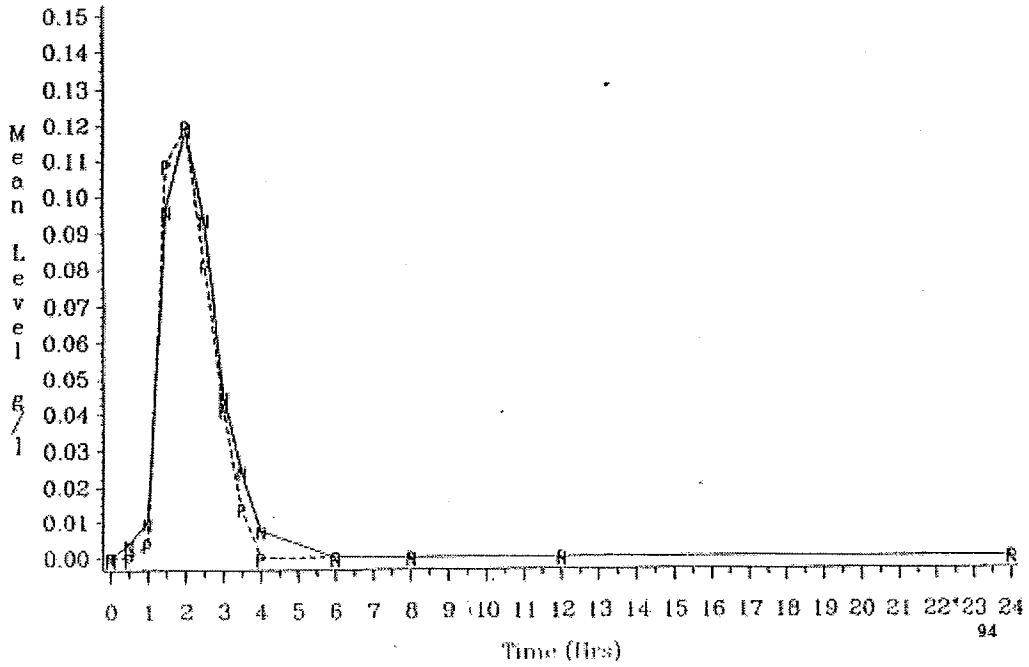
Figure 3: Linear mean plasma concentration-time plot after single oral intake of 5 mg nebivolol alone (○) or in combination with 0.23 g/kg alcohol (●) given to fourteen extensive metabolisers (upper graph) and two poor metaboliser (lower graph).



(Reproduced from Sponsor, GBR-14, Figure 3, page 90)

Figure 96 shows the mean level of alcohol versus time. For two patients receiving nebivolol plus alcohol, positive readings were evident at 0.5 hours, even though alcohol was not administered until 1.0 hours.

Figure 96. Blood Levels of Alcohol Over Time (GBR-14)



(Reproduced from Sponsor, Figure 7, page 94)

Summary statistics for AUC are shown in Table 123.

Table 123. Alcohol Blood Levels (AUC) Statistical Analysis (GBR-14)

Treatment	n	mean	St. Dev	Minimum	Maximun	P
Nebivolol	16	0.205	0.110	0.12	0.59	0.552
Placebo	16	0.184	0.079	0.08	0.37	NS

(Reproduced from Sponsor, GBR-14, Table 10, page 51)

Performance Tests

ANOVA for the Critical Flicker Fusion Test (Thinking Time) demonstrated the nebivolol + alcohol group had a slower response time than nebivolol + placebo ($p = 0.006$). A significant period interaction ($p < 0.001$) was identified with the 4 and 6 hour response times slower than the pre-dose, 2, and 24 hour times. For the total time, the nebivolol and alcohol group had a slower response time than the alcohol and placebo group ($p = 0.012$). There were statistically significant period effects for movement time and total time.

There were statistically significant period interactions in both the number of correct and incorrect responses ($p < 0.001$) in the Digit Substitution Test.

Thayer's activation-deactivation check list showed the following statistically significant period effects:

- general activation ($p = 0.004$)
- general deactivation ($p < 0.001$)
- active ($p = 0.010$)
- sleepy ($p < 0.001$)
- energetic ($p = 0.008$)
- calm ($p = 0.011$)
- tired ($p = 0.040$)
- at-rest ($p = 0.035$)
- drowsy ($p = 0.001$)
- lively ($p = 0.006$)
- still ($p < 0.001$)
- wide awake ($p = 0.009$)
- quiet ($p = 0.004$)
- full-of-pep ($p = 0.016$)
- wakeful ($p = 0.007$)

Vital Signs

For supine systolic blood pressure, there was a statistically significant treatment effect ($p = 0.012$), standing systolic blood pressure ($p = 0.011$), and standing heart rate (p , 0.001). In each case, the alcohol alone treatment group had higher readings than the nebivolol + alcohol group or the nebivolol group alone, or both.

Significant period interactions were evident for supine diastolic blood pressure as well as standing systolic and diastolic blood pressure and heart rate. "There were statistically significant treatment by period interactions for supine systolic and diastolic blood pressure and for all standing vital signs measurements."

Safety Results

A total of 27 adverse events were reported by 11/17 (65%) of the subjects. In eight cases, subjects complained of headache. Other adverse events included lower back stiffness, red pustular rash at the site of the prior electrodes, dizziness, stomach ache, visual impairment od lasting for 2 weeks, diarrhea and stomach ache, and a sensation of coolness, fatigue, and hunger 30 minutes after receiving study medication on Day 2.

Laboratory Analyses

Subject 7's ALT value increased from 18 IU/l to 124 IU/l during the study, but decreased to 27 IU by the post-study visit. Otherwise, there were no clinically significant abnormalities observed.

Conclusions: There were no statistically significant differences seen between treatments for Multiple Sleep Latency Tests. For both MSLTs and other Performance Tests, however, there were statistically significant period interactions which were inconsistent. The co-administration of alcohol did not affect the pharmacokinetics of unchanged nebivolol and d-nebivolol plus hydroxylated metabolites. The Cmax and $AUC_{0\text{-}24h}$ of l-

nebivolol plus hydroxylated metabolites on co-administration of alcohol was 12% and 15% higher, respectively, compared to that after intake of nebivolol, which was not clinically relevant in this study. Nebivolol did not appear to affect the pharmacokinetics of alcohol at a dose of 0.23 g/kg.

1.64 LMD No. 106642. Study ID GBR-22. ("Effect of Nebivolol on Lung Function in Normal Subjects: A Comparison with Atenolol and Propranolol. Clinical Research Report NEB-GBR-22. December 1989") (Trial Period: August 1988 – May 1989) (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the effect of nebivolol on lung function in normal subjects.

Methods: This double blind, double dummy, randomized, latin square design crossover trial evaluated the effect of atenolol, nebivolol, and propranolol on lung function. Healthy male volunteers, ages 18 to 65, attended a pre-entry visit, a single-blind placebo run-in visit, and 4 double-blind test sessions separated by at least 7 days. In the double-blind test sessions, subjects were randomized to receive placebo, atenolol 100 mg, nebivolol 5 mg, or propranolol 40 mg as a single dose per visit. The investigators performed the assessments listed in Table 124.

Table 124. Assessments (GBR-22)

Assessments	Pre-entry	Placebo	Test session 1	Test session 2	Test session 3	Test session 4
. Blood pressure	X	X	X	X	X	X
. Heart rate	X	X	X	X	X	X
. Treadmill exercise test	X	X	X	X	X	X
. Borg Score	X	X	X	X	X	X
. Symptom VAS		X	X	X	X	X
. Specific airways resistance (SGAW)	X	X	X	X	X	X
. Thoracic gas volume (TGV)	X	X	X	X	X	X
. Forced expiratory volume (FEV_1)	X	X	X	X	X	X
. Forced expiratory flow (FEF)	X	X	X	X	X	X
. Peak expiratory flow rate (PEFR)	X	X	X	X	X	X
. ECG	X					
. Salbutamol dose response		X	X	X	X	X
. Debrisoquine metaboliser status	X					
. Adverse Events		X	X	X	X	X
. Clinical laboratory parameters	X					
Statistical methods	Analysis of variance for a crossover design study followed by a paired t-test.					

(Reproduced from Sponsor, GBR-22, page 2)

Using a constant volume body plethysmograph, investigators measured airway resistance (Raw) and thoracic gas volume (TGV) and from these values calculated specific airways conductance (SGaw) using the following formula:

SGaw = 1/Raw X 1/TGV

SGaw was determined pretreatment at time 0 and after sitting quietly for 15 minutes and 105 minutes post trial medication. Subjects then inhaled increasing doses of salbutamol (12, 42, 132, 252, 732, and 1692 mcg), and specific airways conductance was measured 15 minutes following each inhalation.

Investigators examined the dose response of specific airways conductance to salbutamol two hours following treatment. Other parameters of lung function were evaluated before and after salbutamol. Blood pressure and heart rate were measured at rest and at exercise post-dose.

The Borg score was recorded at 1, 2, 3, 4, 5, 6, and 8 minutes. The Borg score at 6 and 8 minutes corresponded to +1 and +3 minutes after stopping exercise respectively.

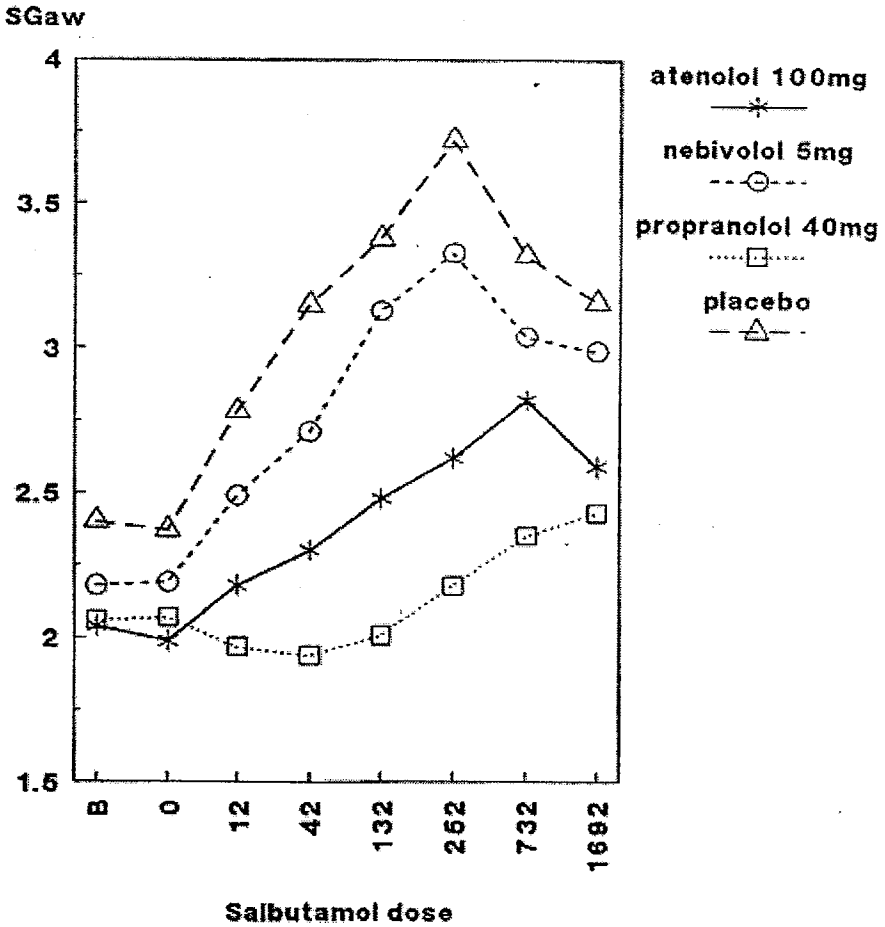
Results: Six male volunteers with a mean age of 32.2 years entered the study. All volunteers were extensive metabolizers of CYP2D6. There were no adverse events reported.

Lung Function Tests

The mean (SD) lung specific airways conductance (SGaw) before placebo was 2.4 (1.19) $s^{-1}kPa^{-1}$ in these healthy volunteers. Two hours (105 minutes) following dosing with placebo, propranolol, nebivolol, or atenolol, there was no significant change in resting specific airways conductance.

After placebo treatment, salbutamol inhalation increased lung specific airways conductance to a peak of 3.72 s-1kPa-1 at 252 µg. Increasing the dose of salbutamol beyond 252 µg did not improve lung specific airways conductance. As seen in , atenolol 100 mg and propranolol 40 mg produced a parallel shift of the dose-response curves to the right in a significant fashion ($p < 0.001$). Nebivolol shifted the curve only slightly to the right.

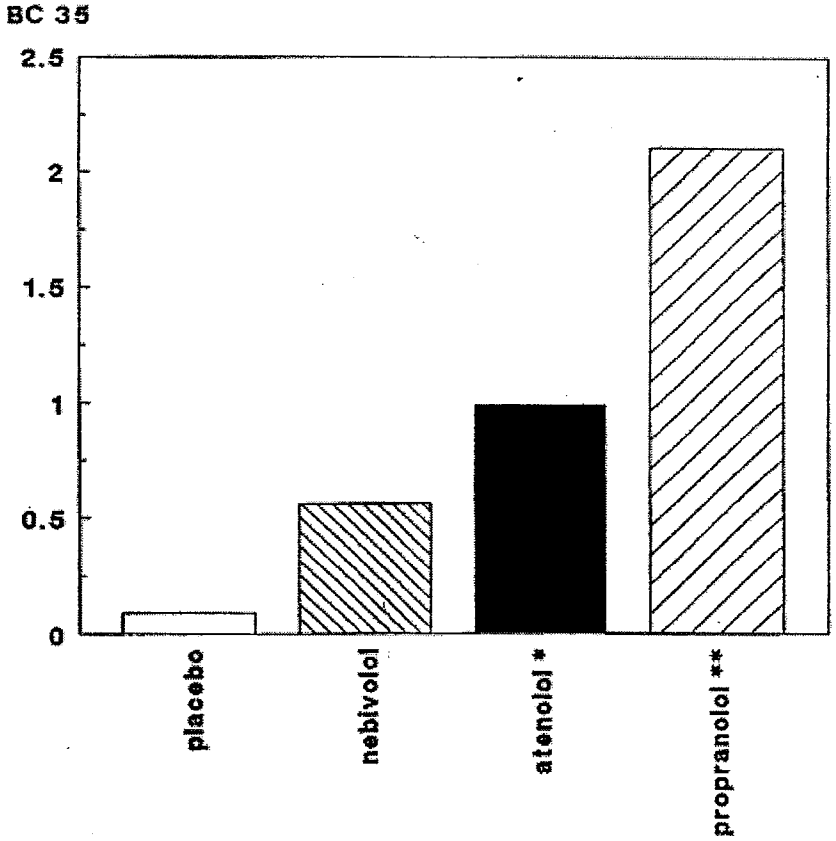
Figure 97. Dose Response Curves of SGaw (GBR-22)



(Reproduced from Sponsor, GBR-22, Figure 1, page 14)

For each treatment, the dose of salbutamol which produced a 35% increase in airway conductance was calculated and derived from the dose response curve. Atenolol and propranolol significantly affected specific airways conductance, compared with placebo ($p < 0.001$ ANOVA), as seen in Figure 98. Nebivolol did not significantly affect specific airways conductance. Overall, nebivolol and atenolol had significantly less effect on specific airways conductance, compared with propranolol.

Figure 98. Effect of Nebivolol on Specific Airways Conductance (n = 6)



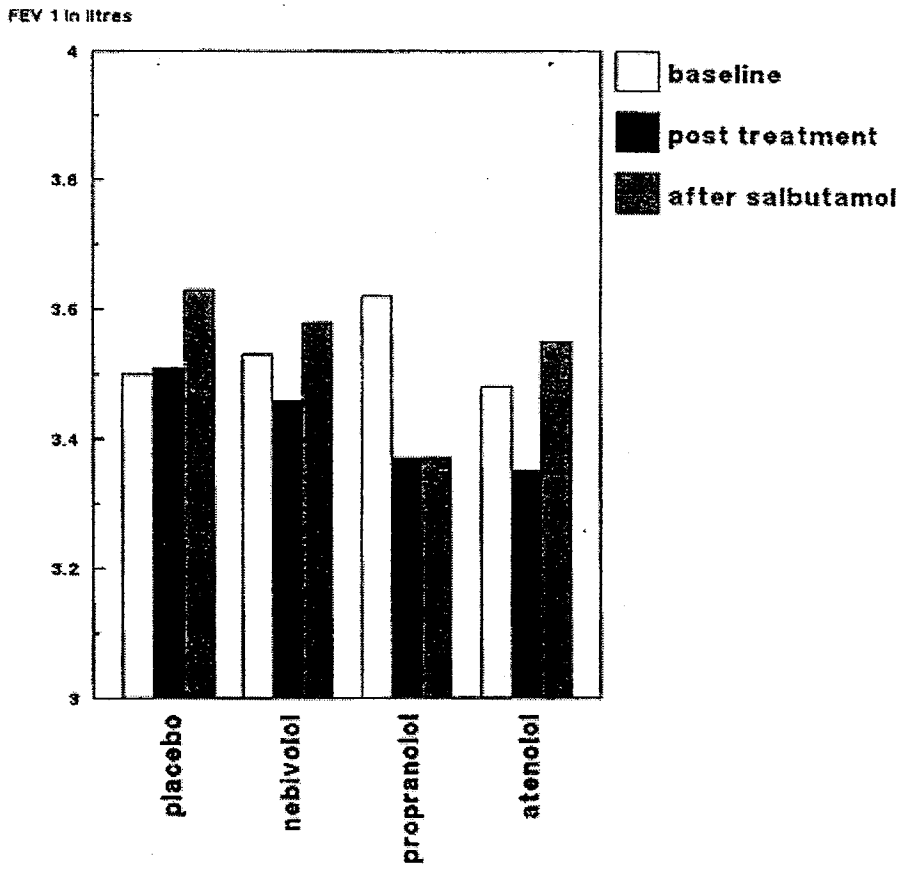
(Reproduced from Sponsor, GBR-22, Figure 2, page 15)

Nebivolol, propranolol, and atenolol decreased FEV_1. FEV_1 improved after salbutamol in subjects treated with nebivolol and atenolol, but not propranolol, as seen in Figure 99. The post salbutamol FEV1 was significantly lower on propranolol ($p = 0.004$).

Peak expiratory flow rate was increased by salbutamol ($p = 0.001$), and there was a significant influence of the order of treatment ($p = 0.032$). Propranolol and atenolol slightly decreased PEFR in a nonsignificant fashion. Nebivolol had no significant effect on PEFR and the response to salbutamol was normal.

Propranolol significantly reduced $FEF_{75-85\%}$ ($p = 0.02$), and this effect could not be overcome by salbutamol.

Figure 99. Forced Expiratory Volume in 1 Second (Baseline, Post-Treatment, and After Salbutamol) (GBR-22)



(Reproduced from Sponsor, GBR-22, Figure 3, page 16)

Heart Rate

Two hours after treatment, nebivolol produced a net reduction of 4 bpm in resting heart rate which was nonsignificant. Atenolol and propranolol significantly reduced resting heart rate with net mean changes of 13 bpm and 10 bpm, respectively. After salbutamol, atenolol and propranolol also significantly reduced heart rate.

During exercise, treatment significantly reduced exercise heart rate ($p < 0.001$) with a trend for a period effect ($p = 0.061$). The greatest increase in heart rate was found on the first visit. Heart rates at subsequent visits were comparable, which could reflect a training effect. Atenolol and propranolol significantly reduced exercise heart rate more than nebivolol. Nebivolol 5 mg, atenolol 100 mg, and propranolol 40 mg decreased exercise heart rate by 8.2%, 22.9%, and 31.7%.

Atenolol increased fatigue, as measured by the Borg score, by a median of 5.75 units, which was greater than the other treatments but not significantly different.

Blood Pressure

Atenolol significantly reduced resting diastolic blood pressure ($p = 0.011$). At 4 hours post treatment, atenolol decreased blood pressure from baseline by a mean of 10/7 mm Hg, compared with nebivolol 3/5 mm Hg and propranolol 10 mm Hg systolic. Placebo increased blood pressure by 11/3.4 mm Hg. There was a significant period effect seen in the change in diastolic blood pressure ($p = 0.05$) with the largest effect seen at the fourth clinic visit.

At 1 minute post-exercise, propranolol significantly reduced the exercise –induced increase in diastolic blood pressure ($p = 0.033$).

Sponsor's Conclusions: Atenolol 100 mg and propranolol 40 mg produced a parallel shift of the dose-response curve to salbutamol to the right. Nebivolol had a significantly less deleterious effect on specific airways conductance, compared with propranolol. In general, propranolol decreased FEV_1, PEFR, and $FEF_{75-85\%}$, and these effects were not reversed by salbutamol. Nebivolol did not significantly affect FEV_1, PEFR, and $FEF_{75-85\%}$ and had a normal response to salbutamol. Atenolol and propranolol decreased heart rate to a greater extent than nebivolol at rest and post exercise.

1.65 LMD No. 92579. Study ID ITA-2. ("Open Trial with Nebivolol 5 mg Once Daily in Hypertension with Renal Artery Stenosis. Clinical Research Report NEB-ITA-2. March 1993") (Trial Dates: January 4, 1991 – May 28, 1991) (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the antihypertensive efficacy and safety of 4 weeks of daily nebivolol 5 mg on patients with renovascular hypertension.

Methods: 10 hypertensive patients, ages ≥ 18 and ≤ 70 years, with unilateral or bilateral renal artery stenosis/occlusion or fibromuscular hyperplasia as diagnosed by renal arteriography were enrolled in a single-centre, open, 4-week study. The study had three periods including wash-out, run-in, and treatment. After 2 weeks of wash-out and 1 week of single-blind placebo run-in, patients received 4 weeks of nebivolol 5 mg daily. All other antihypertensives were prohibited, as well as tricyclic antidepressants, MAO inhibitors, salt-retaining medications, corticosteroids and non-steroidal anti-inflammatory drugs. Study assessments are described in Table 125.

Table 125. Assessments (NEB-ITA-2)

Assessments	Start	End wash-out	End run-in	Treatment Week 2	Treatment Week 4
- blood pressure: • trough	x	x	x	x	x
• peak			x	x	x
- heart rate	x	x	x	x	x
- body weight	x	x	x	x	x
- ECG	x		x		x
- renal function			x		x
- plasma renin activity			x	x	x
- serum aldosterone			x	x	x
- urinary aldosterone			x	x	x
- urinary K^+, Na^+			x	x	x
- plasma sample					x
- adverse events		x	x	x	x
- clinical laboratory parameters	x		x		x

(Reproduced from Sponsor, NEB-ITA-2, page 11)

Control visits occurred before and after the wash-out period, after the placebo run-in, and after 2 and 4 weeks of open treatment.

The Trial was performed according to the Declaration of Helsinki.

Blood pressure was measured in the supine position (after at least 5 minutes) and after 2 minutes' standing. Investigators performed these measurements at "trough drug level (i.e. immediately before intake of placebo in the run-in period, or before nebivolol dosing in the treatment period). At baseline (placebo) and after 2 and 4 weeks of treatment, blood pressure and heart rate were also measured at peak drug level (i.e. 2 hours after drug intake).

Investigators measured urinary sodium, potassium, aldosterone, plasma renin activity (PRA), and serum aldosterone (SA) at baseline and after 2 and 4 weeks of treatment. Blood samples for PRA were obtained between 8 and 9:30 a.m. after patients had been supine for 30 minutes. After incubating the PRA sample in the presence of angiotensinase and converting enzyme inhibitors, the amount of angiotensin I produced was determined by radioimmunoassay. Investigators also measured plasma concentrations of *d*-nebivolol plus hydroxylated metabolites and *l*-nebivolol plus hydroxylated metabolites.

Results: A total of 10 patients participated in the trial (7 females, 3 males, median age 54 years). Three patients had bilateral renal artery stenosis, 7 patients had unilateral or bilateral renal arteriosclerosis, and 3 patients had renal unilateral or bilateral fibromuscular hyperplasia. All patients had a baseline serum creatinine $\leq$ 1.5 mg/dl. Five patients took antianginal medication, and one patient took an antiplatelet aggregation agent. Six patients had concomitant diseases including peripheral vascular disease, eosinophilia, arthropathy, dyslipidemia, diverticulosis (colon), and rheumatoid arthritis.

Blood Pressure

At 2 and 4 weeks, nebivolol significantly reduced DBP at trough level in the supine position, as shown in Table 126. At 2 weeks, nebivolol significantly reduced supine and standing DBP at peak. Nebivolol did not significantly affect SBP.

Table 126. Efficacy Results: Blood Pressure (ITA-2)

	trough		peak	
	supine	standing	supine	standing
Mean DBP, mmHg				
baseline	107.8	110.0	105.0	107.8
treatment week 2	101.8**	106.2	95.3**	98.6**
week 4	100.4*	104.6	97.6	102.4
Mean SBP, mmHg				
baseline	168.4	166.0	160.6	157.2
treatment week 2	163.4	163.4	154.6	156.2
week 4	168.7	168.3	161.6	161.0

Asterisks refer to changes from baseline. Levels of statistical significance:

◊ $p \leq 0.1$; * $p \leq 0.05$; ** $p \leq 0.01$

DBP was significantly decreased after 2 and 4 weeks, at trough level, in supine position, and after 2 weeks at peak level, in supine and standing positions (Displays 4, 5).

SBP did not significantly change from baseline values (Displays 6, 7).

(Reproduced from Sponsor, ITA-2, page 16).

In 3 patients, nebivolol normalized supine DBP at trough (≤ 90 mm Hg).

Other efficacy results are displayed in Table 127.

Table 127. Efficacy Results (ITA-2)

Clinical findings	Baseline (n = 10)		Week 4 (n = 10)	
Primary parameter (mean values)				
• diastolic blood pressure, supine, trough, mmHg	107.8		100.4*	
Secondary parameters (mean values)	supine	standing	supine	standing
Blood pressure				
• diastolic blood pressure, trough, mmHg		110.0		104.6
• diastolic blood pressure, peak, mmHg	105.0	107.8	97.6	102.4
• systolic blood pressure, trough, mmHg	168.4	166.0	168.7	168.3
• systolic blood pressure, peak, mmHg	160.6	157.2	161.6	161.0
Heart rate				
• trough, bpm	70.4	76.4	64.0*	68.0*
• peak, bpm	69.8	76.4	63.0*	66.0**
Blood hormones				
• plasma renin activity, ng/ml/h	0.9		0.6*	
• serum aldosterone, pg/ml	169.5 (n=8)		126.8	
Urinary hormones				
• urinary aldosterone, pmol/l	9.0 (n=4)		11.3 (n=8)	
• urinary potassium, mEq/24h	57.3		57.9	
• urinary sodium, mEq/24h	167.1		164.6	
Renal function (n=9)				
• effective renal plasma flow, ml/min	607.8		545.70	
• renal plasma flow, ml/min	821.4		737.40	
• glomerular filtration rate, ml/min	138.3		133.6	
• filtration fraction, ml/min	0.2		0.2	
• renal blood flow, ml/min	1412.4		1290.8	
• renal vascular resistance, dyn.s.cm^{-5}	6698.3		7002.8	

Asterisks refer to differences with baseline.
Levels of significance: ◊ $p \leq 0.1$; * $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$

(Reproduced from Sponsor, ITA-2, page 7

The mean and median trough to peak ratios for supine and standing DBP at week 4 was 1.0.

Blood Hormonal Factors

At 4 weeks, nebivolol significantly decreased plasma renin activity ($p = 0.014$) (median: from 0.9 ng.ml^{-1}.h^{-1} at baseline to 0.4 ng.ml^{-1}.h^{-1}), as shown in Table 128.

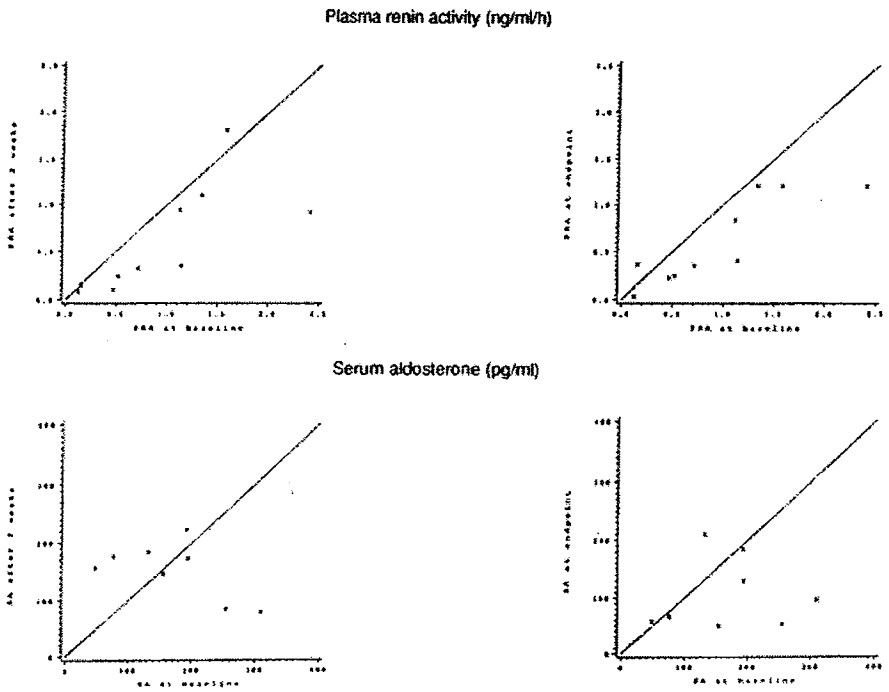
Table 128. Blood Hormonal Factors (ITA-2)

Blood hormonal factor	Time	N	mean (SEM)	median (min;max)	Intragroup changes p-values	
					Overall change (Friedman test)	Baseline vs time specified (Wilcoxon test)
Plasma renin activity, ng ml^{-1} h^{-1}	Baseline	10	0.9 (0.22)	0.9 (0;2)	0.013	
	Treatment					
	Week 2	10	0.6 (0.18)	0.3 (0;2)		0.033
	Week 4	10	0.6 (0.14)	0.4 (0;1)		0.014
Serum aldosterone, pg/ml	Baseline	8	169.5 (30.72)	172.5 (48;309)	0.670	
	Treatment					
	Week 2	10	148.6 (15.96)	164.5 (79;223)		
	Week 4	10	126.8 (22.71)	112.5 (49;226)		

(Reproduced from Sponsor, ITA-2, Display 9, page 30)

In all patients except one, PRA decreased, as seen in Figure 100. Median serum aldosterone nonsignificantly decreased from 172.5 pg/ml at baseline to 112.5 pg/ml after 4 weeks' treatment.

Figure 100. Plasma Renin Activity and Serum Aldosterone at 2 and 4 Weeks of Treatment



The line divides values in increases (above the line) and decreases from baseline (below).

(Reproduced from Sponsor, ITA-2, Display 10, page 31)

Plasma Concentrations of the Separate Enantiomers and Their Hydroxylated Metabolites

Plasma concentrations at 50 minutes to 2 hours and 20 minutes post nebivolol are shown in Table 129 below.

Table 129. Plasma Concentration of Nebivolol (ITA-2)

Plasma concentration of nebivolol	
Concentration at 50 min to 2h 20min post dosing: - d-nebivolol + hydroxylated metabolites, ng/ml - l-nebivolol + hydroxylated metabolits, ng/ml	 2.20 to 15.9 2.75 to 31.8

(Reproduced from Sponsor, ITA-2, page 7)

Heart Rate

Heart rate significantly decreased throughout the course of the study, as seen in Table 130 and Figure 101.

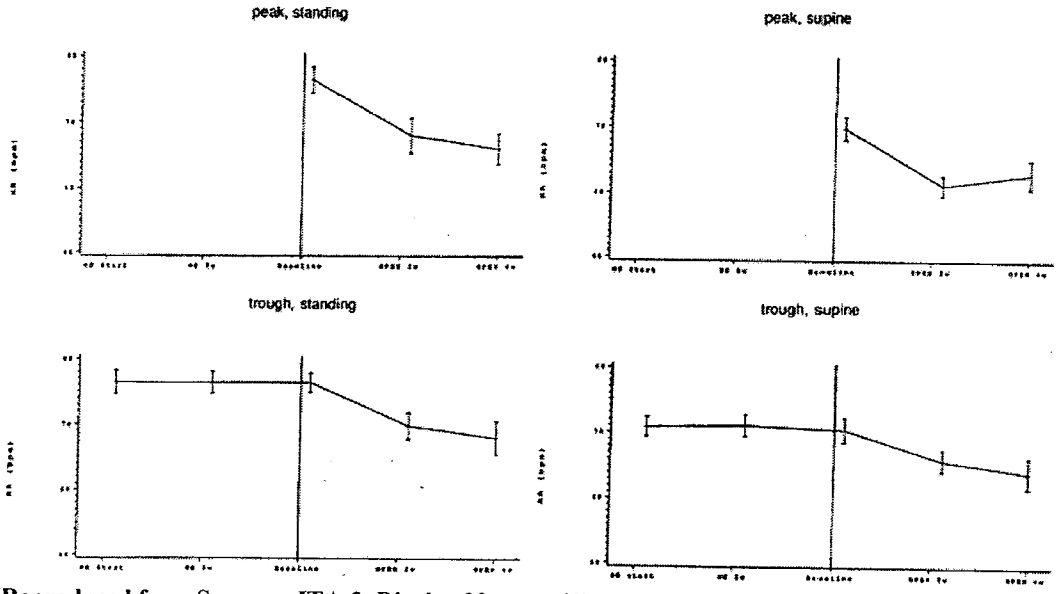
Table 130. Heart Rate (ITA-2)

	Time	HR: trough, bpm (n = 10)		Intragroup changes p-values		HR: peak, bpm (n = 10)		Intragroup changes p-values	
		mean (SEM)	median (min;max)	Overall change (Friedman test)	Baseline vs time specified (Wilcoxon test)	mean (SEM)	median (min;max)	Overall change (Friedman test)	Baseline vs time specified (Wilcoxon test)
Supine	Wash-out								
	Start	70.6 (1.47)	72.0 (60;76)						
	Week 2	71.0 (1.61)	70.0 (64;80)						
	Baseline	70.4 (1.83)	72.0 (62;80)			69.8 (1.75)	72.0 (60;76)		
	Treatment			0.017				0.003	
	Week 2	65.8 (1.65)	64.0 (60;76)		0.012	61.2 (1.55)	60.0 (56;72)		0.004
	Week 4	64.0 (2.29)	60.0 (58;80)		0.039	63.0 (2.18)	60.0 (56;80)		0.027
Standing	Wash-out								
	Start	76.4 (1.83)	78.0 (64;84)						
	Week 2	76.4 (1.73)	76.0 (70;88)						
	Baseline	76.4 (1.51)	77.0 (70;84)			76.4 (2.02)	80.0 (64;84)		
	Treatment			0.013				0.007	
	Week 2	69.8 (2.01)	68.0 (62;84)		0.017	68.0 (2.67)	66.0 (60;86)		0.020
	Week 4	68.0 (2.53)	66.0 (60;84)		0.010	66.0 (2.31)	64.0 (60;84)		0.004

480

(Reproduced from Sponsor, ITA-2, Display 19, page 40)

Figure 101. Graphical Presentation of Heart Rate (HR) (ITA-2)



(Reproduced from Sponsor, ITA-2, Display 20, page 41)

ECG

Two patients had an abnormal ECG at baseline which was unchanged at the end of the study. One patient had a first degree AV block, and another patient had an incomplete left bundle branch block and a right bundle branch block. One patient started with a

normal ECG but ended the study with an ECG read as "myocardial ischemia." The exact tracing was not in the report for review.

Adverse Events

One patient had polymenorrhoea which began during the run-in week and continued through the treatment period. Investigators suspected a hysteromyoma as the etiology of the polymenorrhoea. There were no significant changes in chemistry or hematology parameters.

Table 131. Safety Results (ITA-2)

Safety	
Body weight	no change
Electrocardiogram:	
- normal at baseline/abnormal at end	1 (myocardial ischaemia)
Adverse event (AE):	
- polymenorrhoea (during run-in and treatment period)	1
Total No. of patients assessed	10
No. of patients with one or more AE	1
No. of drop-outs because of AE	0
Haematology-biochemistry-urinalysis	no clinically significant changes during treatment

(Reproduced from Sponsor, ITA-2, page 7)

Conclusions: Supine DBP at trough was significantly decreased after 4 weeks of therapy with nebivolol 5 mg daily. This antihypertensive effect was evident at 2 weeks of treatment. Decrease of DBP at peak was only significant at week 2. SBP was essentially unchanged. Nebivolol reduced plasma renin levels, and renal function was preserved in the participating patients. Nebivolol significantly decreased heart rate at 2 and 4 weeks. There was no effect on body weight, chemistry, or ECG intervals. There were no adverse events, although an ECG at the end of study in one patient was apparently interpreted as "myocardial ischemia." There were no patient drop-outs.

1.66 LMD No. 49643. Study ID N/A. ("Randomized Double-Blind Cross-Over Study of the Effects of Topical R67555 as Compared with Timolol on the Intraocular Pressure, Blood Pressure and heart Rate in Human Healthy Volunteers. April 1986") (Reviewer: Karen A. Hicks, M.D.)

Objectives: To determine the effects of topical R 67 555, a selective beta-1-blocker with vasodilating properties, and of 0.25% timolol eye drops on intraocular pressure (IOP), blood pressure, and heart rate at rest.

Methods: This was a randomized double-blind cross-over study in 6 healthy male volunteers with a median age of 29 years. Subjects received one eye drop of either a 0.1% ——————— solution of R 67 555 (nebivolol), a 0.25% — — — ——————— : solution of R 67 555 (nebivolol), or a 0.25% solution of timolol maleate (Timoptol®) in three sessions, separated by a 48-hour interval. Investigators randomly selected one eye for treatment, and the other eye served as a control. Intraocular pressures were measured "in the upright position with a Goldmann applanation tonometer, mounted on a slitlamp biomicroscope before treatment and after

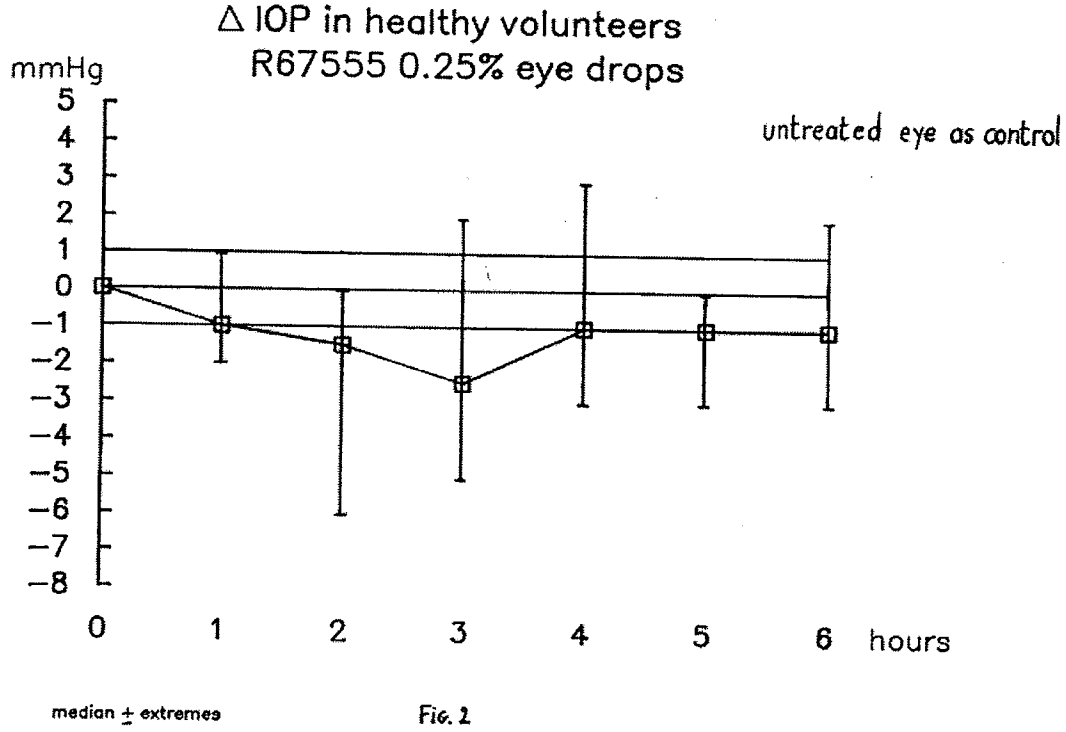
1, 2, 3, 4, 5, and 6 hours." Up to three intraocular pressure measurements were obtained from the treated eye.

Blood pressure and heart rate were measured with an electronic sphygmomanometer and manually by pulse counting, prior to the determination of intraocular pressure

Results

At 3 hours following administration of 0.25% solution of R 67 555, there was a 2.5 mm Hg reduction which was not statistically significant, as shown in Figure 102.

Figure 102. Change in Intraocular Pressure in Healthy Volunteers with R67555 0.25% Eye Drops

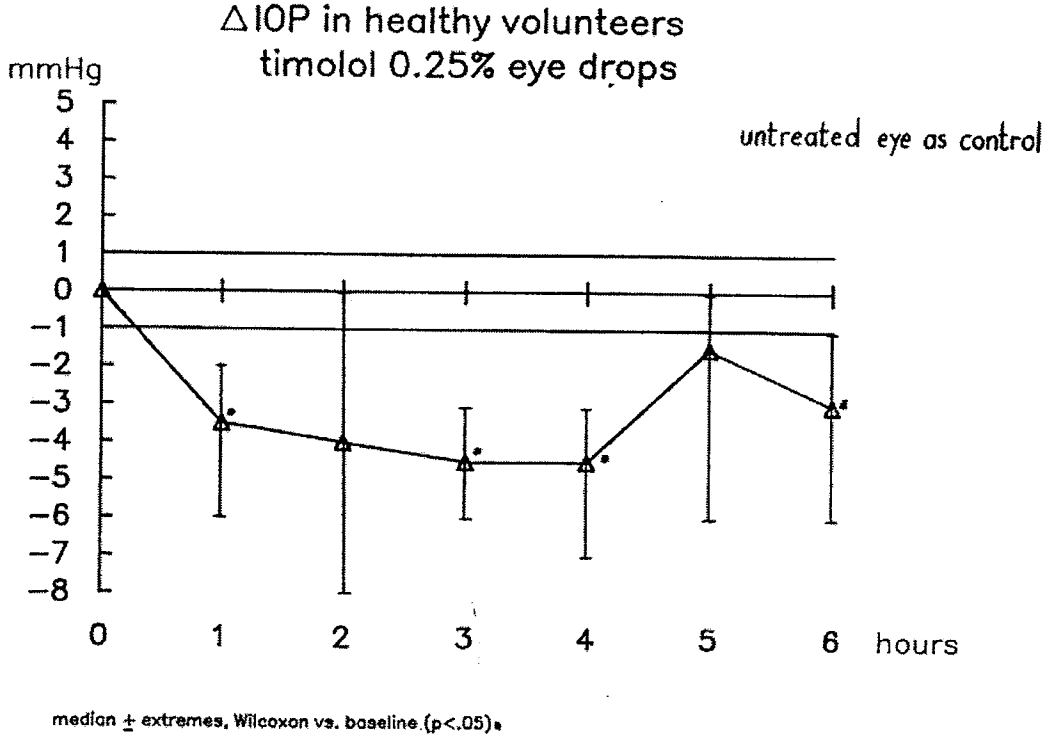


(Reproduced from Sponsor, Figure 2, page 8)

On the other hand, 0.25% timolol eye drops lowered the intraocular pressure by 3.5 mm Hg after one hour, 4 mm Hg after two hours, and 4.5 mm Hg after three and four hours. All reductions, except the one at two hours, were statistically significant (Wilcoxon test, $p = 0.03$).

Appears This Way
On Original

Figure 103. Change in Intraocular Pressure in Healthy Volunteers with Timolol 0.25% Eye Drops



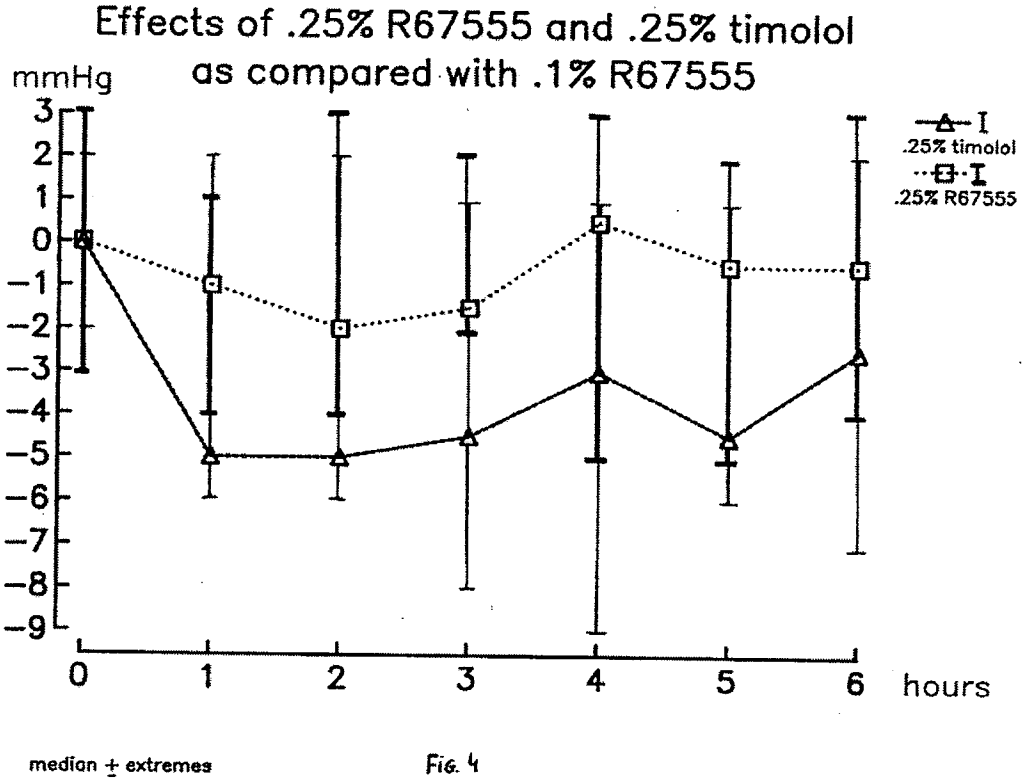
(Reproduced from Sponsor, Figure 3, page 9)

The sponsor notes that possible systemic absorption of the drug may underestimate the actual reduction of intraocular pressure.

Compared with 0.1% R 67 555, 0.25% R 67 555 lowered the intraocular pressure 2 mm Hg after 2 hours and 0.25% timolol lowered intraocular pressure 5 mm Hg after one hour. There was no statistical significance between these values.

Appears This Way
On Original

Figure 104. Effects of .25% R67555 and .25% Timolol as compared with .1% R67555



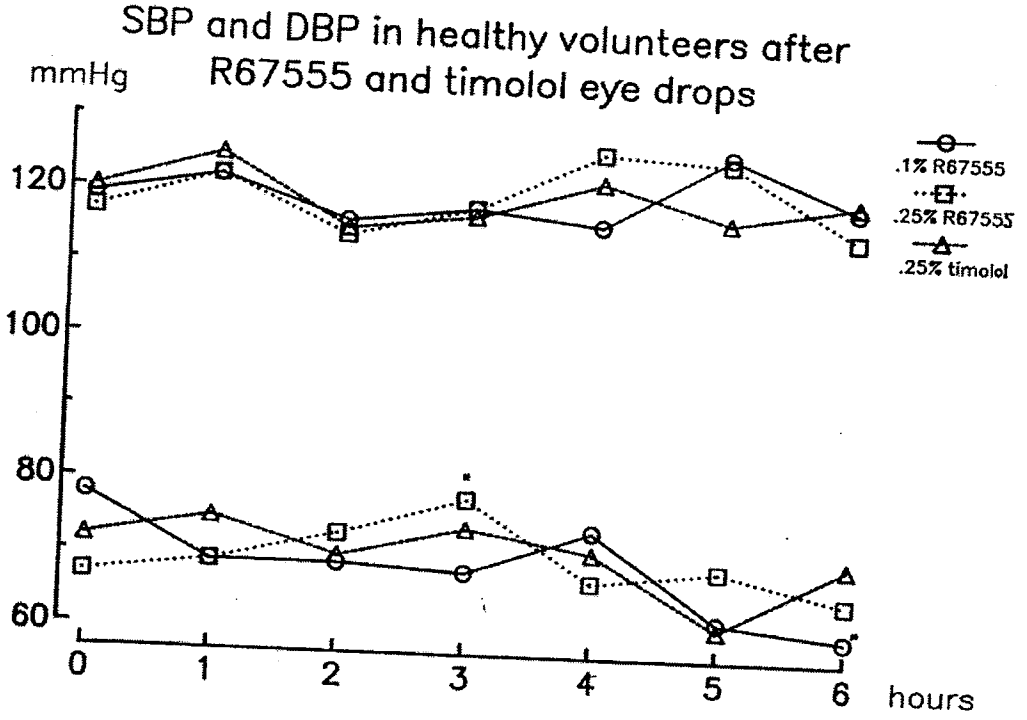
(Reproduced from Sponsor, Figure 4, page 10)

Blood Pressure

At 6 hours, median diastolic blood pressure decreased significantly from 78 to 60 mm Hg following treatment with R 67 555 0.1% (Wilcoxon versus baseline, $p < 0.05$). The higher dose of R 67 555 and Timolol, however, did not significantly alter median diastolic blood pressure. Median systolic blood pressure did not change significantly with any of the treatments, as shown in Figure 105.

Appears This Way
On Original

Figure 105. SBP and DBP in Healthy Volunteers after R67555 and Timolol Eye Drops



median values; Wilcoxon vs. baseline ($p<.05$) *

(Reproduced from Sponsor, Figure 5, page 11)

Heart Rate

Timolol significantly decreased heart rate both 2 and 3 hours following dosing. There was no statistically significant change in heart rate with 0.1% R 67 555. With the .25% solution, however, there was a statistically significant decrease in heart rate ($p < 0.05$), with a minimum of 61 bpm at 4 hours post dosing. The investigators question the statistical significance of this finding, as there was an abnormally high median heart rate of 78 bpm at study initiation.

Appears This Way
On Original

Figure 106. Heart Rate in Healthy Volunteers after R67555 and Timolol Eye Drops

(Reproduced from Sponsor, Figure 6, page 12)

Adverse Effects

One subject developed blurred vision after treatment with 0.1% R 67 555. Investigators wonder whether or not the blurred vision was related to an extremely low intraocular pressure between 4 and 6 mm Hg during treatment. There were no adverse events with the other treatments.

Conclusions: The 0.1% solution of R67 555 had no effect on intraocular pressure. The effect of 0.25% R 67 555 was less pronounced than that of 0.25% timolol eye drops three hours after administration, but this difference was not statistically significant ($p > 0.05$) (maximal reduction of 2.5 mm Hg versus 4.5 mm Hg, respectively). Timolol and not nebivolol (R 67 555), caused a clinically significant drop of the median heart rate at rest from 70 to 55 bpm. Neither R 67 555 nor Timolol significantly affected blood pressure. Investigators recommended studying higher concentrations of R 67 555 in the event poor diffusion into the eye resulted in less of an effect than Timolol.

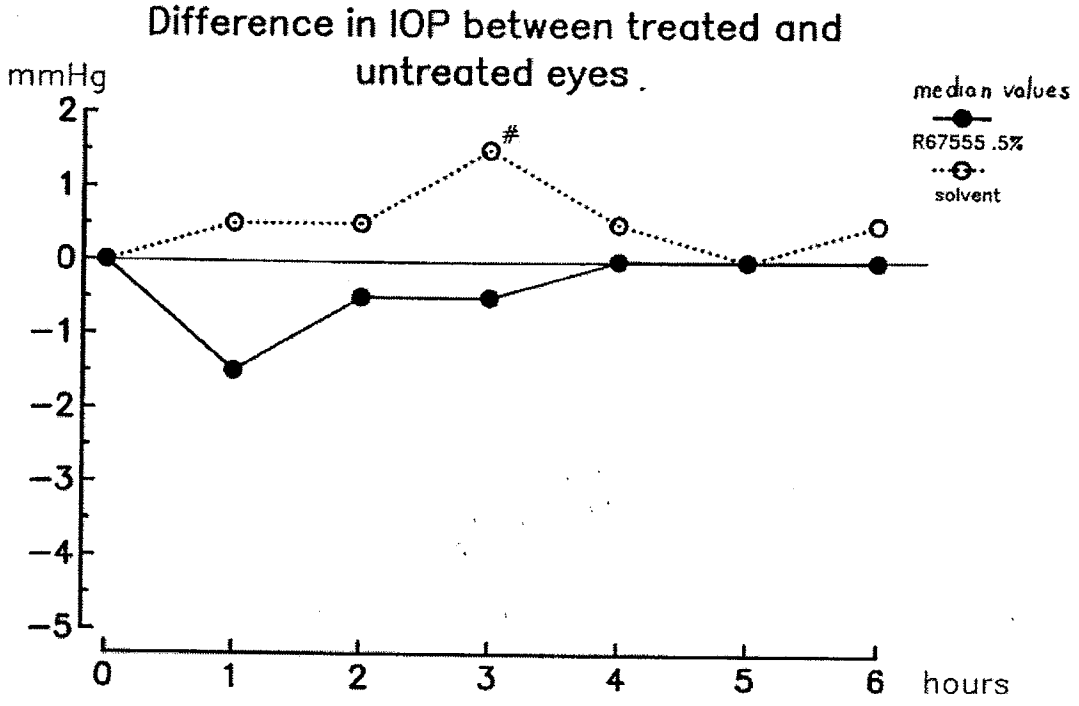
1.67 LMD No. 51686. Study ID N/A. ("Randomized Double-Blind Cross-Over Study of the Effects of Topical R67555 as Compared with R67555 Solvent and Timolol, on the Intraocular Pressure, Blood Pressure, and Heart Rate in Human Healthy Volunteers. July 1986") (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the effects of 0.5% solution of R 67555, topical R 67555 solvent, and 0.25% timolol eye drops on intraocular pressure (IOP), blood pressure, and resting heart rate.

Methods: 6 healthy male volunteers with a median age of 29 years enrolled in this randomized double-blind cross-over study. Subjects were randomized to one drop of R 67555 solvent [redacted], a 0.5% solution of R 67555, or a 0.25% timolol maleate solution (Timoptol®) in three sessions separated by 48 hour intervals. Investigators randomly selected the treated eye and used the other eye as the control. IOP was measured in the upright position with a Goldmann applanation tonometer, mounted on a slitlamp biomicroscope before treatment and after 1, 2, 3, 4, 5, and 6 hours. Up to three IOP measurements were obtained. The scale readings were subsequently averaged for each eye.

Results: R 67555 0.5% eye drops maximally reduced the median IOP by 1.5 mm Hg after 1 hour, compared with 0.25% R 67555 which maximally decreased the IOP by 2.5 mm Hg after 3 hours (data from prior study). These differences were not statistically significant. The R 67555 solvent which contained [redacted], however, increased median IOP by 1.5 mm Hg at three hours. This result approached statistical significance ($p = 0.0625$), as shown in Figure 107.

Figure 107. Difference in IOP Between Treated and Untreated Eyes

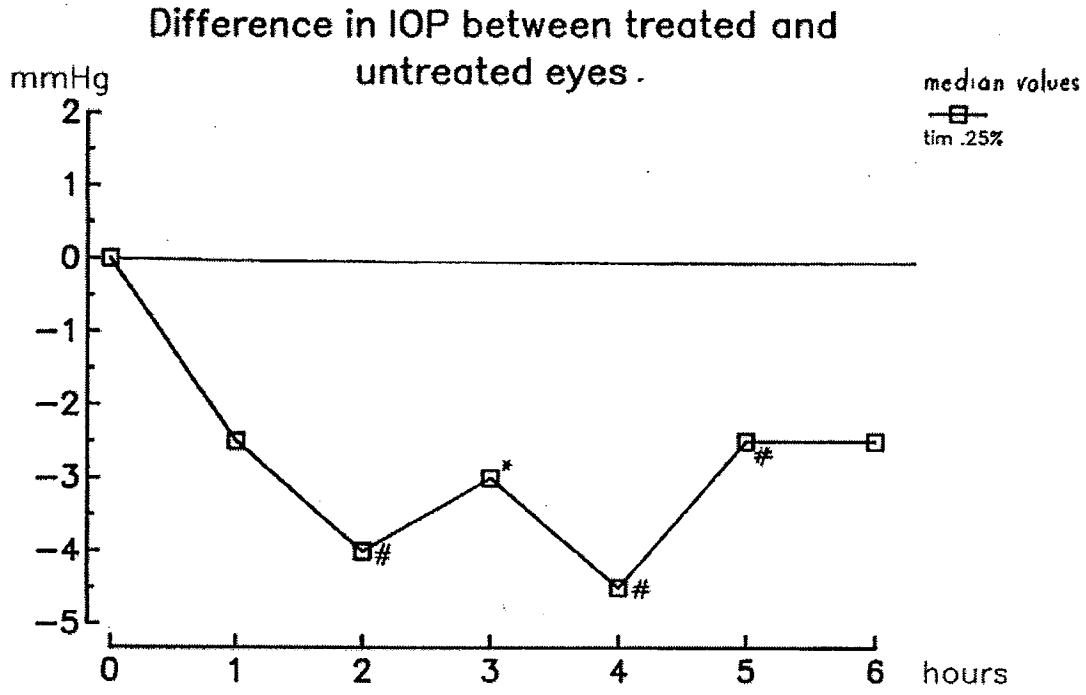


(Reproduced from Sponsor, Figure 1, page 5)

Timolol 0.25% eye drops decreased IOP by 2.5 mm Hg after one hour, 4 mm Hg after two hours, 3 mm Hg after three hours, and 4.5 mm Hg after four hours, as seen in Figure 108. Only the three hour value was statistically significant (Wilcoxon M.P.S.R. test versus baseline p = 0.03), because of the range in results at the other two timepoints).

Appears This Way
On Original

Figure 108. Difference in IOP Between Treated and Untreated Eyes



* Wilcoxon vs. baseline p<.05; # p=.06

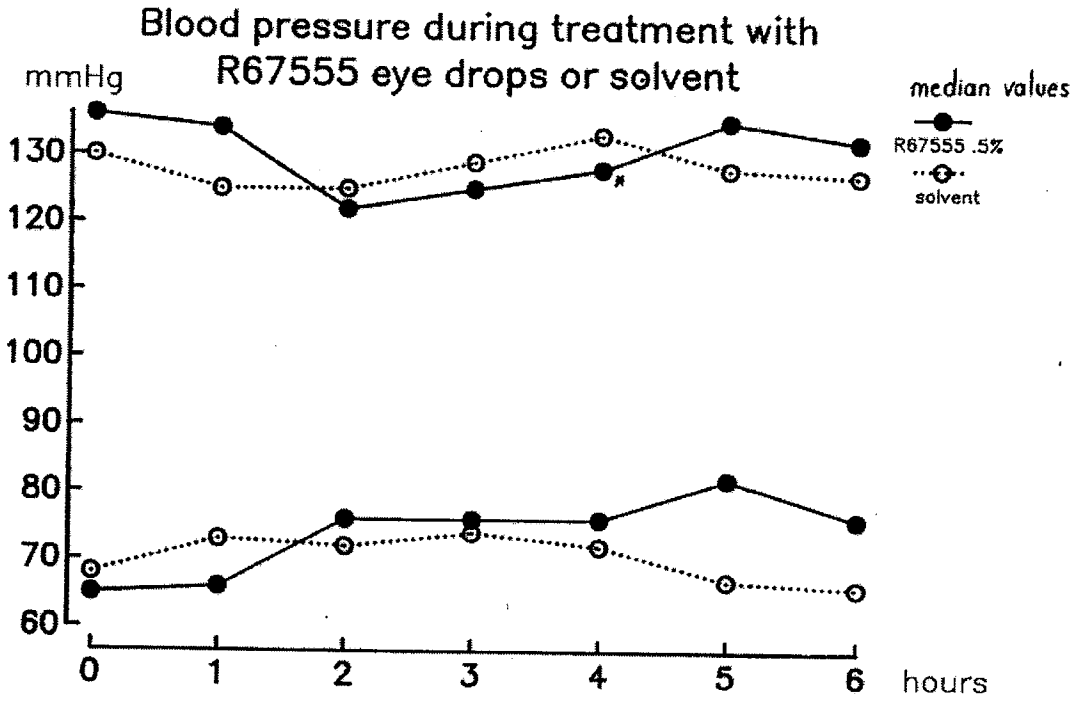
(Reproduced from Sponsor, Figure 2, page 6)

Blood Pressure

R 67555 maximally lowered median SBP from 136 to 122 mm Hg after 2 hours. Compared with baseline, reduction in SBP after 4 hours was statistically significant (128 mm Hg; Wilcoxon M.P.S.R. test versus baseline $p < 0.05$), but these results were comparable to those seen with the R 67555 solvent (Wilcoxon M.P.S.R. test between 0.5% and solvent p = n.s.), as shown in Figure 109. Timolol 0.25% eye drops did not significantly affect SBP. R 67555 0.5% eye drops, R 67555 solvent, and Timolol 0.25% eye drops had no significant affect on DBP.

Appears This Way
On Original

Figure 109. Blood pressure During Treatment with R67555 Eye Drops or Solvent



7

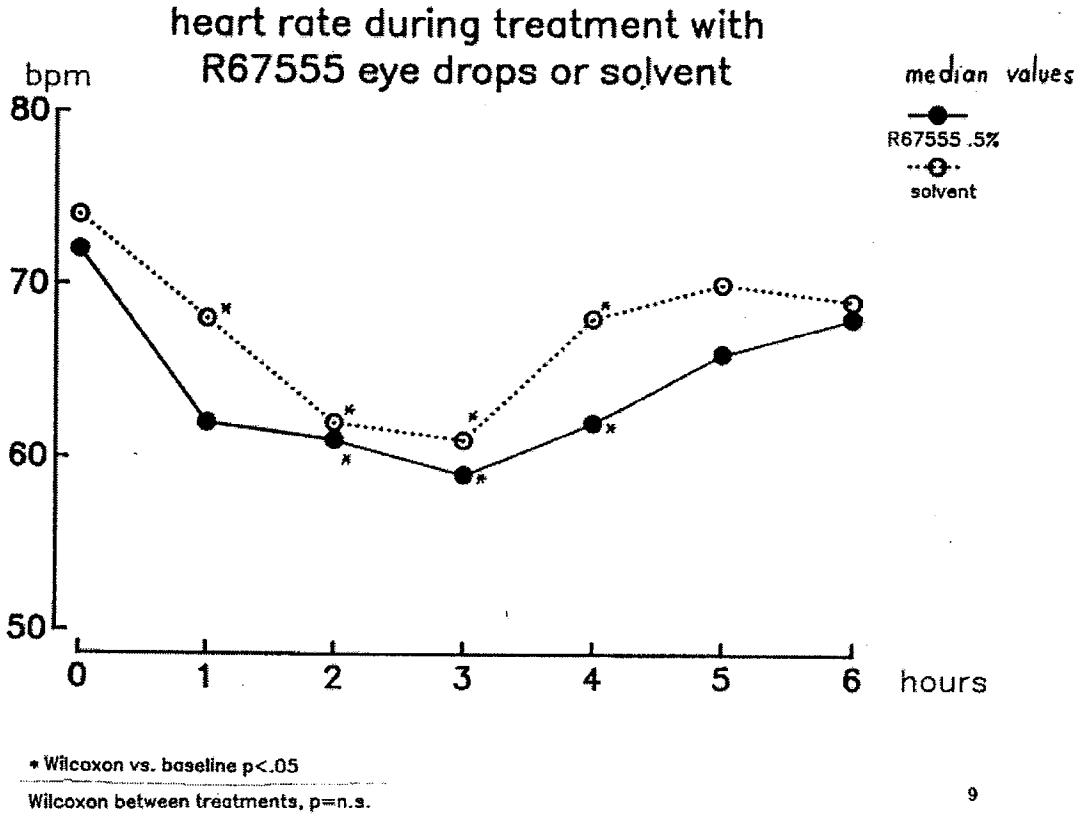
(Reproduced from Sponsor, Figure 3, page 7)

Heart Rate

After treatment with 0.5% R 67555 eye drops, resting heart rate decreased from 72 bpm at baseline to 59 bpm after 3 hours, which was statistically significant (Wilcoxon M.P.S.R. test $p < 0.05$). The 2 and 4-hour heart rates of 61 and 62 bpm were also statistically significant (Wilcoxon M.P.S.R. test $p < 0.05$). The R 67555 solvent had comparable effects at these time points (Wilcoxon M.P.S.R. test between 0.5% and solvent p = n.s.). The heart rate results for 0.5% R 67555 eye drops and R 67555 solvent are shown in Figure 110. Timolol 0.25% eye drops significantly decreased heart rate from 76 bpm at baseline to 60 bpm after 6 hours (Wilcoxon test p M 0.05), as shown in Figure 111.

Appears This Way
On Original

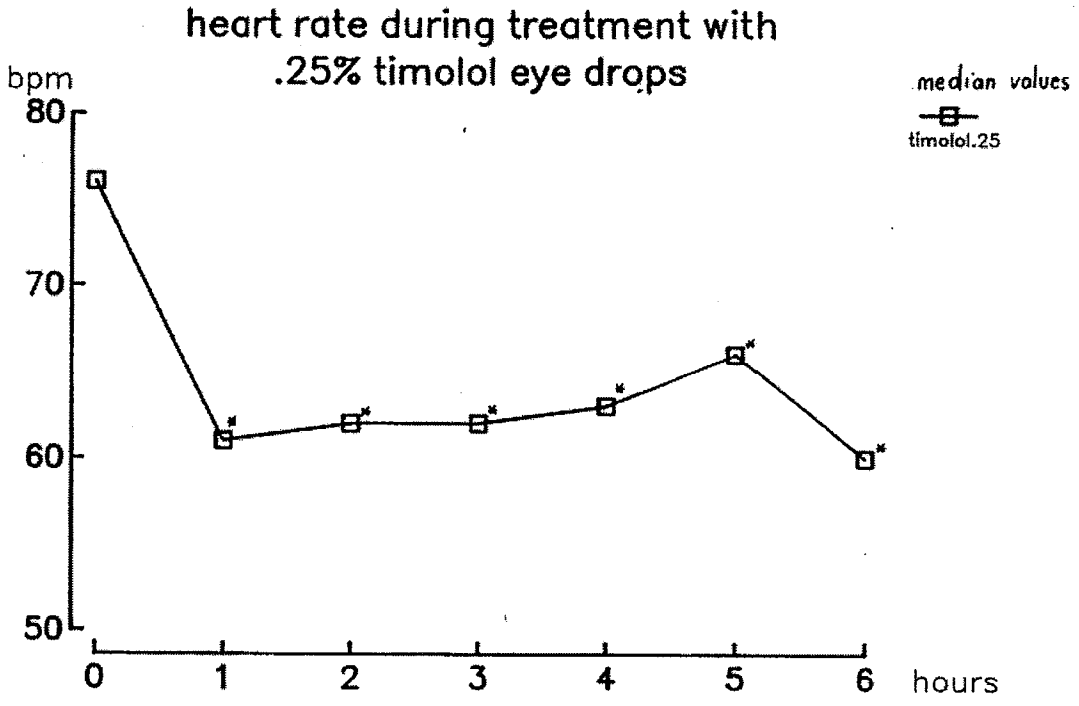
Figure 110. Heart Rate During Treatment with R67555 Eye Drops or Solvent



(Reproduced from Sponsor, Figure 5, page 9)

Appears This Way
On Original

Figure 111. Heart Rate During Treatment with 0.25% Timolol Eye Drops



(Reproduced from Sponsor, Figure 6, page 10)

Adverse Reactions

During the administration of 0.5% R 67555 eye drops, 3 out of 6 volunteers experienced a "short-lasting burning sensation." These three subjects and one additional subject had conjunctival redness lasting a few hours. One volunteer had blurred vision with timolol 0.25% eye drops. Another volunteer receiving timolol felt "something was wrong." These two volunteers receiving timolol developed low IOPs of 4 and 5 mm Hg, respectively.

Conclusions: Compared with Timolol 0.25% eye drops, R 67555 0.1%, 0.25%, and 0.5% solutions were less effective in lowering IOP in healthy volunteers. To explain the reduced efficacy, the investigator suggested R 67555 may form a tight complex with the cyclodextrin, lowering the free concentration of R 67555 available for penetration into the eye.

R 67555 0.5% concentration reduced IOP a maximum of 1.5 mm Hg, compared with 4.5 mm Hg for timolol 0.25%. The R 67555 solvent, however, increased IOP and approached statistical significance after 3 hours (+1.5 mm Hg, Wilcoxon vs. baseline $p = 0.06$). R67555 0.5% eye drops and R67555 solvent had comparable effects on blood pressure and heart rate. Timolol 0.25% solution significantly lowered heart rate from 76 bpm to 60 bpm (Wilcoxon vs. baseline, $p < 0.05$) but did not significantly affect blood pressure.

1.68 LMD No. 46816. Study ID N/A. ("Safety Data After Oral Administration of R65824 5 mg/day for 7 Consecutive Days in 6 Human Volunteers. December 1985") (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the safety of R 65824 5 mg/day after 7 consecutive days of treatment.

Methods: This was an open-label study in 6 healthy volunteers, ages 27 to 47. Subjects received R 65824 5 mg/day for 7 consecutive days. Serum laboratory sampling was performed prior to study initiation and after 1 week.

Results: 6 healthy volunteers (4 men, 2 women) with a median age of 32 participated in the study. The sponsor concluded there were no significant changes in hematological and biochemical parameters, as shown in Table 132. Only one patient had what was regarded as a "pathological" chloride value at the end of study as seen in Table 133. Several patients had increases in glucose, LDH, BUN, and lymphocytes at the end of study. Some patients had an increase in lymphocytes prior to study initiation.

Table 132. Comparison of Frequency Distributions of Laboratory Values After 7 Days of R 65824 Intake 5 mg/day with Frequency Distributions of Laboratory Values Before Tablet Intake

Bertek Pharmaceuticals, Inc. NDA #21-742

Table 3 : Comparison of frequency distributions of laboratory values after 7 days of R 65824 intake with frequency distributions of laboratory values at the start of the study, the normal range dividing the data into 3 classes (below, within, and above normal range) and descriptive statistics (median, mean and standard error) of laboratory values before and after 7 days of R 65824 intake.

SUMMARY OF LABORATORY TEST RESULTS

STUDY : 5MG OF R65824/DAY FOR 7 CONSECUTIVE DAYS HEALTHY VOLUNTEERS
STUDY GROUP :ACTIVE DRUG :R65824

LABORATORY TEST / RANGE,UNIT	BASELINE N	MEAN	SE	MEDIAN	AFTER 7 DAYS N	MEAN	SE	MEDIAN	(1) (2) (3) B	BELOW W	BELOW A	BELOW M	WITHIN B	WITHIN W	WITHIN A	WITHIN M	ABOVE B	ABOVE W	ABOVE A	ABOVE M	N	MISS (4)
1. HEMATOLOGY																						
HEMOGLOBIN																						
FEMALE 11.5-16.4 G/DL	2	13.7	1.35	13.7	12.7	0.80	12.7			1				5							6	
MALE 13.5-18 G/DL	4	15.5	0.38	15.4	14.1	0.58	14.3															
RBC																						
FEMALE 4-5.6 10E6/MM3	2	4.55	0.15	4.55	4.25	0.05	4.25			2				4							6	
MALE 4.5-5.6 10E6/MM3	4	5.02	0.13	5.05	4.65	0.18	4.60															
HEMATOCRIT																						
FEMALE 36-47 VOL-%	2	41	3.00	41	39	1.00	39			1				5							6	
MALE 40-54 VOL-%	4	46	1.29	46	42.8	2.02	43															
WBC																						
4-10 1E3/MM3	6	6.38	0.34	6.35	6.45	0.50	6.30							6							6	
NONSEGM NEUTROPHILS																						
0-7 %	6	0.00	0.00	0.00	1.67	0.42	2.00							6							6	
SEGM NEUTROPHILS																						
40-70 %	6	64	5.11	65	55.2	5.21	52							3	2			1			6	
LYMPHOCYTES																						
20-40 %	6	30.8	5.10	31	38.3	5.85	41						1	2				2	1		6	
MONOCYTES																						
0-8 %	6	4.00	0.58	4.00	3.67	0.99	4.00							6							6	
EOSINOPHILS																						
0-4 %	6	1.17	0.31	1.00	0.83	0.40	0.50							6							6	
BASOPHILS																						
0-2 %	6	0.00	0.00	0.00	0.33	0.21	0.00							6							6	
PLATELET COUNT																						
150-400 1E3/MM3	6	230	15.9	238	231	13	219							6							6	
2. BIOCHEMISTRY																						
CALCIUM																						
9-10.5 MG/DL	6	9.82	0.13	9.80	9.55	0.11	9.55							6							6	
CHLORIDE																						
100-108 MEQ/L	6	106	0.72	105	107	1.54	106							5				1			6	
PHOSPHORUS																						
2.2-4.2 MG/DL	6	3.55	0.15	3.55	3.18	0.17	3.00							6							6	
POTASSIUM																						
3.6-4.9 MEQ/L	6	4.33	0.07	4.35	4.40	0.14	4.50							6							6	
SODIUM																						
137-148 MEQ/L	6	144	1.17	145	145	1.30	146							6							6	

(1) No. of laboratory values below, within and above normal range at the end of the study.

(2) No. of laboratory values below (B), within (W) and above (A) normal range or missing (M) at the start of the study.

(3) Change in laboratory values, comparing laboratory values at the end of the study with laboratory values at the start of the study (= : no change; ↑ : increase; ↓ : decrease; ? : unknown).

(4) No. of laboratory values available only at the start of the study.

(Reproduced from Sponsor, Table 3, page 5)

Table 133. Individual Laboratory Values

		No. 1		No. 2		No. 3		No. 4		No. 5		No. 6	
LABORATORY TEST	RANGE, UNIT	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY
1. HEMATOLOGY													
HEMOGLOBIN	13.5-18 G/DL	14.9	12.7 B	14.9	13.8	16.4	14.8	15.9	15.3	15.1	13.5	12.4	11.9
RBC	4.5-5.6 1E6/MM3	5	4.3 B	4.7	4.4 B	5.1	4.8	5.3	5.1	4.7	4.3	4.4	4.2
HEMATOCRIT	40-54 VOL-%	45	38 B	43	41	49	45	47	47	44	40	38	38
WBC	4-10 1E3/MM3	6.6	5.3	5.1	5.1	6.5	6.5	6.2	7.4	7.7	8.3	6.2	6.1
NONSEGM NEUTROPHILS	0-7 %	0	1	0	3	0	2	0	2	0	0	0	2
SEGM NEUTROPHILS	40-70 %	79 A	54	61	40	74 A	70	45	46	56	50	69	71 A
LYMPHOCYTES	20-40 %	15 B	35	36	56 A	21	23	49 A	48 A	38	47 A	26	21
MONOCYTES	0-8 %	4	7	2	0	4	5	6	4	5	2	3	4
EOSINOPHILS	0-4 %	2	2	1	1	1	0	0	0	1	0	2	2
BASOPHILS	0-2 %	0	1	0	0	0	0	0	0	0	1	0	0
PLATELET COUNT	150-400 1E3/MM3	257	201	248	257	192	209	227	224	177	214	278	283
2. BIOCHEMISTRY													
CALCIUM	9-10.5 MG/DL	9.9	9.4	10.2	9.6	9.7	9.5	10.1	10	9.7	9.6	9.3	9.2
CHLORIDE	100-108 MEQ/L	108	114 AA	103	105	105	107	107	104	105	104	105	106
PHOSPHORUS	2.2-4.2 MG/DL	3.3	3.8	3.3	3	3.9	3	3.8	2.7	3.9	3.6	3.1	3
POTASSIUM	3.6-4.9 MEQ/L	4.3	4.6	4.4	4.5	4.4	4.5	4.6	4.8	4.1	4.1	4.2	3.9
SODIUM	137-148 MEQ/L	147	148	146	145	147	147	144	144	140	145	142	139
TOTAL PROTEIN	6.5-8.1 G/DL	7.3	6.6	7.5	6.9	7.2	6.5	7.5	7.4	7.3	8	7	7.2
ALBUMIN	4.1-5.2 G/DL	4.6	4.4	4.8	4.5	4.6	4.4	4.5	4.6	4.6	4.8	4.3	4.4
HAPTOGLOBIN	6-330 MG/DL	136	108	176	151	142	125	221	189	150	169	87	89
GLUCOSE	54-118 MG/DL	130 A	94	63	72	91	124 A	94	106	106	91	70	91
CHOLESTEROL, TOTAL	124-302 MG/DL	179	131	234	211	245	225	197	193	176	190	155	166
TRIGLYCERIDES	0-200 MG/DL	124	63	110	125	71	84	132	102	82	74	84	90
PHOSPHOLIPIDS	160-300 MG/DL	209	156 B	248	239	246	210	246	195	230	222	209	209
BILIRUBIN, TOTAL	0.2-1.2 MG/DL	0.34	0.4	0.55	0.33	0.69	0.8	0.45	0.51	0.43	0.39	0.58	0.5
ALKALINE PHOSPHATASE	35-129 U/L	65	43	64	64	62	54	118	103	48	48	45	44
SGGT	1-44 U/L	28	27	41	41	23	20	24	24	18	19	15	15
LDH	0-250 U/L	279 A	281 A	288 A	291 A	224	234	232	282 A	216	224	271 A	298 A
ASAT	2-39 U/L	19	19	17	21	13	12	18	19	14	16	14	15
ALAT	1-55 U/L	6	7	19	20	10	7	12	13	6	5	10	10
CHOLINESTERASE	4.6-14.5 U/L	8.2	7	11.6	10.8	9.2	8.4	5.4	5.4	7.8	8.4	6.7	6.4
BLOOD UREA NITROGEN	4.5-18 MG/DL	18	15	11.1	13.9	19 A	20 A	13	13	13	11	10.5	12.9
CREATININE	0.6-1.4 MG/DL	1.03	1.01	1.02	1.06	1.04	1	0.9	0.93	0.69	0.68	0.74	0.81
URIC ACID	3.5-7 MG/DL	5.4	5.7	5.4	5.9	5.3	5.3	5.2	5.6	3.3	3.5	1.9	2.3

(Reproduced from Sponsor, Table 5, page 8)

1.69 LMD No. 46817. Study ID N/A. ("Safety Data After a Single Oral Administration of 5 mg and 10 mg of R65824 in 8 Human volunteers. December 1985") (Reviewer: Karen A. Hicks, M.D.)

Objective: To determine the safety of a single oral administration of 5 mg and 10 mg of R 65824 in 8 healthy volunteers.

Methods: This was an open-label study in 8 healthy volunteers, ages 27 to 47. Subjects received a single oral 5 mg and 10 mg dose of R 65824 at least one week apart.

Results: 8 patients (6 men, 2 women) with a median age of 32 years participated in this study. Hematological and biochemical parameters were sampled prior to study initiation and 2 hours following the single oral dose of R 65824 5 mg or 10 mg. There were no significant differences in these parameters from baseline to 2 hours following the single oral dose of R 65824.

Table 134. Comparison of Frequency Distributions of Laboratory Values 2 Hours After Intake of 5 mg of R 65824 with Frequency Distributions of Laboratory Values Before Tablet Intake

Bertek Pharmaceuticals, Inc. **NDA #21-742**

Table 1 : Comparison of frequency distribution of laboratory values 2 hours after intake of 5 mg of R 65824 with frequency distributions of laboratory values before tablet intake, the normal range dividing the data into 3 classes (below, within and above normal range) and descriptive statistics (median, mean and standard error) of laboratory values before and 2 hours after intake of 5 mg of R 65824.

SUMMARY OF LABORATORY TEST RESULTS

STUDY : SINGLE INTAKE OF R65824 5MG HEALTHY VOLUNTEERS
STUDY GROUP :ACTIVE DRUG :R65824

LABORATORY TEST / RANGE.UNIT	BASELINE N	BASELINE MEAN	BASELINE SE	BASELINE MEDIAN	AFTER INTAKE MEAN	AFTER INTAKE SE	AFTER INTAKE MEDIAN	(1) BELOW (2) B	BELOW W	BELOW A	BELOW M	WITHIN B	WITHIN W	WITHIN A	WITHIN M	ABOVE B	ABOVE W	ABOVE A	ABOVE M	N	MISS (4)
1. HEMATOLOGY																					
HEMOGLOBIN																					
FEMALE 11.5-16.4 G/DL	2	12.8	0.70	12.8	13	0.65	13						8							8	
MALE 13.5-18 G/DL	6	15.6	0.23	15.6	15.3	0.36	15.3														
RBC																					
FEMALE 4-5.6 1E6/MM3	2	4.15	0.05	4.15	4.25	0.15	4.25						8							8	
MALE 4.5-5.6 1E6/MM3	6	5.17	0.10	5.25	5.18	0.08	5.20														
HEMATOCRIT																					
FEMALE 36-47 VOL-%	2	40	2.00	40	39.5	1.50	39.5						8							8	
MALE 40-54 VOL-%	6	46.3	0.76	46.5	45.7	0.99	46														
WBC																					
4-10 1E3/MM3	8	6.32	0.25	6.30	6.45	0.24	6.40						8							8	
NONSEGM NEUTROPHILS																					
0-7 %	8	0.75	0.53	0.00	1.88	0.58	2.00						8							8	
SEGM NEUTROPHILS																					
40-70 %	8	60.6	4.08	62.5	57.6	4.16	60.5						6	2						8	
LYMPHOCYTES																					
20-40 %	8	32.5	3.97	29.5	34.1	4.20	31						5	1			1	1		8	
MONOCYTES																					
0-8 %	8	3.63	0.46	3.00	3.63	0.56	4.00						8							8	
EOSINOPHILS																					
0-4 %	8	1.88	0.44	2.00	2.00	0.38	2.00						8							8	
BASOPHILS																					
0-2 %	8	0.63	0.26	0.50	0.63	0.26	0.50						8							8	
PLATELET COUNT																					
150-400 1E3/MM3	8	231	11	229	236	12.4	228						8							8	
2. BIOCHEMISTRY																					
CALCIUM																					
9-10.5 MG/DL	8	10	0.10	10	9.94	0.13	10						8							8	
CHLORIDE																					
100-108 MEQ/L	8	106	0.97	106	106	1.39	107		1				4				1	2		8	
PHOSPHORUS																					
2.2-4.2 MG/DL	8	3.34	0.18	3.25	3.79	0.18	3.55						7				1			8	
POTASSIUM																					
3.6-4.9 MEQ/L	8	4.41	0.09	4.45	4.59	0.07	4.60						8							8	
SODIUM																					
137-148 MEQ/L	8	145	1.66	145	146	1.38	147						7					1		8	

(1) No. of laboratory values below, within and above normal range 2 hours after intake of 5 mg of R 65824.

(2) No. of laboratory values below (B), within (W) and above (A) normal range or missing (M) before tablet intake.

(3) Change in laboratory values, comparing laboratory values 2 hours after intake of 5 mg of R 65824 with laboratory values before tablet intake (= : no change; ↑ : increase; ↓ : decrease; ? : unknown).

(4) No. of laboratory values available only before tablet intake.

Table 3 : Comparison of frequency distributions of laboratory values 2 hours after intake of 5 mg of R 65824 with frequency distributions of laboratory values before tablet intake, the normal range dividing the data into 3 classes (below, within and above normal range) and descriptive statistics (median, mean and standard error) of laboratory values before and 2 hours after intake of 5 mg of R 65824. (cont'd).

SUMMARY OF LABORATORY TEST RESULTS

STUDY : SINGLE INTAKE OF R65824 5MG HEALTHY VOLUNTEERS
STUDY GROUP :ACTIVE DRUG :R65824

LABORATORY TEST RANGE,UNIT	BASELINE N	BASELINE MEAN	BASELINE SE	BASELINE MEDIAN	AFTER INTAKE MEAN	AFTER INTAKE SE	AFTER INTAKE MEDIAN	(1) (2) (3)	BELOW B	BELOW W	BELOW A	BELOW M	WITHIN B	WITHIN W	WITHIN A	WITHIN M	ABOVE B	ABOVE W	ABOVE A	ABOVE M	M	MISS (4)
2. BIOCHEMISTRY																						
TOTAL PROTEIN																						
6.5-8.1 G/DL	8	7.40	0.16	7.55	7.47	0.14	7.45							7				1			8	
ALBUMIN																						
4.1-5.2 G/DL	8	4.92	0.15	5.00	4.94	0.11	5.00							7	1						8	
HAPTOGLOBIN																						
6-330 MG/DL	8	178	25.6	187	182	27.9	190							8							8	
GLUCOSE																						
54-118 MG/DL	8	90.1	6.47	94	96.6	1.53	97.5							8							8	
CHOLESTEROL, TOTAL																						
124-302 MG/DL	8	209	11.8	210	204	9.99	203							8							8	
TRIGLYCERIDES																						
0-200 MG/DL	8	110	12.2	101	90.6	15	75							8							8	
PHOSPHOLIPIDS																						
160-300 MG/DL	8	239	8.20	240	230	6.14	226							8							8	
BILIRUBIN, TOTAL																						
0.2-1.2 MG/DL	8	0.57	0.19	0.41	0.49	0.16	0.34							7					1		8	
ALKALINE PHOSPHATASE																						
35-129 U/L	8	77	9.68	77	71.8	8.68	67.5							8							8	
SGOT																						
1-44 U/L	8	26.3	2.74	25	24.9	2.51	23.5							8							8	
LDH																						
0-250 U/L	8	260	16.6	272	231	11.2	231							3	3				2		8	
ASAT																						
3-39 U/L	8	18.6	0.73	18.5	18	0.57	17.5							8							8	
ALAT																						
1-55 U/L	8	18.3	2.53	17	14.6	1.73	14							8							8	
CHOLINESTERASE																						
4.6-14.5 U/L	8	8.86	0.73	9.25	8.80	0.69	9.20							8							8	
BLOOD UREA NITROGEN																						
4.5-18 MG/DL	8	14.8	1.98	14	13	1.40	13							7					1		8	
CREATININE																						
0.6-1.4 MG/DL	8	0.92	0.05	0.99	0.90	0.04	0.91							8							8	
URIC ACID																						
FEMALE 1.5-6 MG/DL	2	3.35	0.85	3.35	3.10	1.10	3.10							8							8	
MALE 3.5-7 MG/DL	6	5.42	0.36	5.40	5.32	0.23	5.25															

(1) No. of laboratory values below, within and above normal range 2 hours after intake of 5 mg of R 65824.

(2) No. of laboratory values below (B), within (W) and above (A) normal range or missing (M) before tablet intake.

(3) Change in laboratory values, comparing laboratory values 2 hours after intake of 5 mg of R 65824 with laboratory values before tablet intake (= : no change; ↑ : increase; ↓:decrease; ? : unknown).

(4) No. of laboratory values available only before tablet intake.

(Reproduced from Sponsor, Table 3, pages 6 and 7)

Table 135. Comparison of Frequency Distributions of Laboratory Values 2 Hours After Intake of 10 mg of R 65824 with Frequency Distributions of Laboratory Values Before Tablet Intake

Bertek Pharmaceuticals, Inc. NDA #21-742

Table 4 : Comparison of frequency distributions of laboratory values 2 hours after intake of 10 mg of R 65824 with frequency distributions of laboratory values before tablet intake, the normal range dividing the data into 3 classes (below, within and above normal range) and descriptive statistics (median, mean and standard error) of laboratory values before and 2 hours after intake of 10 mg of R 65824.

SUMMARY OF LABORATORY TEST RESULTS

STUDY : SINGLE INTAKE OF R65824 10MG HEALTHY VOLUNTEERS
STUDY GROUP :ACTIVE DRUG :R65824

LABORATORY TEST RANGE,UNIT	BASELINE N	MEAN	SE	MEDIAN	AFTER INTAKE MEAN	SE	MEDIAN	(1) (2) (3)	BELOW B	W	A	M	WITHIN B	W	A	M	ABOVE B	W	A	M	M	MISS (4)
1. HEMATOLOGY																						
HEMOGLOBIN																						
FEMALE 11.5-16.4 G/DL	2	12.9	0.60	12.9	12.9	0.45	12.9							8							8	
MALE 13.5-18 G/DL	6	15.5	0.23	15.7	15.5	0.18	15.5															
RBC																						
FEMALE 4-5.6 10E6/MM3	2	4.25	0.05	4.25	4.30	0.00	4.30			1				6					1		8	
MALE 4.5-5.6 10E6/MM3	6	5.35	0.20	5.35	5.35	0.30	5.45															
HEMATOCRIT																						
FEMALE 36-47 VOL-%	2	40	1.00	40	39.5	2.50	39.5							8							8	
MALE 40-54 VOL-%	6	45.3	0.95	46	45.5	0.85	45.5															
WBC																						
4-10 10E3/MM3	8	6.55	0.38	6.70	6.66	0.19	6.70							8							8	
MONSEGN NEUTROPHILS																						
0-7 %	8	0.63	0.42	0.00	1.63	0.46	2.00							8							8	
SEGN NEUTROPHILS																						
40-70 %	8	61	4.08	64	57.5	4.42	59							6	1				1		8	
LYMPHOCYTES																						
20-40 %	8	32.6	4.15	29.5	34.6	4.44	32							5	1			1	1		8	
MONOCYTES																						
0-6 %	8	2.75	0.41	2.00	3.13	0.58	3.00							8							8	
EOSINOPHILS																						
0-4 %	8	2.13	0.44	2.00	2.50	0.33	2.50							8							8	
BASOPHILS																						
0-2 %	8	0.88	0.35	1.00	0.88	0.30	1.00							7	1						8	
PLATELET COUNT																						
150-400 10E3/MM3	8	221	8.90	220	224	9.14	224							8							8	
2. BIOCHEMISTRY																						
CALCIUM																						
9-10.5 MG/DL	8	10	0.12	10	10	0.12	10							8							8	
CHLORIDE																						
100-108 MEQ/L	8	108	0.80	109	106	1.10	105							4	2				2		8	
PHOSPHORUS																						
2.2-4.2 MG/DL	8	3.41	0.16	3.40	3.76	0.24	3.50							6	1			1			8	
POTASSIUM																						
3.6-4.9 MEQ/L	8	4.49	0.10	4.50	4.54	0.10	4.50							7				1			8	
SODIUM																						
137-148 MEQ/L	8	148	1.51	149	146	0.65	147							4	4						8	

(1) No. of laboratory values below, within and above normal range 2 hours after intake of 10 mg of R 65824.

(2) No. of laboratory values below (B), within (W) and above (A) normal range or missing (M) before tablet intake.

(3) Change in laboratory values, comparing laboratory values 2 hours after intake of 10 mg of R 65824 with laboratory values before tablet intake (- : no change; ↑ : increase; ↓ : decrease; ? : unknown).

(4) No. of laboratory values available only before tablet intake.

Table 4 : Comparison of frequency distributions of laboratory values 2 hours after intake of 10 mg of R 65824 with frequency distributions of laboratory values before tablet intake, the normal range dividing the data into 3 classes (below, within and above normal range) and descriptive statistics (median, mean and standard error) of laboratory values before and 2 hours after intake of 10 mg of R 65824. (cont'd).

SUMMARY OF LABORATORY TEST RESULTS

STUDY : SINGLE INTAKE OF R65824 10MG HEALTHY VOLUNTEERS
STUDY GROUP :ACTIVE DRUG :R65824

LABORATORY TEST RANGE,UNIT	BASELINE N	MEAN	SE	MEDIAN	AFTER INTAKE N	MEAN	SE	MEDIAN	(1) (2) (3)	BELOW B	BELOW W	BELOW A	BELOW M	WITHIN B	WITHIN W	WITHIN A	WITHIN M	ABOVE B	ABOVE W	ABOVE A	ABOVE M	N	MISS (4)
2. BIOCHEMISTRY																							
TOTAL PROTEIN																							
6.5-8.1 G/DL	8	7.41	0.15	7.50	7.47	0.15	7.60								8							8	
ALBUMIN																							
4.1-5.2 G/DL	8	4.87	0.12	4.90	4.94	0.10	4.90								6	1			1			8	
HAPTOGLOBIN																							
6-330 MG/DL	8	178	21.1	180	186	26.3	191								8							8	
GLUCOSE																							
54-110 MG/DL	8	89.6	5.86	85.5	90.6	2.89	89								7	1						8	
CHOLESTEROL, TOTAL																							
124-302 MG/DL	8	203	13.5	204	200	12.3	204								8							8	
TRIGLYCERIDES																							
0-200 MG/DL	8	104	7.95	97.5	92.9	19.1	73.5								8							8	
PHOSPHOLIPIDS																							
160-308 MG/DL	8	230	5.99	229	220	7.83	219								8							8	
BILIRUBIN, TOTAL																							
0.2-1.2 MG/DL	8	0.49	0.12	0.38	0.50	0.11	0.39								7	1						8	
ALKALINE PHOSPHATASE																							
35-129 U/L	8	72.5	7.94	72	71.9	7.97	70.5								8							8	
SGOT																							
1-44 U/L	8	25.5	2.69	25	26	2.90	25								8							8	
LDH																							
0-250 U/L	8	258	26	246	241	13.3	257								2	1			3	2		8	
ASAT																							
3-39 U/L	8	19	1.15	19.5	18	0.87	18								8							8	
ALAT																							
1-55 U/L	8	16.4	2.20	15	14.5	1.75	12.5								8							8	
CHOLINESTERASE																							
4.6-14.5 U/L	8	8.75	0.61	9.05	8.76	0.73	8.90								8							8	
BLOOD UREA NITROGEN																							
4.5-18 MG/DL	8	14.5	1.54	13	13	1.00	13.5								5	3						8	
CREATININE																							
0.6-1.4 MG/DL	8	0.96	0.04	0.95	0.92	0.04	0.93								8							8	
URIC ACID																							
FEMALE 1.5-6 MG/DL	2	3.35	1.05	3.35	3.20	1.00	3.20								5	1	2					8	
MALE 3.5-7 MG/DL	4	5.87	0.47	5.65	5.32	0.30	5.45																

(1) No. of laboratory values below, within and above normal range 2 hours after intake of 10 mg of R 65824.

(2) No. of laboratory values below (B), within (W) and above (A) normal range or missing (M) before tablet intake.

(3) Change in laboratory values, comparing laboratory values 2 hours after intake of 10 mg of R 65824 with laboratory values before tablet intake (→ : no change; ↑ : increase; ↓ : decrease; ? : unknown).

(4) No. of laboratory values available only before tablet intake.

(Reproduced from Sponsor, Table 4, pages 7 and 8)

There were three subjects receiving 5 mg of R 65824 with important abnormalities in sodium, total bilirubin, and blood urea nitrogen. Two of these subjects had these abnormalities prior to treatment, and one patient had the abnormality before and during treatment.

In the 10 mg group of R 65824, there were three important abnormalities in RBC and sodium. Two subjects had abnormal sodium values prior to study initiation. One patient developed an abnormal RBC value during treatment or in the last sample during treatment.

Individual laboratory values for the 5 mg and 10 mg groups of R 65824 are shown in Table 136and Table 137.

Table 136. Individual Laboratory Values: 5 mg R 65824

		No.1		No.2		No.3		No.4		No.5		No.6		No.7		No.8	
LABORATORY TEST	RANGE, UNIT	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY
1. HEMATOLOGY																	
HEMOGLOBIN	13.5–18 G/DL	15.2	15.2	14.6	14.8	15.8	15.4	15.7	15.9	13.5	13.4	12.3	12.5	15.7	15.6	16.2	16
RBC	4.5–5.6 1E6/MM3	5.3	5.3	4.6	4.1 B	5.1 A	5.3 AA	5.5	5.6	4.3	4.3	4.2	4.3	5.4	5.2	5.2	5.6
HEMATOCRIT	40–54 VOL-%	47	48	41	42	45	45	45	46	41	42	39	37	47	47	47	45
WBC	4–10 1E3/MM3	6.7	6.7	6.7	6.8	6.8	6.7	6.4	6.6	7.7	7.6	7.5	6.9	6.4	6.6	6.2	5.6
MONSEGM NEUTROPHILS	0–7 %	0	0	0	2	0	2	0	2	3	4	2	2	0	1	0	0
SEGM NEUTROPHILS	40–70 %	71 A	69	60	41	72 A	71 A	41	42	47	50	69	69	68	65	60	53
LYMPHOCYTES	20–40 %	22	24	35	54 A	24	23	51 A	49 A	47 A	39	24	23	23	25	37	40
MONOCYTES	0–8 %	3	2	2	0	2	3	5	5	2	4	2	3	4	5	2	3
EOSINOPHILS	0–4 %	3	4	2	3	2	1	2	3	0	2	3	3	4	2	1	2
BASOPHILS	0–2 %	1	1	1	0	0	0	1	1	1	1	0	0	3 A	2	0	2
PLATELET COUNT	150–400 1E3/MM3	270	222	260	256	198	197	232	238	197	195	192	197	220	225	250	258
7. BIOCHEMISTRY																	
CALCIUM	9–10.6 MG/DL	9.6	10.3	10.3	10.5	9.9	9.8	10.2	10	10.1	10.3	9.8	9.6	10.5	10	9.6	9.9
CHLORIDE	100–108 MEQ/L	105	100	111 A	106	111 A	104	110 A	109 A	107	108	109 A	109 A	108	104	106	104
PHOSPHORUS	2.2–4.2 MG/DL	3.2	3.3	3.4	5.2 A	3.5	3.4	2.8	3.2	4.4 A	4	3.5	3.6	3.4	3.3	3.1	4.1
POTASSIUM	3.6–4.9 MEQ/L	4	4.2	4.7	5 A	4.6	4.4	4.4	4.3	4.3	4.3	4.5	4.6	4.9	4.8	4.5	4.7
SODIUM	137–141 MEQ/L	143	142	152 AA	146	152 AA	146	151 A	148	147	147	151 A	147	142	142	146	145
TOTAL PROTEIN	6.5–8.1 G/DL	7.6	7.7	7.6	8.1	6.9	6.7	7.8	7.6	7.9	7.7	7.4	7.6	7.6	7.3	6.7	7.1
ALBUMIN	4.1–5.2 G/DL	5.3 A	5.2	5.1	5.3 A	4.9	4.8	4.9	4.9	5.1	5.2	4.9	4.8	4.5	4.9	4.3	4.7
HAPTOGLOBIN	6–130 MG/DL	186	220	214	217	132	131	237	241	173	169	106	108	247	318	104	105
GLUCOSE	54–118 MG/DL	81	82	82	87	89	91	98	86	97	92	64	101	82	92	122 A	102
CHOLESTEROL, TOTAL	124–302 MG/DL	164	171	231	245	214	204	194	203	169	148	180	170	270	239	218	221
TRIGLYCERIDES	0–700 MG/DL	89	64	142	176	122	63	95	81	70	33	100	66	94	82	118	178
PHOSPHOLIPIDS	160–300 MG/DL	207	201	242	257	251	222	230	210	209	185	227	216	246	237	228	232
BILIRUBIN, TOTAL	0.2–1.3 MG/DL	1.28 A	1.19	0.33	0.51	0.48	0.43	0.41	0.32	0.4	0.3	0.28	0.26	0.36	0.36	0.35	0.58
ALKALINE PHOSPHATASE	35–129 U/L	101	95	59	63	63	58	100	104	47	47	44	41	81	78	85	87
SGOT	3–44 U/L	21	21	35	39	20	21	29	29	19	19	15	16	13	32	32	32
LDH	0–250 U/L	248	261 A	260 A	273 A	176	172	254 A	229	213	200	244	276 A	427 A	265 A	244	253 A
AGAT	3–19 U/L	24	22	17	20	14	14	20	19	20	18	19	17	22	18	16	16
ALAT	1–55 U/L	11	25	16	19	12	11	14	13	13	11	16	12	17	13	12	12
CHOLINESTERASE	4.6–14.5 U/L	9.6	9.4	10.6	11.7	10.2	9.9	6.2	6	8.5	8.4	6.5	6.3	8	7.6	10.4	10.8
BLOOD UREA NITROGEN	4.5–18 MG/DL	20 A	15	14	15	19 A	16	12	10	12	15	8	9	19 A	11	12	12
CREATININE	0.6–1.4 MG/DL	0.85	0.81	1.02	1.04	1.15	1	1	0.9	0.81	0.77	0.83	0.85	0.91	0.97	1.08	1.02
URIC ACID	3.5–7 MG/DL		4.7	5.6	5.6	5	4.5	7.2 A	5.9	4.4	4.2	2.3	3.2		5.2	5.7	5.3

(Reproduced from Sponsor, Table 7, page 11)

Table 137. Individual Laboratory Values: 10 mg R 65824

		No. 1		No. 2		No. 3		No. 4		No. 5		No. 6		No. 7		No. 8	
LABORATORY TEST	RANGE, UNIT	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY	PRE	ENDSTUDY
1. HEMATOLOGY																	
HEMOGLOBIN	13.5-18 G/DL	15.3	15.4	14.7	13.9	15.7	14.9	15.8	15.7	13.5	13.7	12.3	12.4	15.6	15.3	16.4	16.6
RBC	4.5-5.6 1E6/MM3	5.1	5.3	4.7	4.8	5.2	5.2	5.4	5.2	4.2	4.4	4.1	4.1	5.3	5.2	5.3	5.4
HEMATOCRIT	40-54 VOL-%	48	47	43	41	47	46	46	46	42	41	38	38	46	46	48	48
WBC	4-10 1E3/MM3	6.8	6.4	6.1	6.3	6.3	6.4	6.3	6.5	7.2	7.7	8.1	8.4	8.8	8.7	4.8	5.2
NONSEGM NEUTROPHILS	0-7 %	0	0	0	3	0	2	0	2	4	5	2	2	0	1	0	0
SEGM NEUTROPHILS	40-70 %	70	69	61	40	74 A	70	43	43	46	51	71 A	67	64	63	56	58
LYMPHOCYTES	20-40 %	23	24	34	54 A	22	22	49 A	48 A	47 A	38	22	25	25	27	38	35
MONOCYTES	0-8 %	4	3	3	1	3	4	6	4	2	5	3	4	5	6	3	2
EOSINOPHILS	0-4 %	2	3	2	2	1	0	1	2	0	1	2	2	4	3	3	3
BASOPHILS	0-2 %	1	1	0	0	0	0	1	1	1	0	0	0	2	1	0	2
PLATELET COUNT	150-400 1E3/MM3	230	220	250	250	192	194	227	228	195	192	280	285	213	225	260	282
2. BIOCHEMISTRY																	
CALCIUM	9-10.5 MG/DL	10.1	9.4	10.5	10.2	10	10	9.9	10.5	10.2	10	9.5	9.4	10	10.1	9.8	9.9
CHLORIDE	100-108 MEQ/L	102	98 B	106	107	109 A	109 A	107	109 A	106	106	110 A	110 A	101	105	105	103
PHOSPHORUS	2.2-4.2 MG/DL	2.5	3.5	3.2	4.9 A	3.2	3.5	3.3	3.3	4.2	4.1	3	3.6	3.6	3.5	3.7	3.9
POTASSIUM	3.6-4.9 MEQ/L	3.9	4.6	4.4	4.6	4.3	4.8	4.5	4.6	4.5	4.4	4.4	4.2	4.5	4.8	4.8	4.7
SODIUM	137-148 MEQ/L	140	138	148	145	153 AA	151 A	148	148	146	146	144	148	139	148	142	144
TOTAL PROTEIN	6.5-8.1 G/DL	7.8	7.2	7.8	7.6	6.7	7.1	7.8	8.2 A	7.8	7.8	6.5	7.3	7.1	7.6	7.1	7
ALBUMIN	4.1-5.2 G/DL	6.6 A	5	5.2	5	4.8	5	5	5.2	5	5.2	4.3	4.6	5.1	5.2	4.4	4.3
HAPTOGLOBIN	6-330 MG/DL	214	205	191	194	137	115	238	250	181	183	61	80	287	317	112	110
GLUCOSE	54-118 MG/DL	71	98	75	93	103	100	100	100	108	88	64	94	88	97	112	102
CHOLESTEROL, TOTAL	124-302 MG/DL	207	188	231	229	212	217	185	189	159	169	177	169	255	236	242	236
TRIGLYCERIDES	0-200 MG/DL	91	58	138	141	71	55	111	123	78	46	83	61	150	89	157	152
PHOSPHOLIPIDS	160-300 MG/DL	245	213	276	256	234	222	219	228	221	223	202	210	251	232	260	259
BILIRUBIN, TOTAL	0.2-1.2 MG/DL	1.9 AA	1.58 AA	0.34	0.25	0.48	0.41	0.34	0.3	0.55	0.36	0.22	0.22	0.26	0.32	0.51	0.49
ALKALINE PHOSPHATASE	35-129 U/L	104	81	58	58	59	58	106	110	47	49	44	41	95	77	103	100
SGOT	1-44 U/L	23	20	35	32	20	20	27	27	20	20	16	15	32	30	37	35
LDH	0-250 U/L	284 A	200	301 A	236	199	218	221	225	200	188	305 A	287 A	304 A	243	260 A	255 A
ASAT	1-39 U/L	21	19	18	17	15	17	18	21	17	18	21	16	20	17	19	19
ALAT	1-55 U/L	34	23	16	14	16	10	13	14	10	10	18	14	19	11	20	21
CHOLINESTERASE	4.6-14.5 U/L	9.6	9.3	11.4	11.1	9.8	9.8	6	6.2	8.9	9.1	6.2	6.1	7.8	7.8	11.2	11
BLOOD UREA NITROGEN	4.6-18 MG/DL	27 AA	21 A	11	9	14	15	13	9	8	10	17	13	14	13	14	14
CREATININE	0.6-1.4 MG/DL	0.7	0.79	1.01	0.93	1.05	1.04	1.01	0.9	0.77	0.71	0.88	0.87	1	0.99	0.98	1
URIC ACID	3.5-7 MG/DL	4.2	4.5	5.5	5.2	5.4	5.6	6.9	6.2	4.2	4.2	2.5	2	5.1	5.1	6.4	5.3

(Reproduced from Sponsor, Table 8, page 12)

Appears This Way
On Original

Conclusions: Single doses of R 65824 5 mg or 10 mg did not significantly affect hematological or biochemical parameters.

1.70 (Corresponds to Study #73 in Table 1) LMD No. 84315. Study ID: USA-3, ("Double-Blind, Placebo-Controlled Study of Nebivolol 30 mg in Hypertensive Patients. Clinical Research Report NEB-USA-3. February 1991") (Reviewer: Katharine R. Lillie, M.D.)

Summary:
This is a review of study JRD 67,555/0104 (NEB USA-3), an evaluation of the safety and tolerability of a 30 mg dose of nebivolol versus placebo in 12 subjects with mild to moderate hypertension. No protocol was provided. Following a 2-week washout period, the duration of the study was 2 weeks. There were no deaths, dropouts, or serious adverse effects. The drug was well tolerated. The sponsor provided mean QT and QTc values and did not indicate when ECGs were done, whether at drug peak or at trough. Values for individual patients and gender were not provided, nor did the sponsor provide information on how the QTc interval was calculated, so no conclusions can be drawn regarding effects on QT or potential gender differences for this study. No conclusion can be drawn whether the drug is safe.

10 APPENDIX

10.1 JRD 67,555/0104

10.1.1 Name of Study
JRD 67,555/0104 (NEB USA-3) Double-blind, placebo-controlled study of nebivolol 30 mg in hypertensive patients., performed by Janssen Research Products.

10.1.1.1 Investigator
Walter Flamenbaum, MD
661 Palisade Avenue
Englewood Cliffs, NY 07632

10.1.2 Basis of Review
The description of the study is based on the summary Clinical Research Report from Janssen Research Products dated February 1991. The protocol for the study was not included in the NDA submission.

10.1.3 Objectives
The purpose of the study was to evaluate the safety and tolerability of nebivolol 30 mg in hypertensive patients. According to the sponsor, from discussions with the FDA, a dose of 30 mg was thought to be appropriate.

10.1.4 Population

Subjects were to be:

- 18 to 70 years old with
- Have mild to moderate hypertension (95 mmHg </= DBP </= 114 mmHg), previously treated or untreated,
- Sign informed consent.

Disallowed medication included other antihypertensives and medication that may affect blood pressure, if used regularly.

Exclusion criteria included:

- Secondary or malignant hypertension.
- Bradycardia (< 55 beats/minute at rest).
- Atrial fibrillation or recurrent tachyarrhythmia requiring antiarrhythmic therapy.
- Sick sinus syndrome or AV block greater than first degree.
- Myocardial infarction or cerebrovascular accident within 6 months of study initiation.
- Heart failure requiring treatment.
- Valvular disease of hemodynamic significance.
- Patients with asthma or chronic obstructive airway disease.
- Patients with insulin-dependent diabetes mellitus or significant renal or hepatic disease (significant renal disease: urine protein > 1+, creatinine > 2.2 mg/dl or >200 micromole/l; significant hepatic disease: AST and/or ALT greater than twice the upper limit of normal).
- Pregnant or nursing women or women of childbearing potential.
- Patients who were 50% over ideal weight range (based on Metropolitan Life Insurance Company's 1983 Height and Weight Table).
- History of sensitivity or significant adverse reaction to beta-blockers.
- Concomitant therapy with medications that may affect blood pressure (e.g., antidepressants, salt-retaining medications).
- Any concomitant condition that could jeopardize adherence to the protocol or ability to complete the trial (e.g., alcohol or drug abuse, disabling or terminal illness, personality or mental disorders).
- Receipt of an investigational drug within 30 days of study initiation.

Patients with concurrent diseases other than those listed above as exclusions could be included in the study at the discretion of the investigator. Type of disease was recorded on the case record form.

10.1.5 Procedures

A total of 15 subjects were screened, and 12 subjects were randomized 2:1 to either nebivolol or placebo. Study drug was initiated after a 2-week wash-out period. Study drug was initiated at 30 mg orally daily with breakfast for 2 weeks.

10.2 Results

10.2.1 Enrollment

The study was initiated November 17, 1989 and completed December 1, 1989.

There was one principal investigator and four sub-investigators. Presumably there was one study site. The number of individual centers is not specified in the report.

Baseline characteristics: Twelve subjects (8 males, 4 females) with mild to moderate hypertension entered the study with no dropouts. Median age, race, and median blood pressures at baseline/end of comparison period are presented below (from page 3 of the Clinical Summary report):

Table 138. Main Features of the Trial Sample and Summary of the Results (USA-3)

Baseline comparability - patient disposition	nebivolol	placebo
Number of patients randomized (M/F)	8 (5/3)	4 (3/1)
Age: median (min-max), yrs	57.5 (21-61)	53.5 (46-56)
Race: white/black, n	7/1	2/2
No. of drop-outs	0	0

Clinical findings			nebivolol (n = 8)	placebo (n = 4)
Mean blood pressures at baseline/end of comparison period, mmHg (shift)				
• DBP,	trough,	supine	105.7/90.9 (-14.8) ***	107.5/106.2 (-1.3)
		standing	106.3/100.3 (-6.0)	106.5/107.0 (+0.5)
	peak,	supine	97.3/86.2 (-11.2) **	98.5/102.0 (+3.5)
		standing	100.8/91.8 (-9.0) ◊	104.5/104.5 (+0.0)
• SBP,	trough,	supine	160.7/142.2 (-18.5) *	155.2/152.3 (-2.8)
		standing	158.0/137.8 (-20.3)	154.5/154.5 (+0.0)
	peak,	supine	150.7/133.5 (-17.2) **	140.3/148.2 (+7.8)
		standing	147.8/134.8 (-13.0) ◊	145.0/148.0 (+3.0)

Asterisks refer to differences with placebo.
Levels of significance: ◊ $p \leq 0.1$; * $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$

(Reproduced from Sponsor, USA-3, page 3)

As seen above, there is a decrease in mean blood pressures at trough and peak, both supine and standing, in subjects receiving nebivolol 30 mg.

Heart rates, ECG values, adverse event, and other parameters are presented below in Table 139 (from page 4 of the Clinical Summary report).

Table 139. Clinical Findings (USA-3)

Clinical findings			nebivolol (n = 8)	placebo (n = 4)
Symptom questionnaire			few symptoms present at start and hardly any changes after treatment	
Mean heart rates at baseline/end of comparison period, bpm (shift)				
• HR,	trough,	supine	69.3/63.5 (-5.8)	74.0/80.0 (+6.0)
		standing	74.0/65.0 (-9.0) *	76.5/80.5 (+4.0)
	peak,	supine	68.5/61.0 (-7.5) ◊	79.0/81.0 (+2.0)
		standing	80.5/61.5 (-19.0) *	85.0/84.0 (-1.0)
Mean ECG values at baseline/end of comparison period				
• HR, bpm			64.9/55.6 (-9.3) ***	70.3/78.3 (+8.0)
• QT, ms			403.0/434.5 (+31.5) **	401.0/386.0 (-15.0)
• QTc, ms			413.5/410.6 (-2.9)	425.0/432.3 (+7.3)
• PR, ms			178.0/178.0 (+0.0)	167.0/165.0 (-2.0)
• QRS, ms			94.5/93.5 (-1.0)	86.0/93.0 (+7.0)
Mean body weight at baseline/end of comparison period, lbs (shift)			208.7/208.2 (-0.5)	206.6/206.9 (+0.3)
Adverse events (AE), n				
• headache			1	3
• paresis			1	
• abdominal pain			1	
• pharyngitis			1	
• back pain			1	
• arthritis aggravated				1
• vomiting				1
• heart disorder				1
• palpitation				1
Total No. of patients with AE (%)			4 (50%)	3 (75%)
No. of patients who permanently stopped due to AE			0	0
Haematology, blood chemistry, urinalysis			no clinically relevant changes	
Chest X-ray			no clinically relevant changes	

Asterisks refer to differences with placebo.
Levels of significance: ◊ $p \leq 0.1$; * $p \leq 0.05$; **$p \leq 0.01$, ***$p \leq 0.001$

(Reproduced from Sponsor, USA-3, page 3)

Mean heart rate decreased and mean QT interval increased in subjects receiving nebivolol. The mean QTc interval at baseline (413.5) was not significantly changed at the end of the comparison period (410.6) for the patients receiving nebivolol. However, the sponsor does not indicate which correction method was used. This reviewer calculated mean QTc's using Bazett's (baseline 419; end of comparison 418) and Fridericia (baseline 414; end of comparison 424) that were different from the results presented by the sponsor. The sponsor did not present individual subject QT data or the

ranges for the QT or QTc data. Individual values by gender were not presented. The summary report does not indicate whether the ECGs were done at peak or at trough.

10.2.2 Conduct

10.2.2.1 Interim analyses

There were no interim analyses.

10.2.2.2 Protocol violations

Patients #0403, #0406, and #0409 had visits on dates that were earlier or later than the date specified in the protocol. Patients #0403 and #0407 were not enrolled in date order. Trough blood pressures for patients #0404 and #0411 were measured before the 23- to 25-hour range.

GGT was to be done as part of the biochemistry panel per protocol. It was not analyzed because routine panels at [redacted] do not include it, and the investigator forgot to request it.

10.2.2.3 Dosing

All subjects received three tablets of nebivolol 10 mg or matching placebo daily for 2 weeks.

10.2.3 Endpoints

No primary or secondary endpoints were specified.

10.2.3.1 Safety and Tolerability

The analysis was based on an intent-to-treat approach (using all patients randomized). A significant p-value was less than 0.05, and the sponsor defined a marginally significant p-value as between 0.05 and 0.10. Two-sided p-values were used for all analyses.

For within-group comparisons, paired t-tests were used to compare each time point to baseline for each parameter.

For between-group comparisons, two-sample t-tests were used to compare the treatment groups for each parameter at each visit. Analyses at baseline used baseline values; analyses at other visits used differences from baseline.

10.2.3.2 Unplanned analysis

10.2.3.2.1 Concomitant diseases

None reported.

10.2.3.2.2 Concomitant and previous medications

All 12 patients used prior hypertensive medication, which was discontinued before the double-blind phase. Tylenol (three patients from each group) was the most common concurrent medication.

10.3 Summary and Conclusions

10.3.1 Population in Context

10.3.1.1 Intent

The population studied was to have mild to moderate hypertension and a baseline diastolic pressure of >/= 95 or </= 114 at the end of the washout period.

10.3.1.2 Comparison on the basis of data collected

10.3.1.2.1 Concomitant medications

Subjects off all other antihypertensives.

10.3.2 Summary

1. This is an evaluation of the safety and tolerability of a 30 mg dose of nebivolol versus placebo in 12 subjects with mild to moderate hypertension. No protocol was provided.
2. Following a 2-week washout period, the duration of the study was 2 weeks. There were no deaths, dropouts, or serious adverse effects. There were some protocol violations that did not seriously compromise the trial.
3. The nebivolol 30 mg dose was well tolerated.
4. The sponsor provided mean QT values and did not indicate when ECGs were done, whether at drug peak or at trough.
5. Values for individual patients and values by gender were not provided
6. The sponsor did not provide information on how the QTc interval was calculated, so no conclusions can be drawn regarding effects on QT or potential gender differences for this study.
7. No conclusion can be drawn whether the drug is safe.

10.3.3 Conclusions

In this small 2-week study, the study drug appeared to be well tolerated.

1.71 (Corresponds to Study #76 in Table 1) LMD No. 101044. Study ID: BEL-3/6. ("Double-Blind, Placebo-Controlled, Multicentre Trial with Oral nebivolol 2.5, 5 and 10 mg Once Daily in Essential Hypertension, Followed by an Open Nebivolol 5 mg Treatment for Up to 4 Years. Clinical Research Report NEB-BEL-3/6. November 1993.") (Reviewer: Katharine R. Lillie, M.D.)

Summary:

This is a review of the Janssen Research Foundation study N 101044/1 (NEB-BEL-3/6), in which the antihypertensive effects of oral solution nebivolol at doses of 2.5, 5 and 10 mg once daily vs. placebo were studied in 134 adult patients with essential hypertension. There were four parallel groups, 2-4 weeks placebo run-in followed by 4 weeks double-blind treatment. After the double-blind part of the trial, 81 patients continued on open-label nebivolol 5 mg for up to 4 years. According to the summary, this study was one of the first therapeutic trials with the compound.

No protocol was included in the NDA submission. No ECGs were submitted for this study.

For the double-blind portion, patients received 10 ml once daily of an oral solution of either placebo or nebivolol. For the open-label portion, patients received either nebivolol 0.5 mg/ml solution or 5 mg tablets. Based on the brief information given in the submission, this reviewer is unable to determine whether the solution is the same formulation as the tablet and whether the solution and tablet are equivalent in bioavailability. (This was discussed with chemist Dr. Ram Mittal.) Therefore, no conclusion can be made whether this study supports the safety and efficacy of the nebivolol formulation in the NDA submission.

The primary efficacy parameter was the shift from baseline for trough diastolic blood pressure (DBP) in sitting position vs. placebo and to investigate the dose-response relationship.

Response to treatment was defined as a decrease in sitting trough DBP to 90 mmHg or below or a decrease of at least 10 mmHg versus baseline, absolute DBP values still being above 90 mmHg. All results in the summary provided in the NDA are presented as means and percentages.

During the double-blind treatment, all doses including placebo met the definition for responder. The shifts from baseline in DBP were not significant at endpoint. The shift from baseline to endpoint was -11.3 (placebo), -15.7 (nebivolol 2.5), -16.1 (nebivolol 5), and -15.7 (nebivolol 10). At the endpoint, the response rate for nebivolol was higher than for placebo, but the difference was not statistically significant for any dose.

For systolic blood pressure (which was a secondary endpoint), the shift from baseline to endpoint was -14.5 (placebo), -24.5 (nebivolol 2.5), -22.5 (nebivolol 5), and -22.5 (nebivolol 10).

Increasing effect with dose was not statistically significant, although dose dependent increments in blood pressure reduction were demonstrated with this dose range in this study.

During the open-label portion (up to 48 months), the blood pressure lowering effect of the nebivolol was maintained. No information was given as to who was on solution and who was on tablet.

There was an inconsistent dose-related effect on heart rate. At the end of the double-blind treatment, heart rate was significantly lower with nebivolol 2.5 (74.6 bpm) and nebivolol 10 (67.6 bpm) compared to placebo (77.2 bpm). For nebivolol 5, heart rate was not significantly lower (75.5) compared to placebo.