Nervous system disorders

Somnolence in 9 (0.4%); postural dizziness in 8 (0.3%); hypoesthesia in 7 (0.3%); sleep apnea syndrome in 2; scotoma in 1, syncope in 1; amnesia in 1;

Gastrointestinal disorders

Constipation in 20 (0.8%); abdominal pain NOS and upper abdominal pain in 11 (0.5%) each; vomiting and flatulence in 10 (0.4%) each; gastroesophageal reflux disease in 7; aggravated esophageal reflux in 6 (0.2%); abdominal distension in 6; hemorrhoids in 5, rectal hemorrhage in 4 and anal hemorrhage in 1; irritable bowel syndrome in 2; diverticulitis in 2; intestinal functional disorder and irritable bowel syndrome aggravated in 1 each; ischemic colitis in.1; gastric ulcer in 1;

General disorders

Influenza-like illness in 11 (0.5%); pain NOS in 11; malaise in 9 (0.4%); weakness in 8 (0.3%); edema in 16 (edema NOS in 7 + edema aggravated in 5 + pitting edema in 4); chest pressure sensation, chest tightness and chest discomfort in 4 and 3 and 2 respectively; pyrexia in 4; sluggishness in 2; lethargy in 1;

Investigations

LDL increased in 15 (0.6%); hematocrit decreased in 8 (0.3%); protein in urine present in 6 (0.2%); RDW increased in 4 (0.2%); Blood potassium increased in 3; blood bilirubin increased in 3; blood urea increased in 3; eosinophil count increased in 3; red blood cells in urine in 3; WCC increased in 3; ECG P wave abnormal in 2; potassium decreased in 2; ECG ST-T change NOS in 2; transaminase increase in 2; urinary occult blood positive in 2; WCC decreased in 2; ECG ST segment abnormal in 1; ECG PR shortened in 1; cardiovascular Function Test abnormal in 1; ECG Q wave in 1; ECG ST segment depression in 1; neutrophil count decreased in 1; red blood cell count decreased in 1;

Musculoskeletal and connective tissue disorders

Pain in limb in 22 (0.9%); neck pain in 15 (0.6%); Muscle cramps in 12 (0.5%), myalgia in 10 (0.4), fibromyalgia in 2 (0.08%); muscle fatigue NOS in 2; myositis in 1; polymyalgia in 1;

Respiratory disorders

Pharyngolaryngeal pain in 21 (0.9%); sinus congestion and nasal congestion in 0.7% each; epistaxis in 10 (0.4%); allergic rhinitis in 3 (0.4%); pulmonary congestion in 5 (0.2%); wheezing in 4 (0.2%); seasonal rhinitis in 3 (0.1%); chronic obstructive airway disease exacerbated in 1; asthma aggravated in 1; emphysema in 1; lung infiltration in 1;

Injury, poisoning and procedural complications

Road traffic accident in 2;

Skin and subcutaneous tissue disorders

Rash in 22 (0.9%); contusions in 11 (0.5%); pruritus in 8 + pruritic rash in 2 + generalized pruritus in 1; contact dermatitis in 8 (0.3%); angioedema in 5 (face edema in 3 + angioneurotic edema in 1 + tongue edema in 1); urticaria NOS in 3 (0.1%); alopecia in 1; exacerbated eczema in 1 + seborrheic eczema in 1; intertrigo in 1 + skin depigmentation in 1 + skin discoloration in 1;

Cardiac disorders

Sinus bradycardia in 18 (0.7%); first degree atrioventricular block in 4 (0.2%); angina pectoris in 3 (0.1%); ventricular extrasystoles in 3; tachycardia NOS in 2; CHF in 2; MI in 3; sinus arrhythmia in 2; supraventricular extrasystoles in 2; supraventricular tachycardia in 2; unstable angina in 2; left ventricular hypertrophy in 2; myocardial ischemia in 2; left bundle branch block in 1; atrial fibrillation in 1; extrasystole NOS in 1; supraventricular arrhythmia in 1; withdrawal arrhythmia in 1;

Psychiatric disorders

Depression in 14 (0.6%); anxiety in 10 (0.4%); libido decreased in 4 (0.2%); insomnia exacerbated in 4; disorientation in 3; confusion in 3; depression aggravated in 3; anxiety aggravated in 2; listless and nightmares in 1 each; irritability and nervousness in 1 each; short-term memory loss in 1;

Metabolism and nutrition

DM aggravated in 9 (0.4%); gout and gout aggravated in 5 (0.2%) each; dehydration in 4 (0.2%); appetite decreased in 3 (0.1%); DM NOS in 3; hyperkalemia in 2; non-insulin dependent DM in 2; hyperuricemia in 2; anorexia in 1; glucose tolerance impaired in 1; hyperhomocysteinemia in 1; hypokalemia in 1; metabolic syndrome in 1 and xanthelasma in 1;

Eye disorders

Blurred vision in 13 (0.5%); eye pain in 5 (0.2%); visual disturbances in 3 NOS; conjunctivitis in 3; diplopia in 1; vision abnormal NOS in 1; visual acuity reduced in 1; diplopia in 1; cataract in 2; acquired dacryostenosis in 1; glaucoma in 1; mydriasis in 1;

Renal and urinary disorders

Urinary frequency in 8 (0.3%); renal/ureteric calculus in 8 (0.3%); hematuria in 7; proteinuria in 5 (0.2%); dysuria in 1; difficulty in micturition in 1; micturition urgency in 1; urinary incontinence in 1; urinary retention in 1;

Reproductive system and breast disorders

Erectile dysfunction in 10 (0.4%); dysmenorrheal in 5 (0.2%); prostatitis in 4 (0.2%); breast cyst in 2; sexual dysfunction NOS in 1; amenorrhea in 1; breast mass NOS in 1; breast pain and breast tenderness in 1 each; dysfunctional uterine bleeding in 1; galactorrhea in 1; menopausal symptoms in 1; menorrhagia in 1; nipple pain in 1; post-menopausal bleeding in 1; vaginal discharge in 1;

Vascular disorders

Flushing in 9 (0.4%); hot flushes in 7 (0.3%); orthostatic hypotension in 5 (0.2%); hypotension NOS in 2; hematoma in 2; peripheral coldness in 1; hot flushes aggravated in 1; DVT in 2;

Ear and labyrinth disorders

Ear pain in 9 (0.4%); vertigo in 8 (0.3%); cerrumen impaction in 2; deafness NOS in 2; motion sickness in 2; tinnitus in 2; neurosensory deafness in 1; hearing impaired in 1; positional vertigo in 1;

Immune system disorders

Seasonal allergy in 13 (0.5%); hypersensitivity in 6 (0.2%); allergy aggravated in 3; drug hypersensitivity in 1;

Neoplasms

Breast lump in 4 (0.2%); lipoma in 3; solar keratosis in 3; colon cancer in 2; bladder cancer, breast cancer, lung squamous cell carcinoma, small cell lung cancer, throat cancer, peripheral nervous system neoplasm NOS, and skin papilloma in 1 each;

Blood and lymphatic system disorders

Anemia in 3; anemia aggravated in 3; eosinophilia in 2; leucopenia in 1; WBC disorder NOS in 1;

Endocrine disorders

Goiter in 3; hypothyroidism in 3; hyperparathyroidism in 1;

Hepatobiliary disorders

Hepatic disorders in 2; hyperbilirubinemia in 1; cholecystitis NOS in 1;

5.3.1.4.3 Adverse Event profile of study population subgroups in the PP

Table 27. Comparison of adverse events by metabolizing status

Adverse events	Metabolic Profile	
	PM N = 144 n (%)	EM N = 2310 n (%)
Infections any	30(20.1)	371(16.1)
Nasopharyngitis	9(6.3)	82(3.6)
Upper respiratory tract infection	6(4.2)	64(2.8)
Dyspepsia	4(2.9)	25(1.1)
Neoplasms	3(2.1)	17(0.7)
CRP↗	3(2.1)	29(1.3)
Viral infections	3(2.1)	12(0.5)
Ear and labyrinth	1(0.7)	26(1.1)
Reproductive	00	35(1.5)
Rash	00	22(1.0)
Calculus renal NOS	00	7(0.03)
Breast lumps	00	4

Table 28. Comparison of adverse events by age

Adverse events	Age		Adverse events	Age	
	< 65 N = 2028 n (%)	≥ 65 N = 436 n (%)		< 65	≥ 65
Fatigue	84(4.1)	27(6.2)	hemoglobin↘	6	00
Sinusitis	43(2.1)	6(1.4)	Protein in urine	6	00
Blood triglyceride ↗	31(1.5)	2(0.5)	platelet count↘	7	00

Adverse events	Age		Adverse events	Age	
	< 65 N = 2028 n (%)	≥ 65 N = 436 n (%)		< 65	≥ 65
Insomnia	30 (1.5)	1 (0.2)	T-wave abnormality	6	00
C-reactive protein↗	29(1.4)	3(0.7)	Arthritis aggravated	5	00
Pharyngolaryngeal pain	21(1.0)	00	Eye pain	5	00
cholesterol ↗	22(1.1)	3(0.7)	Epistaxis	5(0.3)	5(1.2)
Chest pain	20(1.0)	00	Angioedema	4	00
glucose ↗	19	00	Breast lumps	4	00
Rash	16(0.8)	6(1.4)	Chest pressure	4	00
Uric acid	15(0.7)	2(0.5)	Hepatobiliary disorders	4	00
Dizziness	15(0.7)	00	Insomnia exacerbated	4	00
Nasal congestion	15(0.7)	1(0.2)	Muscle spasm	4	00
Bradycardia	14(0.7)	10(2.3)	Orthostatic hypotension	4	00
Dyspnea	14(0.7)	11(2.5)	Prostatitis	4	00
LDL cholesterol	14(0.7)	1(0.2)	QT prolongation	4	00
ALT↗	13	00	Anemia	3	00
Palpitations	13	00	Anemia aggravated	3	00
AST↗	12	00	Depression aggravated	3	00
Vision blurred	12(0.6)	1(0.2)	Eosinophil count ↗	3	00
Muscle cramps	11(0.5)	1(0.2)	Lipoma NOS	3	00
Pain NOS	10(0.5)	1(0.2)	T-wave inversion	3	00
Hypertriglyceridemia	9 (0.4)	00	Urticaria	3	00
Gout/gout aggravated	9	1	Visual disturbances	3	00
Migraine	9(0.4)	1(0.2)	Blood potassium ↘	2	00
Hematocrit ↘	8	00	hyperuricemia	2	00
Pruritus	8	00	Left ventricle hypertrophy	2	00
Allergic rhinitis	8(0.4)	1(0.2)	MI	2	00
DM aggravated	8(0.4)	1(0.2)	Transaminase ↗	2	00
Dry mouth	8(0.4)	5(1.2)	Postural dizziness	0	5(1.2)

Table 29. Comparison of adverse events by gender

Adverse events	Gender		Adverse events	Gender	
	M N = 1345 n (%)	F N = 1119 n (%)		M	F
Headache	79(5.9)	110(9.8)	Gout/gout aggravated	8(0.6)	2(0.2)
triglyceride ↗	25(1.9)	8(0.7)	Pharyngitis	7(0.5)	9(0.8)
Nausea	23(1.7)	28(2.5)	DM aggravated	6(0.5)	3(0.3)

Adverse events	Gender		Adverse events	Gender	
	M N = 1345 n (%)	F N = 1119 n (%)		M	F
Dyspnea	16(1.2)	9(0.8)	Hematuria	6(0.5)	1(0.09)
Glucose ↗	15(1.1)	4(0.4)	Platelet count ↘	6(0.5)	1(0.09)
Bradycardia	15(1.1)	9(0.8)	Sweating ↗	6(0.5)	2(0.2)
Bronchitis NOS	15(1.2)	22(2.0)	Dry mouth	5(0.4)	8(0.7)
Insomnia	14(1.0)	17(1.5)	Gastroenteritis viral NOS	5(0.4)	9(0.8)
Edema peripheral	11(0.8)	17(1.5)	Palpitation	5(0.4)	8(0.7)
UTI	11(0.8)	45(4.0)	Abdominal pain	4(0.3)	8(0.6)
ALT↗	10(0.7)	3(0.3)	Vomiting	3(0.2)	7(0.6)
AST↗	10(0.7)	2(0.2)	Edema	1(0.07)	6(0.5)
Chest pressure	10(0.7)	17(1.5)	Peripheral swelling	1(0.07)	8(0.6)
Hypertriglyceridemia	9(0.7)	00	Heart rate ↘	00	4 (0.4)
Dyspepsia	9(0.7)	20(1.8)	QT prolongation	00	4
Pain in limb	9(0.7)	13(1.2)			

Table 30. Comparison of adverse events by race

Adverse events	Race		Adverse events	Race	
	NB N = 1812 n (%)	B N = 652 n (%)		NB	B
Headache	121(6.7)	68(10.4)	ALT	12(0.7)	1(0.2)
Sinusitis	47(2.1)	2(0.9)	Seasonal allergies	11(0.6)	2(0.3)
Diarrhea	37(2.0)	20(3.1)	Muscle cramps	10(0.6)	2(0.3)
Bronchitis NOS	35(1.6)	2(0.9)	Anxiety	9(0.5)	1(0.2)
Triglyceride↗	31(1.7)	2(0.3)	Myalgia	9(0.5)	1(0.2)
C-reactive protein↗	29(1.6)	3(0.5)	Gout/gout aggravated	9(0.5)	1(0.2)
Cholesterol ↗	22(1.2)	3(0.5)	Hypertriglyceridemia	8(0.4)	1(0.2)
Dyspnea	22(1.2)	3(0.5)	Palpitation	8(0.4)	5(0.8)
Rash	19(1.1)	3(0.5)	Allergic rhinitis	4(0.2)	5(0.8)
Pharyngolaryng. pain	18(1.0)	3(0.5)	LFTs NOS abn	4 (0.2)	0
Glucose ↗	17(0.9)	2(0.3)	Blood urea ↗	3(0.2)	0
Sinus bradycardia	16(0.9)	2(0.3)	DM aggravated	3(0.2)	6(0.9)
hyperlipidemia	14(0.8)	2(0.3)	Peripheral swelling	3(0.2)	5(0.8)
LDL cholesterol ↗	14(0.8)	1(0.2)	Angioedema	2(0.1)	3(0.5)
Pharyngitis	14(0.8)	2(0.3)			

5.3.1.4.3.1 Conclusion

Poor metabolizers experienced nasopharyngitis, viral infections, upper respiratory tract infection, dyspepsia, neoplasm, and increase in C-reactive proteins, at higher rate compared to extensive metabolizers, but one should keep in mind that the numbers driving these results are very small.

Younger subjects experienced adverse events in excess compared to older ones. Eighty percent of the adverse events for which a difference by age was observed were experienced by younger subjects. Of interest are the following:

Chest pain (with all 20 cases), chest pressure (all 4 cases), T wave abnormalities (all 6), T wave inversion (all 3), QT prolongation (all 4), MI and left ventricular hypertrophy.

Hypertriglyceridemia (all 9 cases), increase in triglycerides (3 times as many), increase in C-reactive proteins (twice as many), increase in blood cholesterol and increase in LDL cholesterol (3 times as many);

Increase in ALT (all 13 cases), increase in AST (all 12 cases), increase in transaminase and hepatobiliary disorders;

Gout and gout aggravated, hyperuricemia and increase in uric acid;

Angioedema (all 5), urticaria (all 3) and pruritus (all 8);

Glucose increased (all 19) and diabetes mellitus aggravated;

Anemia (all 3) and anemia aggravated (all 3); decrease in hematocrit (all 8), hemoglobin (all 6), platelets (all 7); increase in eosinophil count; and Breast lumps and prostatitis;

Palpitation (all 13 cases), orthostatic hypotension, dizziness (all 15 cases), insomnia (7 times as many) and insomnia exacerbated, blurred vision (3 times as many), nasal congestion (3 times as many) and allergic rhinitis;

Others include pain, muscle cramps and muscle spasms, lipoma NOS and a decrease in blood potassium;

Older subjects experienced bradycardia dyspnea, dry mouth, rash, and postural dizziness more often than younger subjects.

Males accounted for all the hypertriglyceridemia (all 9), and for most of the increase in ALT and AST, the decrease in platelets and the hematuria, and the gouts and gouts aggravated (3 times as many). They experienced increases in triglycerides and blood glucose at almost 3 times the rate in females, and they exhibited an excess in dyspnea and increased sweating.

Females accounted for all QT prolongations observed, all the decrease in heart rate, most of the edema and peripheral swelling. They exhibited an excess in chest pressure, palpitations, headache, insomnia, nausea, vomiting, dyspepsia, urinary tract infections, bronchitis, viral gastroenteritis, abdominal pain, and pain in limb.

Non-black subjects accounted for all liver function abnormalities and for most of the increase in ALT, for two thirds of the increase in C-reactive protein, most of the hypertriglyceridemia, hyperlipidemia, increases in triglycerides, increase in total and LDL cholesterol, and increase in blood glucose. They also accounted for most of the sinus bradycardia, dyspnea, sinusitis, rash and bronchitis.

Black subject exhibited an excess in the aggravation of diabetes mellitus, in peripheral swelling, and face swelling.

5.3.1.4.4 General Adverse Events that occurred in the Active-control trial[8]

The numbers in this trial were too small for comparison of adverse events between the two treatment groups.

Thirteen adverse events were observed in this trial with 6 on NEB and 7 on atenolol. The events that were associated with NEB are micturition urgency, urinary frequency, erectile dysfunction, pharyngeal pain, allergic rhinitis NOS, and acne NOS. And the events that were seen on atenolol included disturbance in attention, dizziness, postural dizziness, 2 headaches, restlessness and one ovarian cyst.

5.3.1.4.5 Adverse Events in the Pharmacology Studies

The rate of adverse events in the pharmacology program was as follows: headache 19.1% (70), dizziness 7.9% (29), vomiting 4.6% (17), nausea 3.5% (17), fatigue 3.0% (11), diarrhea 0.8 (3), insomnia and chest pain each 1.4% (5), dyspepsia, nasal congestion, rhinitis and pharyngolaryngeal pain each 1.1% (4).

Headache and dizziness were observed at a rate that is at least 2.5 times, chest pain at a rate 1.5 times, nausea at a rate that is twice, and vomiting at a rate that is 4.5 times the rates observed in the placebo-controlled trials. Diarrhea on the other hand occurred at a rate that is about 1/3 that observed on NEB in the placebo trials.

5.3.1.4.6 Adverse Events Profile in Patients with Ischemic Heart Disease

One subject on NEB had an increase in liver enzymes.

One patient who received placebo developed jaw pain characterized as a SAE.

Three patients dropped out of the study. Two NEB cases dropped out for aggravated angina pectoris and dizziness, and one placebo dropped out for aggravated angina pectoris.

The number of subjects enrolled in this study was too small (133 on NEB and 34 on placebo) for meaningful interpretations of frequencies. Only headache and influenza-like symptoms were observed in more than one subject on NEB (3 each).

5.3.1.4.7 Conclusion on adverse events

Nebivolol was found to be associated with many beta-adrenergic blocking adverse events including, bradycardia, palpitations, dyspnea, sinus and nasal congestion, dry mouth, eye disorders including blurred vision, insomnia, depression or anxiety, dizziness, parasthesia, fatigue and first degree atrioventricular block.

Nebivolol was also associated with headache, peripheral edema, and infections including sinusitis, pharyngitis, bronchitis, influenza and viral infections.

C-reactive protein: An increase was observed on NEB with the highest relative risk on the highest dose.

[8] Analysis completed by the sponsor

Serum uric acid: an increase was observed in 11 NEB vs. no placebo subjects and in additional subjects who participated in the extension non-controlled trial.

Myocardial ischemia: Symptoms suggestive of myocardial ischemia including ECG abnormalities angina and chest pain were observed solely on NEB.

Angioedema observed in the controlled trial with 3 on NEB vs. none on placebo and 2 additional ones were observed in the long-term trial.

Reproductive and/or estrogen-related events were observed in excess on NEB in the controlled and in the long term trial including cycle abnormalities, post-menopausal uterine bleeding and DVT in this study population and should be considered potentially related to the study drug. These events assessed in the light of the preclinical leydig cell tumerogenesis and its potential estrogen-related mechanism raises the flag for these events;

The highest tested doses (20 to 40 mg) were significantly associated with bradycardia, dyspnea, insomnia, psychiatric disorders including depression, eye disorders including blurred vision, parasthesia, fatigue, dizziness, diarrhea and headache.

Twenty milligrams of NEB was significantly associated with bradycardia, insomnia, psychiatric disorders, general disorders including fatigue and viral gastroenteritis.

Neoplasms were observed in twice as many NEB as placebo subjects with 0.6% and 0.3% respectively.

Other adverse events included gout, aggravation of gout and hyperuricemia, deafness and impairment of hearing, sleep apnea, ischemic colitis, irritable bowel syndrome, decrease in hematocrit and hemoglobin, proteins in urine, fibromyalgia and myositis, pruritus, and increased sensitivity of the immune system to foreign bodies.

The following demographics interacted with the following events:

Poor metabolizing status and C-reactive protein;

Younger age: Liver function abnormalities; lipid profile worsening; symptoms suggestive of myocardial ischemia; increase in C-reactive protein; increase in uric acid and gout; increase in glucose and diabetes aggravated; anemia; insomnia; and peripheral beta-adrenergic blocking symptoms;

Older age: Bradycardia; and dyspnea;

Male gender: Liver abnormalities, lipid profile; gout; and dyspnea;

Female gender: QT prolongation; GI disorders; infections; palpitation; headache and insomnia;

Non-black race: Liver function profile; lipid profile; blood glucose; C-reactive protein; and dyspnea;

Black race: swelling of the face and aggravation of DM;

5.3.1.4.8 Interaction with concomitant substances

5.3.1.4.8.1 Interaction with Alcohol

Two cases of potential interaction with alcohol were encountered.

The first was a death which occurred in a subject who was taking 30 mg of NEB in the USA-1 trial after consuming alcohol. This death was attributed to alcohol intoxication and aspiration of vomit by the sponsor, but review of the pathology described the findings of the lungs without referring to the presence of vomit material in them.

The second was reported as serious adverse event of alcohol intolerance in a subject who was participating in GBR-17 and taking 5 mg in a pharmacokinetic trial. Other adverse events listed for this patient included abdominal pain, hyperventilation and vomiting.

5.3.1.4.8.2 Interaction with medication

Table 31. Interaction with medications in the placebo-controlled trials

Adverse even	CCB		NSAIDs		CYP2D6		Insulin		None	
	P N=5 n(%)	NEB N=24 n (%)	P N=62 n (%)	NEB N=313 n (%)	P N=69 n (%)	NEB N=466 n (%)	P N=29 n (%)	NEB N=132 n (%)	P N=212 n (%)	NEB N=1402 n (%)
Headache	1	0	3 (4.8)	11 (9.9)	2 (2.9)	33 (7.1)	00	7 (5.3)	16 (7.5)	153 (10.9)
Dizziness	00	00	1 (1.6)	13 (4.2)	2 (2.9)	18 (3.9)	1 (3.4)	3 (2.3)	7 (3.3)	65 (4.6)
Diarrhea	0	1	00	11 (3.5)	1 (1.5)	12 (2.3)	00	4 (3.0)	7 (3.3)	5 (3.9)
Nausea	0	0	1 (1.6)	11 (3.5)	1 (1.5)	11 (2.4)	0	2 (1.5)	3 (1.4)	34 (2.8)
Fatigue	0	0	1 (1.6)	17 (5.4)	2 (2.9)	28 (6.0)	0	0	7 (3.3)	83 (5.9)
Influenza	0	0	00	8 (2.6)	00	10 (2.2)	1	0	1 (0.5)	18 (1.3)
Chest pain	0	1	00	5 (1.6)	00	8 (1.7)	0	3	0	7 (0.5)
CRP↗	0	0	00	2 (0.6)	00	8 (1.7)	0	1	1 (0.5)	22 (1.6)
Psychiatric	0	1	00	14 (4.5)	1 (1.5)	21 (4.5)	1	0	3 (1.4)	58 (4.1)
Insomnia	0	1	00	5 (1.6)	00	8	00	1	1 (0.5)	25 (1.8)
Pain in limb	0	0	00	06	00	07 (1.5)	0	3	1 (0.5)	16 (1.1)
Arthralgia	0	0	1 (1.6)	14 (4.5)	2 (2.9)	15 (3.2)	0	1	6 (2.8)	31 (2.2)
UTI	0	0	00	9 (2.9)	1 (1.5)	12 (2.6)	1	2	8 (3.8)	41 (2.9)
Bronchitis	0	0	00	7 (2.2)	2 (2.9)	15 (3.2)	0	0	2 (0.9)	23 (1.6)
Sinusitis	0	0	00	7 (2.2)	2 (2.9)	13 (2.8)	0	2	3 (1.4)	30 (2.1)
Metabolism	1	0	1 (1.6)	12 (3.8)	3 (4.4)	15 (3.2)	3	3	8 (3.8)	44 (3.1)
Gastro-intestinal			7 (11.3)	47 (15.0)	7 (10.0)	61 (13.1)			13 (6.1)	80 (5.7)

CYP2D6

An excess of the following events were observed in subjects receiving the combination containing NEB compared to those receiving the combination containing placebo: headache, influenza and chest pain.

NSAID

An excess of the following was observed in subjects receiving the combination containing NEB compared to those receiving the combination containing placebo: dizziness especially at the highest dose, headache, chest pain, arthralgia and influenza,

Insulin

Two events were observed in excess in subjects receiving the combination containing insulin and these are chest pain and pain in limb.

Calcium channel blockers

The number of subjects receiving CCB in combination with NEB and placebo was too small for any meaningful comparisons to be conducted.

Diuretics, calcium channel blockers and other non-specified drugs were taken in combination with NEB in the non-controlled, open-label extension trial. The small number of subjects taking the combinations and the absence of a comparator rendered the data less reliable for assessing the interaction of NEB with other drugs. Nonetheless, few interactions or hints of interaction were observed including the total incidence of adverse events that was higher on NEB/diuretics and NEB/calcium channel blockers compared to NEB alone. Adverse events combined by system were observed at a higher rate on NEB/diuretics.

Table 32. Interaction with other medications in the long-term follow-up

Adverse events	NEB N = 535	NEB + Diuretics N = 183	NEB +CCB N = 13
Total incidence	122 (22.8)	66 (36.1)	5 (38.5)
Infections and infestations	40 (7.5)	17 (9.3)	3 (23.1)
Musculo-skeletal	19 (3.6)	13 (7.1)	1
Nervous system	18 (3.4)	9 (4.9)	00
Gastrointestinal disorders	15 (2.8)	9 (4.9)	1
Injury	11 (2.1)	8 (4.4)	1
General disorders	8 (1.5)	9 (4.9)	00
Respiratory	8 (1.5)	4 (2.2)	

5.3.1.4.8.3 Conclusion

Chest pain, headache and influenza: occurred on NEB/CYP2D6 and NEB/NSAIDs at a higher rate than on NEB alone. Arthralgia occurred on NEB/NSAID at higher rate than on NEB alone. The increase of headache, arthralgia and influenza on the combination containing NSAID could be explained by the fact that NSAID are commonly taken for these conditions.

Dizziness occurred on NEB/NSAIDs at 3 times the rate on placebo and on the highest dose at an even greater relative risk while it occurred at similar rates on NEB alone compared to its placebo. But here, it is the placebo/NSAIDs which has a lower rate of dizziness than the placebo/placebo group and drove the relative risk high.

In the long-term trial, the incidence of all adverse events, musculoskeletal, gastrointestinal, general disorder and respiratory events seem to be higher on the NEB/diuretic combination.

5.3.1.4.9 Timing of adverse events

Most infections started in the first seven days of treatment to peak between 7 and 30 days. Viral gastroenteritis started between 7 and 30 days and peaked between 30 and 180 days;

Headache and dizziness, diarrhea, nausea, fatigue, chest pain, dyspnea, palpitations and insomnia peaked between 1 and 7 days and tapered down afterward;

Dyspepsia and bradycardia peaked before the end of 30 days

Sinus bradycardia and hypertriglyceridemia peaked between 30 and 180 days;

ALT and AST increase were observed between 30 and 180 days.

5.3.1.4.10 Dose effect analysis

A dose effect was observed with the following adverse events: sinusitis NOS, gastroenteritis viral NOS, diarrhea, dyspnea, bradycardia and sinus bradycardia, hyperlipidemia and aggravation of DM,

Excess with the highest dose (s) was observed for headache, dizziness, migraine NOS, fatigue, depression and erectile dysfunction,

Excess with the 20 mg dose was observed for chest pain, malaise, weight increase, back pain and orthostatic hypotension;

5.3.1.4.11 Common Adverse Events in the Secondary Program

Table 33. Type and incidence of adverse events in the Secondary Program[9]

Preferred Term	Dose Finding Data		Therapeutic-dose Data			
			Placebo-controlled		Active-controlled	
	Placebo N=222	NEB N = 858	Placebo N = 387	NEB N = 419	Other anti-HTN N = 493	NEB N = 521
Any AE	87 (39%)	326 (37.0)	33.6	35.3	54.8	41.8
Headache	33 (14.8)	59 (6.7)	11.1	6.0	14.0	10.6
Dizziness	5 (2.2)	31 (3.5)	2.3	4.8	--	18 (3.5)
Nausea	6 (2.7)	13 (1.5)	2.1	1.9	--	--
Fatigue	8 (3.6)	23 (2.6)	2.3	4.3	3.0	3.3
Rhinitis	9 (4.0)	17 (1.9)	1.0	2.6	--	--
Viral infection	--	--	--	--	3.0	2.9
Cough	6 (2.7)	11 (1.3)	2.1	1.2	4.3	1.5
Dyspnea	--	--	1.2	2.1	--	--
Bronchospasm	--	--		2 (0.5)	--	--
Palpitations	--	--	--	--	2.2	1.5
Common cold	--	--	--	--	2.6	1.7
Dependent edema	0.0	7 (0.8)	--	--	3.9	1.2

[9] These events were captured from the Jansen repot; no raw data was available for confirmation and/or recalculation;

Preferred Term	Dose Finding Data		Therapeutic-dose Data			
			Placebo-controlled		Active-controlled	
	Placebo N=222	NEB N = 858	Placebo N = 387	NEB N = 419	Other anti-HTN N = 493	NEB N = 521
Edema	--	--	--	--	3.2	0.8
Parasthesia	0.0	12 (1.4)	0.3	2.6	2.2	3.3
Flushing	--	--	--	--	7.5	1.5
Vertigo	--	--	--	--	2.2	1.0
Rash	--	--	1 (0.3)	2 (0.5)	2.0	0.6
Bradycardia	0.0	10 (1.1)	--	--	--	--
Impaired vision	--	--	0.3	0.5	0.0	0.4
Depression	0.0	10 (1.1)	1 (0.3)	2 (0.5)	0.0	5 (1.0)
Nightmares	--	--	0.2	0.2	0.0	1.3
Impotence	--	--	00	1 (0.2)	0.0	3 (0.6)
Injury	2 (0.9)	11 (1.3)	--	--	--	--
Back pain	--	--	--	--	2.0	1.5
Diverticulitis	--	--	0.0	1	0.0	1
Diarrhea	2 (0.9)	11 (1.3)	0.8	1.2	0.0	1.3
Abdominal pain	--	--	3 (0.8)	3 (0.7)	0.0	7 (1.3)

The rate of adverse events on NEB was similar to that on placebo in the placebo controlled trials, and it was lower than the rate observed on other antihypertensive medications in the active-controlled trials except for dizziness, depression, abdominal pain, impotence and diarrhea.

Except for dizziness, diarrhea, and impotence, the findings of this program are not similar to those of the primary program with regard to general adverse event. These differences are not important because many factors could have accounted for them including the difference in dosage, duration, population just to list a few.

5.3.1.4.12 Comparison of the general adverse events profile of NEB and carvedilol in the placebo-controlled trials

Table 34. Comparison of NEB and carvedilol with regard to general adverse events

Preferred Term	Placebo N = 372 n (%)	NEB N = 2313 n (%)	RR	Placebo N= 462 n (%)	Carvedilol N = 1142 n (%)	RR
Insomnia	1 (0.3)	25 (1.1)	3.7	3 (0.6)	18 (1.6)	2.7
Dyspnea	1 (0.3)	19 (0.8)	2.6	4 (0.9)	16 (1.4)	1.6
Bradycardia	1 (0.3)	17 (0.7)	2.3	1 (0.2)	24 (2.1)	10.5
Nausea	3 (0.8)	39 (1.7)	2.1	8 (1.7)	16 (1.4)	0.8
Infection viral	1 (0.3)	13 (0.6)	2.0	6 (1.3)	20 (1.8)	1.4

Preferred Term	Placebo N = 372 n (%)	NEB N = 2313 n (%)	RR	Placebo N= 462 n (%)	Carvedilol N = 1142 n (%)	RR
Fatigue	7 (1.9)	83 (3.4)	1.8	18 (3.9)	49 (4.3)	1.1
Edema peripheral	2 (0.5)	21 (0.9)	1.8	2 (0.4)	16 (1.4)	3.5
Sinusitis	3 (0.8)	30 (1.3)	1.6	16 (3.5)	39 (3.4)	1.0
Headache	16 (4.3%)	153 (6.6)	1.5	81 (17.5)	123 (10.8)	0.6
Dizziness	7 (1.9)	65 (2.8)	1.5	25 (5.4)	71 (6.2)	1.1
Abdominal pain	1 (0.3)	10 (0.4)	1.3	6 (1.3)	16 (1.4)	1.1
Diarrhea	7 (1.9)	54 (2.3)	1.2	6 (1.3)	25 (2.2)	1.7
Somnolence	1 (0.3)	7 (0.3)	1.0	7 (1.5)	20 (1.8)	1.2
Hypertriglyceridemia	1 (0.3)	6 (0.3)	1.0	1 (0.2)	14 (1.2)	6.0
Upper resp. tract inf.	8 (2.2)	46 (2.0)	0.9	27 (5.8)	65 (5.7)	1.0
UTI	8 (2.2)	41 (1.8)	0.8	3 (0.6)	21 (1.8)	3.0
Dyspepsia	4 (1.1)	18 (0.8)	0.7	12 (2.6)	15 (1.3)	0.5
Injury	15 (4.0)	56 (2.4)	0.6	12 (2.6)	33 (2.9)	1.1
Chest Pain	00	20 (0.9)	NA	11 (2.4)	27 (2.4)	1.0
Pharyngitis NOS	00	10 (0.4)	NA	3 (0.6)	17 (1.5)	2.5
Rhinitis	00	8 (0.4)	NA	9 (1.9)	24 (2.1)	1.1
Pain	00	7 (0.3)	NA	5 (1.1)	13 (1.1)	1.0
Postural hypotension	00	4 (0.2)	NA	00	21 (1.8)	NA
Back pain	00	1 (0.04)	NA	7 (1.5)	26 (2.3)	1.5
Thrombocytopenia	00	00	NA	1 (0.2)	13 (1.1)	5.5

In comparison to carvedilol, the differences observed with NEB concern the following:

Chest pain occurred on NEB in 20 subjects vs. none on placebo while it occurred at same rate on carvedilol and its placebo;

Dyspnea occurred on NEB at 2.5 times the rate of its placebo while it occurred on carvedilol at 1.5 the rate of its placebo;

Fatigue, dizziness occurred on NEB at > 1.5 times the rate of placebo while the rate on carvedilol and its placebo were similar;

insomnia occurred on NEB at almost 3.5 times the rate of its placebo while it occurred on carvedilol at 2.6 times the rate of placebo;

Viral infections occurred on NEB at twice the rate of its placebo while it occurred on carvedilol at < 1.5 times the rate of its placebo;

Rhinitis occurred in 10 on NEB vs. none on placebo while it occurred on carvedilol at a similar rate as its placebo;

Urinary tract infection occurred at the same rate on NEB and placebo while it occurred on carvedilol at 3 times the rate of its placebo;

Bradycardia occurred on NEB at 2.3 times the rate on placebo while it occurred on carvedilol at 10.5 times the rate of its placebo;

Orthostatic hypotension was observed on NEB at a rate of 0.2% (4) vs. 00 on placebo compared to carvedilol's 1.8% vs. 00 on placebo;

Edema peripheral occurred on NEB at about twice the rate of placebo while it occurred on carvedilol at 3.5 times the rate of placebo;

Hypertriglyceridemia occurred at the same rate on NEB as its placebo while it occurred on carvedilol at 6 times the rate of its placebo;

Thrombocytopenia was not observed on NEB or its placebo while it occurred on carvedilol at 5.5 times the rate of its placebo;

Diarrhea was observed at a similar rate or very slightly higher on NEB compared to its placebo while it occurred on carvedilol at about twice the rate of its placebo;

5.3.1.4.12.1 Conclusion

The association of NEB with chest pain, dyspnea, insomnia, fatigue, dizziness, rhinitis and viral infections seems to be stronger than that of carvedilol with the same adverse events. On the other hand, the association of NEB with bradycardia, orthostatic hypotension, edema peripheral, hypertriglyceridemia, thrombocytopenia and urinary tract infection seems to be weaker than that observed with carvedilol;

5.3.1.5 ECG Findings and QT intervals

5.3.1.5.1 Definition of ECG Abnormalities

PR Interval > 200 msec;
QRS Interval > 120 msec;
RR Interval < 600 or > 1200 msec;
QTc (B) Interval > 450 msec and > 500 msec,
Δ QTc (B) Interval > 30 msec and > 60 msec;
QTc (F) Interval > 450 msec and > 500 msec,
Δ QTc (B) Interval > 30 msec and > 60 msec;

5.3.1.5.2 ECG findings in the 2/3 phase trials

A total of 126 (5.9%) and 21 (1.0%) had a prolongation, which was not present at baseline, in QTc (F) > 450 msec and > 500 msec at the end of the study.

Five hundred and fifty (23.6%) and 137 (6.2%) had a change in QTc (F) > 30 msec and > 60 msec respectively, and 600 (29.6%) and 165 (7.4%) had a change from baseline in QTc (B) > 30 msec and > 60 msec respectively; and

5.3.1.5.3 ECG findings in the placebo-controlled trials

Table 35. Mean changes in ECG parameters in all placebo-controlled trials

QT interval	Placebo	Nebivolol (mg)						
	N = 324	1.25 N = 75	2.5 N = 119	5 N = 550	10 N = 560	20 N = 574	30/40 N = 200	Any N = 2078
Δ HR±SD	-0.01±0.5	-3.5±1.0	-4.4±0.8	-7.4±0.6	-8.4±0.4	-9.7±0.4	-10.8±0.6	-8.3±0.2

QT interval	Placebo N = 324	Nebivolol (mg) 1.25 N = 75	2.5 N = 119	5 N = 550	10 N = 560	20 N = 574	30/40 N = 200	Any N = 2078
Δ QRS±SD	1.1±0.6	1.5±0.7	-0.6±1.5	2.2±1.3	0.9±0.4	1.3±0.5	1.0±0.6	1.3±0.4
Δ RR±SD	2.3±8.3	48.9±13.3	57.6±10.9	101.5±6.9	131.6±7.1	143.3±6.0	169.7±10.7	123.3±3.4
ΔQT±SD	1.1±1.9	10.3±2.1	6.4±2.7	14.0±1.2	20.2±1.4	22.9±1.4	26.5±1.8	18.8±0.7
ΔQTc(F)±SD	-1.2±3.0	3.5±1.7	-1.1±2.6	-5.3±3.3	-2.6±2.8	2.9±1.3	2.2±2.8	-1.0±1.3
ΔQTc(B)±SD	-3.9±5.0	0.2±2.3	-5.2±3.0	-18.3±6.8	-17.3±5.4	-7.5±1.4	-11.3±4.6	-13.0±2.4

As can be seen from the table above, heart rate decreased significantly in a dose response fashion, and uncorrected QT increased significantly in a dose response fashion as well.

Corrected QT appears to have shortened on both NEB and placebo except for the 20 and 30/40 mg dose levels where a change in QTc(F) was positive and of 2- 3 msec.

Table 36. Clinically significant QTc (F) findings in all placebo-controlled trials

QT interval	Placebo	Nebivolol (mg) 1.25	2.5	5	10	20	30/40	Any
N= QTc (F) > 450[10]	309 13 (4.2)	73 00	113 3 (2.7)	518 14 (2.7)	530 10 (1.9)	553 17 (3.0)	191 6 (3.1)	1978 50 (2.5)
N= QTc (F) >500[10]	319 1 (0.3)	75 (0.0)	117 1 (0.8)	540 3 (0.5)	551 1 (0.2)	571 3 (0.5)	195 1 (0.5)	2049 9 (0.4)
N= ΔQTc (F) > 30	322 39 (12.1)	75 2 (2.7)	119 19 (0.2)	549 63 (11.5)	558 68 (12.2)	573 74 (12.9)	198 18 (9.1)	2072 244 (11.8)
N= ΔQTc (F) > 60	322 17 (5.3)	75 00	119 6 (5.0)	549 18 (3.3)	558 18 (3.2)	573 13 (2.3)	198 6 (3.0)	2072 61 (2.9)*

A prolongation of QTc (F) to greater than 500 msec was observed in 9 NEB subjects vs. 1 placebo with a RR of 1.40. Apart from that, the proportion of subjects on different doses of NEB who had a significant change in QTc (F) is either similar to or smaller than that on placebo;

5.3.1.5.4 ECG changes by subgroup categories in monotherapy placebo-controlled trials

Table 37. Significant ECG changes in subgroup analyses in the rimary Program

Subgroup category	Δ QTc > 30 QTc (B)	> 30 QTc (F)	> 60 QTc (B)	> 60 QTc (F)
Monotherapy Trials (Studies 202, 302, 305)				
Poor Metabolizers				
Placebo N = 8	0.0	0.0	00	00

[10] Not clinically significant at baseline
* Denotes a 95 CI that does not include 1;

Subgroup category	Δ QTc			
	> 30		> 60	
	QTc (B)	QTc (F)	QTc (B)	QTc (F)
NEB N = 96	20 (20.8)	14 (14.6)	00	3 (3.1)
Extensive Metabolizers				
Placebo N = 180	30 (16.7)	17 (9.4)	7 (3.9)	00
NEB N = 1551	269 (17.3)	126 (8.1)	38 (2.5)	00
Blacks				
Placebo N = 65	17 (26.2)	14 (21.5)	7 (10.8)	4 (6.2)
NEB = 420	102 (24.3)	68 (16.2)	27 (6.4)	22 (5.2)
Non-Blacks				
Placebo N = 123	13 (10.6)	3 (2.4)	00	00
NEB N = 1227	187 (15.2)	72 (5.9)	14 (1.1)	4 (0.3)
Males				
Placebo N = 99	13 (13.1)	6 (6.1)	2 (2.0)	2 (2.0)
NEB N = 882	150 (17.0)	75 (8.5)	21 (2.4)	14 (1.6)
Females				
Placebo N = 89	17 (19.1)	11 (12.4)	5 (5.6)	2 (2.3)
NEB N = 765	139 (18.2)	65 (8.5)	20 (2.6)	12 (1.6)
Trial with Adjuvant therapy (Study 321)				
Poor Metabolizers				
Placebo N = 7	01 (14.3)	00	00	01 (4.8)
NEB N = 21	7 (33.3)	7 (33.3)	00	02 (9.5)
Extensive Metabolizers				
Placebo N = 123	26 (21.1)	21 (17.1)	13 (10.6)	12 (9.8)
NEB N = 394	108 (27.4)	94 (23.9)	38 (9.6)	33 (8.4)
Blacks				
Placebo N = 43	7 (16.3)	7 (16.3)	3 (7.0)	2 (4.7)
NEB N = 131	41 (31.3)	33 (25.2)	13 (9.9)	12 (9.2)
Non-Blacks				
Placebo N = 91	21 (23.1)	15 (16.5)	11 (12.1)	11 (12.1)
NEB N = 294	76 (25.9)	71 (24.2)	27 (9.2)	23 (7.8)
Males				
Placebo N = 74	15 (20.3)	12 (16.2)	9 (12.3)	9 (12.2)
NEB N = 238	45 (27.3)	57 (24.0)	21 (8.8)	20 (8.4)
Females				
Placebo N = 60	13 (21.7)	10 (16.7)	5 (8.3)	4 (6.7)
NEB N = 187	52 (27.8)	47 (25.1)	19 (10.2)	15 (8.0)

Poor metabolizing subjects on NEB experienced a change in QTc (F) > 30 msec in 14.6% (14) compared to none on placebo, and compared to 8.1% (126) in the EM subjects on NEB.

Non-black subjects on NEB had a change in QTc (F) > 30 msec in 5.9% (72) compared to 2.4% (3) on placebo, and in QTc (F) > 60 msec in 0.3% (4) vs. none on placebo. The relative risk of a change in QTc (F) > 30 msec was 2.41 CI (0.77, 7.52).

Males on NEB had a slight increase in the relative risk of a change in QTc (F) > 30 for all doses combined RR = 1.4 CI (0.63, 3.14) which became more prominent, RR = 3.1 CI (1.22, 7.67) on 2.5 mg (13 out of 70) compared to placebo (6 out of 99).

5.3.1.5.5 Conclusion of ECG Findings

The effect of NEB on QT was evaluated in 90% of the subjects enrolled in the placebo-controlled trials. Despite that ECG data were collected casually and analyses were not completed centrally for all trials, the validity of these data in assessing the effect of NEB on QT intervals is likely to be adequate because the randomized, placebo-controlled design of the studies during which these data were collected allows for controlling for a number of biases including the misclassification bias that is more likely to be problematic in ECG data collection.

The change in means was negative on NEB which points to an inaccurate correction by the two methods, Fridericia and Bazzet, used in this program.

In comparing all subjects on NEB to their baseline parameters, 6% and 1% of all subjects on NEB had their QTc(F) prolonged on NEB to > 450 and > 500 msec respectively. A higher proportion 24% and 6 % had a change in QTc (F) > 30 and 60 msec respectively.

In placebo-controlled trials, only a small excess in QTc (F) prolonged to > 500 msec was observed on NEB compared to placebo. Almost twice as many subjects on placebo had a change from baseline in QTc (F) > 60 msec.

Subgroup analyses:

Poor metabolizers with 14 (14.6%) on NEB vs. none on placebo and 3 on vs. none on placebo experienced a change in QTc(F) > 30 msec and > 60 msec respectively.

Non-black subjects and **males** on NEB experienced a change in QTc > 30 msec at a greater rate than on placebo.

The prolongations observed with NEB should be considered real given the inaccurate correction and tendency of the two methods to bias the changes toward negativity.

5.3.1.6 Laboratory Findings

5.3.1.6.1 Definition of Laboratory abnormalities

These abnormalities were defined in the primary program and only the ones alluded to in this review are defined below:

5.3.1.6.1.1 Hematology Parameters

Hematocrit ≤ 37% in males and ≤ 32 % in females;
Hemoglobin ≤ 11.5 g/dL in males and ≤ 9.5 g/dL in females;
WBC count ≤ 2.8 or ≥ 16.0 Thou/mcL;
Platelet count ≤ 75.0 or ≥ 700.0 x $10^3/mm^3$;

Eosinophils ≥ 10%;

5.3.1.6.1.2 Chemistry Parameters

-ALT (SGPT) UNL 48 U/L;
-AST (SGOT) UNL 42 U/L (29 to 68 years) and 55 U/L (64 to 79 years);
-Alkaline phosphatase 20.00 to 125.00 U/L;
-Total bilirubin UNL 1.3 mg/dL;
-BUN range 7 to 25 or 7 to 30 mg/dL for 29-68 and 64 -79 year old subjects;
-Creatinine range 0.5 to 1.4 mg/dL;
-Uric Acid 2.5 – 7.5 mg/dL and 4.0 – 8.5 mg/dL in females and males respectively;
-Glucose range: 70 – 115 mg/dL in 24 to 49 old females and in 27 to 49 old males, and 70 – 125 mg/dL in 49 to 79 year old females and 49 to 82 year old males.
-C-Reactive proteins > 1.9 mg/L;
-Calcium range 8.5 to 10.3 mg/dL;
-Chloride 95 to 108 mEq/L;
-HDL cholesterol < 35 mg/dL;
-LDL > 130 mg/d/L; Total cholesterol > 199 mg/dL;
-Triglycerides UNL 199 mg/dL;
-Potassium 3.50 – 5.3 mEq/L;
-Sodium 135 – 146 mEq/L;
-Phosphorous range 2 – 4 mg/dL;
-Total Protein range 5.8 – 8.5 mg/dL;

5.3.1.6.2 Laboratory Findings in the Primary Program

5.3.1.6.2.1 Clinically significant laboratory findings

As can be seen from the table below, only few of the sponsor-defined clinically significant laboratory findings were observed. Of importance are the findings of the liver function tests, uric acid, BUN, creatinine and eosinophils even if the numbers are small;

Table 38. Clinically Significant Laboratory Findings

Parameter	Monotherapy Placebo-controlled Trials		All phase 2/3 Studies
	Placebo N = 205 n (%)	NEB N = 1811 n (%)	N = 2464 n (%)
Hemoglobin	01 (0.5)	04 (0.2)	18 (0.8)
Hematocrit	03 (1.6)	11 (0.4)	40 (1.8)
Platelets	00	00	03 (0.13)
WBC x 10^3/mcL			
≤ 2.8	00	01 (0.06)	10 (0.43)
≥ 16.0	00	03 (0.2)	05 (0.22)
Neutrophil, Segs ≤ 15%	01	00	02 (0.09)
Eosinophils ≥ 10%	01	14 (0.8)	32 (1.39)
BUN ≥ 30 mg/dL	00	5 (0.3)	25 (1.10)
Creatinine ≥ 2.0 mg /dL	01	01	03 (0.13)
Uric Acid	00	04 (0.2)	27 (1.15)
AST			
≥ 3 x ULN	00	07 (0.4)	10 (0.43)
≥ 5 x ULN	00	02 (0.09)	02 (0.09)
ALT	00	01 (0.06)	03 (0.13)
Alkaline phosphatase ≥ 3x ULN	00	00	01 (0.04)
LDH ≥ 3x ULN	00	00	01 (0.04)
AST or ALT ≥ 5x	00	02	02
AST or ALT + Bilirubin abnormal	00	00	02 (0.09)

5.3.1.6.2.2 Abnormal laboratory findings in the phase 2/3 studies

Table 39. Laboratory parameters that changed in > 2% of all subjects or worth noting on nebivolol

Parameters	Below normal range N = 2464 %	Above normal range %
Hematology		
RDW	--	19.8
Lymphocytes (%)	2.4	6.2
Eosinophils (%)	--	4.6
Hematocrit	7.1	3.3
Hematocrit	--	3.3
Neutrophils segs (%)	3.4	3.2
Eosinophils absolute	--	2.8
MCH	--	2.6
MCH	--	2.6
MCV	--	2.4
WCC	2.5	2.4
Hemoglobin	7.3	--
Erythrocyte	5.4	--
HCMC	10	--
Monocytes absolute	10.6	--
Eosinophil absolute	5.8	--
Neutrophils absolute	3.7	--
Chemistry		
HDL cholesterol	5.6	--
Total cholesterol	--	28.1
Triglycerides	--	21.6
LDL Cholesterol	--	17.8
Glucose	--	11.3
Chloride	--	10.1
ALT (SGPT)	--	5.7
Phosphorus	--	5.6
Uric acid	--	5.3
Potassium	--	4.9
AST	--	3.7
Carbon dioxide	6.4	3.2
Magnesium		2.7

Parameters	Below normal range N = 2464 %	Above normal range %
BUN		2.6
Sodium	--	2.4
Creatinine		2.4
Alkaline phosphatase	--	1.9
Total bilirubin	--	1.7
CRP↗	--	25.0 (73/286)

Urine analysis abnormalities			
Urine protein	15.0	Urine /RBC	10.3
Urine occult blood	8.3	Amorphous sediments	19.0
Urine leukocytes	11.3	Calcium oxalate crystals	40% (10/25)
Squamous epithelial cells	36.0		

C-reactive proteins: a total of 692 subjects were tested, 338 tested above normal range at baseline, and of the remaining 286, 73 (25%) tested abnormal at the end of the study.

Squamoums epithelial: 132 out of 406 subjects who tested normal at baseline, tested abnormal during the study.

5.3.1.6.2.3 Deviations from normal range in all placebo-controlled trials

Laboratory parameters in which an increase in risk on NEB either exceeded 50%, was statistically significant, a dose response effect was observed or the reviewer believed worth noting are summarized in the table below.

Table 40 Abnormal laboratory findings in the monotherapy placebo-controlled trials

Parameters	P	Nebivolol mg						
	N = 205 n(%)	1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 459 n(%)	10 N = 461 n(%)	20 N = 460 n(%)	30/40 N = 217 n(%)	Any N = 1811 n(%)
Hematology								
Eosinophils absolute > NR	00	2 (2.7)	3 (2.6)	5 (1.9)	2 (0.8)	4 (1.6)	3 (1.5)	19 (1.6)
MCV (FL) > NR	00	1 (1.4)	2 (1.7)	6 (1.4)	4 (1.0)	4 (1.0)	00	17 (1.1)
Platelets > NR	00	1 (1.3)	1 (0.8)	3 (0.7)	3 (0.7)	3 (0.7)	00	11 (0.7)
Platelets < NR	1 (0.5)	00	2 (1.7)	7 (1.7)	4 (0.9)	3 (0.7)	3 (1.5)	19 (1.1)
MCH > NR	1 (0.6)	1 (1.4)	00	3 (0.8)	10 (2.5)	4 (1.0)	00	18 (1.2)
RDW > NR	11 (12.2)	7 (12.7)	14 (15.7)	22 (15.1)	26 (16.7)	16 (11.4)	27 (18.6)	112 (15.3)
Hematocrit (%)	3 (1.2)	1 (1.4)	3 (2.6)	8 (2.0)	9 (2.1)	6 (1.4)	7 (3.7)	34 (1.3)

Parameters	P N = 205 n(%)	Nebivolol mg 1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 459 n(%)	10 N = 461 n(%)	20 N = 460 n(%)	30/40 N = 217 n(%)	Any N = 1811 n(%)
> NR								
Chemistry								
Calcium < NR	00	00	00	1 (0.2)	5 (1.1)	7 (1.6)	2 (1.0)	15 (0.9)
Phosphorus < NR	00	1	1	5	1	2	00	10 (0.6)
Creatinine > NR	00	00	1 (0.8)	5 (1.2)	2 (0.5)	00	1 (0.5)	9 (0.5)
Uric Acid > NR	1 (0.5)	2 (2.7)	2 (1.7)	12 (2.8)	5 (1.2)	5 (1.2)	4 (2.0)	30 (1.8)
BUN > NR	1 (0.5)	1 (1.3)	1 (0.8)	1 (0.2)	6 (1.4)	5 (1.2)	4 (2.0)	18 (1.1)
Chloride > NR	8 (4.4)	4 (5.5)	8 (6.8)	21 (5.2)	26 (6.3)	21 (5.1)	13 (6.6)	93 (5.6)
HDL < NR	2 (1.3)	4 (6.5)	1 (1.1)	10 (3.0)	15 (4.4)	14 (4.1)	10 (6.0)	54 (4.1)
Total bilirubin> NR	1 (0.5)	00	2 (1.7)	6 (1.4)	9 (2.1)	4 (0.9)	00	21 (1.3)
Phosphorus > NR	4 (2.1)	2 (2.3)	3 (2.5)	6 (1.4)	9 (2.1)	19 (4.5)	12 (6.1)	51 (3.1)
Potassium < NR	00	00	2	00	1	4	00	7 (0.4)
Potassium > NR	2 (1.0)	1 (1.3)	2 (1.6)	10 (2.4)	7 (1.6)	8 (1.9)	8 (4.0)	36 (2.1)
Carbon dioxide < NR	3 (1.2)	1 (1.3)	1 (0.8)	10 (2.3)	8 (1.9)	9 (2.1)	5 (2.5)	34 (2.0)
Magnesium > NR	1 (0.5)	2 (2.6)	1 (0.8)	10 (2.4)	7 (1.6)	5 (1.2)	1 (0.5)	26 (1.2)
Total cholest. > NR	13 (14.3)	8 (24.2)	8 (16.7)	39 (23.1)	41 (22.3)	31 (17.3)	22 (23.4)	149 (21.1)
Triglycerides > NR	16 (10.5)	12 (19.7)	11 (11.5)	47 (14.3)	57 (17.0)	55 (16.3)	24 (14.2)	206 (15.5)
Glucose < NR	1 (0.5)	00	2 (1.6)	3 (0.7)	1 (0.2)	4 (0.9)	3 (1.5)	13 (0.8)
Urine								
Squamous epith. cells abnormal	3 (9.7)	9 (34.6)	8 (28.6)	18 (27.3)	26 (30.2)	12 (18.8)	12 (22.2)	85 (26.2)
Specific gravity > NR	1 (0.5)	1 (1.4)	3 (2.6)	6 (1.4)	9 (2.1)	5 (1.2)	6 (3.0)	30 (1.8)
Urine ketones abnormal	1 (0.5)	00	1 (0.9)	7 (1.7)	5 (1.2)	5 (1.2)	3 (1.6)	21 (1.3)
Urine protein abnormal	13 (8.6)	7 (11.1)	7 (7.6)	28 (7.7)	35 (10.0)	31 (8.4)	23 (14.3)	131 (9.4)
Urine nitrite abnormal	2 (1.1)	00	1 (0.9)	4 (1.0)	2 (0.5)	7 (1.6)	6 (3.1)	20 (1.2)

The sample size for calcium oxalate test was very small (total of 18).

As with other beta-blocking agents: an increase in the risk (on NEB compared to placebo) of a deviation above normal ranges of bilirubin, creatinine, BUN, uric acid, triglycerides and total cholesterol, and of a deviation below normal of platelets, potassium and glucose were observed.

Observed on NEB vs. none on placebo:

Eosinophils absolute, MCV and platelets deviating above normal ranges, and calcium and phosphorus below normal ranges;

Observed in excess on NEB compared to placebo:

HDL deviating below normal range in 3 as many NEB as placebo subjects;

MCH, RDW, hematocrit (%) potassium, deviating above normal range especially on the highest dose level;

Phosphorus and total cholesterol deviating above normal range especially on the highest two doses;

Chloride and magnesium deviating above normal range, and carbon dioxide deviating below normal range;

Observed abnormalities in urine on NEB:

Presence of squamous epithelial cells;

Deviation of specific gravity above normal range;

Urine proteins abnormal on the highest dose;

Urine nitrites abnormal on the highest dose;

5.3.1.6.2.4 Mean change from baseline in laboratory parameters in the placebo-controlled trials

Changes in means reported here are those that were found to be greater on NEB, and were either statistically significant, consistent across all dose levels or in which a dose response was observed.

Table 41. Mean change from Baseline in placebo-controlled trials of monotherapy

Parameters	P	Nebivolol mg						
	N=205 n(%)	1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 459 n(%)	10 N = 461 n(%)	20 N = 460 n(%)	30/40 N = 217 n(%)	Any N = 1811 n(%)
Hematology								
Δ Platelets x $10^3/mm^3$	-5.13	-9.88	-11.93*	-12.97**	-12.16*	-16.52***	-17.79***	-14.04***
Hematocrit (%)	0.26	0.27	-0.07	-0.08	-0.10	-0.19*	-0.14	-0.10*
Chemistry								
Potassium mEq/L	0.00	0.07	0.05	0.07	0.07*	0.06	0.03	0.06*
Chloride mEq/L	-0.3	0.0	0.2*	0.2	0.2*	0.2*	0.3*	0.2*
Carbon	0.1	-0.1	-0.6	-0.0	-0.2	-0.2	-0.6*	-0.2

Parameters	P N=205 n(%)	Nebivolol mg 1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 459 n(%)	10 N = 461 n(%)	20 N = 460 n(%)	30/40 N = 217 n(%)	Any N = 1811 n(%)
dioxide mEq/L								
Phosphorus mg/dL	0.05	-0.1*	0.08	0.02	0.07	0.11	0.13	0.07
Creatinine mg/dL	-0.0	0.01	0.01	0.02	0.02	0.02	0.01	0.02
BUN mg/dL	0.1	0.5	0.5	0.2	0.8*	0.8**	0.1	0.6
Uric Acid	-0.03	-0.07	0.10	0.17**	0.18**	0.18**	0.16*	0.16***
HDL Cholesterol	1.6	-1.8**	-1.1*	-2.4***	-2.0***	-2.7***	-2.5***	-2.3***
Triglycerides Mg/Dl	1.6	7.9	17.7	5.4	23.3***	14.0	14.5	16.8**
Alkaline Phosphatase U/L	2.1	-0.0	1.2	-0.9**	-0.5*	-1.7**	-3.3***	-1.1***
Urinary pH	-0.00	0.0	-0.01	-0.12*	-0.11*	-0.10	-0.10	-0.10

The mean change from baseline on NEB compared to placebo in platelet count, uric acid, creatinine, triglycerides and HDL supports the findings of increased frequencies of deviation from normal range on NEB compared to placebo.

The change in the mean of alkaline phosphatase was negative and statistically significant for all doses combined and for the three highest dose levels which supports of the frequency findings where almost twice as many placebo subjects as NEB experienced a deviation above the normal range.

The change from baseline in Urine pH was negative and higher on NEB than on placebo, it occurred in dose response fashion and it was statistically significant for the 20 mg dose level.

5.3.1.6.2.5 Laboratory Findings in the Long-Term Extension Trials

Table 42. Mean Change from baseline in laboratory values at 6 and 9-month follow-up[11]

	Day 91 Mean (SD)	Day 182 Mean (SD)	Day 273 Mean (SD)
Triglycerides	18.35* (7.03)	27.96* (8.11)	23.62* (6.50)
HDL	-2.02* (0.75)	-4.13* (0.80)	-5.37* (0.60)
Glucose	2.12 (1.1)	3.26* (1.27)	0.74 (1.16)
ALT	1.20 (0.91)	1.63 (2.05)	1.45* (0.57)

[11] The denominator changed from test to test and from follow-up visit to follow-up visit

	Day 91 Mean (SD)	Day 182 Mean (SD)	Day 273 Mean (SD)
AST	0.87 (0.74)	2.52 (1.63)	1.26* (0.38)
Total bilirubin	-0.02 (0.02)	-0.01 (0.02)	-0.01 (0.02)
Alkaline Phosphatase	-0.97 (1.01)	1.75 (4.59)	-3.46* (0.79)
LDH	4.78* (2.25)	12.41 (12.8)	-0.23 (1.13)
Sodium	0.17 (0.11)	0.05 (0.14)	0.63* (0.15)
BUN	0.01 (0.33)	1.28* (0.32)	0.65* (0.23)
Creatinine	0.17* (0.01)	0.17* (0.01)	0.16* (0.01)
Uric Acid	0.19* (0.07)	0.35* (0.80)	0.32* (0.05)
Potassium	0.11* (0.2)	0.10* (0.2)	0.10* (0.2)
Chloride	0.05 (0.11)	0.27* (0.13)	0.41* (0.15)
Phosphorous	0.11* (0.04)	0.02 (0.05)	0.07* (0.03)
CO_2	-1.12 (0.16)	-1.62* (0.2)	-1.43* (0.2)
Platelets	-13.03	-19.62	-26.89
MCV (FL)	0.16 (0.23)	0.36 (0.32)	0.47* (0.14)

HDL cholesterol, triglycerides, BUN, creatinine, uric acid, platelets count, potassium, chloride and carbon dioxide maintained the trends that were observed in the placebo-controlled trials.

AST and ALT as would be expected changed from baseline in a significant way during the long-term follow-up.

Sodium changed from baseline after 9 months in a statistically significant way.

Table 43. Change from normal range to out of normal range in long-term exposure[11]

	Day 91		Day 182		Day 273	
	NEB	NEB/Diuretics	NEB	NEB/D	NEB	NEB/D
Triglycerides	19 (12.4)	4 (17.4)	15 (11.1)	12 (22.2)	44 (16.6)	23 (18.5)
HDL	3 (2.3)	2 (9.1)	5 (4.0)	2 (4.1)	11 (4.8)	3 (2.9)
LDL	12 (9.9)	2 (9.5)	15 (13.0)	5 (10.9)	30 (13.2)	10 (10.4)
Uric acid	3 (2.0)	2 (8.7)	4 (3.0)	5 (9.3)	8 (3.0)	16 (12.9)
BUN	2 (1.3)	1 (4.3)	4 (3.0)	3 (5.5)	11 (4.2)	2 (1.6)
Creatinine	2 (1.3)	1 (4.3)	2 (1.5)	6 (1.9)	6 (2.3)	6 (4.8)
Uric acid	3 (2.0)	2 (8.7)	4 (3.0)	5 (9.3)	8 (3.0)	16 (12.9)
Glucose	40 (7.0)	12 (6.6)	23 (6.0)	22 (11.4)	13 (4.9)	14 (11.3)
Potassium	19 (3.3)	12 (6.5)	15 (3.9)	4 (2.1)	2 (0.8)	6 (4.8)
Calcium	2 (1.3)	0.0	1 (0.7)	2 (3.7)	1 (0.4)	6 (4.8)
CO_2	29 (5.1)	18 (9.8)	18 (4.7)	7 (3.6)	8 (3.0)	9 (7.3)

Only BUN and to a lesser degree creatinine, uric acid, triglycerides, LDL and HDL, showed a dose response with duration of exposure on NEB in the proportion of subjects who's parameters went out of normal to abnormal range.

5.3.1.6.2.6 Laboratory findings after withdrawal of therapy

The number of subjects was very small for any meaningful assessment of the effect of withdrawal to be conducted.

5.3.1.6.2.7 Laboratory findings in the secondary program

The abnormalities summarized here are those that did not exist at baseline. It is not known in which direction the changes occurred.

In the therapeutic dose data

Laboratory parameters that became abnormal during exposure of 818 subjects to 5 mg of NEB include ALT in 6, AST in 3, alkaline phosphatase in 1, calcium in 16, chloride in 6, GGT in 8, potassium in 5, total bilirubin in 4, total proteins in 8, urea in 11, uric acid in 9, hematocrit in 11 and platelet count in 11.

In the long-term data

The results of a combined analysis including 443 subjects who have taken 5 mg of NEB for long-term (not defined) yielded the following abnormalities.

ALT in 9, AST 5, chloride in 11, glucose in 42, potassium in 15, total bilirubin in 9, urea in 33, uric acid in 11, platelet count in 8, hematocrit in 9, hemoglobin in 7, WBC in 11 and RBC in 6; It is not know in which direction some of the parameters changed.

5.3.1.6.2.8 Conclusions

Platelet count decrease was observed consistently on NEB:

-with negative change from baseline in the mean of all subjects on NEB
-with negative change in the mean on NEB that is dose dependent and statistically significantly different from placebo across all dose levels except the lowest one;
-with a high proportion of all subjects on NEB shifting from normal to below normal range;
-with a higher proportion of subjects on NEB compared to placebo shifting to below normal range;

Hematocrit

-with a negative change in the mean that is statistically significantly different from the change observed on placebo for all doses combined and for the 20 mg dose level;

RDW

-with a shift from normal to above normal range in 20% of all subjects on NEB;
-with a higher proportion of subjects deviating from normal to above normal compared to placebo;
-with a dose response effect;

Eosinophils absolute

-with a shift above normal range in 19 subjects on NEB compared to none on placebo;

Lymphocyte %

-with a shift to above normal range in 6% of all subjects on NEB;

White cell count

-with a shift to below NR in 2.5% of all subjects on NEB;

Erythrocytes

-with shifted below NR in 5.4%;

C-reactive protein

-with a shift to above NR in 25.5% of all subjects who received NEB;
-with an increased incidence of a shift > NR on NEB compared to placebo;
-with a positive change in the mean on the highest three doses compared to placebo;

Triglyceride

-with a shift to above NR in 22% of all subjects exposed to NEB;
-a higher proportion on NEB shifting to above NR compared to placebo
-a shift that is consistent and statistically significant across all dose levels except the second lowest dose;
-a dose response with duration of exposure in the proportion of subjects who's values went out of NR in the long-term trial;
-a change in the mean from baseline that is positive and statistically significant;
-a change in the mean from baseline that increased in magnitude and remained statistically significant at 6 and 9 months;

HDL

-with a shift below NR in 5.6% of all subjects exposed to NEB;
-a decreased below NR in 3 times as many subjects on NEB compared to placebo;
-the difference in incidence between the highest dose and placebo been statistically significant;
-a change in the mean from baseline that was negative and statistically significantly different from that on placebo;
-a dose response with duration of exposure in the proportion of subjects who's values went out of NR in the long-term trial;
-an increase in the magnitude of change in the mean from baseline which doubled at 6 months;

BUN

-with a shifted above NR in 2.6% of all subject who received NEB
-a shift above NR in twice as many subjects on NEB compared to placebo;
-a change in the mean from baseline on NEB that is 6 times the magnitude of the change on placebo;
- a change on the 10 and 20 mg dose levels being statistically significant;
-a dose response with duration of exposure in the proportion of subjects who's values went out of NR in the long-term trial;
-a change from baseline in mean becoming statistically significant at 6 and 9 months

Creatinine

-with a shift above NR in 2.4% of all subjects exposed to NEB;
-a shift above NR in 21 subjects on NEB compared to none on placebo;
-a small but positive change in the mean from baseline on NEB that was not observed on placebo;

-a dose response with duration of exposure in the proportion of subjects who's values went out of NR in the long-term trial;
-a magnitude of the change from baseline increasing many folds at 6 and 9 months and the difference becoming statistically significant;

Uric acid

-with a shifted above NR in 5% of all subjects exposed to NEB;
-a shift on NEB in 3.5 times as many as placebo;
-a change from baseline on NEB that was positive and statistically significantly different from that on placebo;
-a dose response with duration of exposure in the proportion of subjects who's values went out of NR in the long-term trial;
- a magnitude of the change in the mean increasing to ≥ 2 and remaining statistically significant at all long-term follow-up visits;

Potassium

-with a shift > NR in 5.5% of all subjects who received NEB;
-a shift on NEB that is twice that on placebo with the RR on the 30/40 mg dose level been the highest;
-a mean change from baseline on NEB that was positive and statistically significant;

Potassium

-with a shift < NR in 7 subjects on NEB compared to none on placebo;

Phosphorous > NR

-with a shift > NR in 5.6% of all subjects on NEB;
-a shift on the two highest dose of NEB that occurred in twice as many subjects compared to placebo;
-a change in the mean from baseline on the two highest doses that was at least twice that on placebo;
-a change in the mean from baseline that became statistically significant at 9 months;

Phosphorus

-shifted to < NR on 10 NEB subject compared to none on placebo;

Chloride

-with a shift to > NR in 10% of all subjects who received NEB;
-a change from baseline on NEB that was positive and statistically significantly different from placebo for all dose levels except the lowest dose;
-a change in the mean from baseline increasing in magnitude and becoming statistically significant at 9 months;

Calcium

-with a shift to below NR in 1.0% of all subjects on NEB;
-a shift in 15 subjects on NEB compared to none on placebo;

Carbon dioxide

-with a shift to below NR in 6.4%;
-a shift that occurred at a higher rate on NEB compared to placebo;
-a change in the mean from baseline that was negative;
-with the biggest and statistically significant difference between NEB and placebo observed on the highest dose;

-a change in the mean from baseline that increased in magnitude and became statistically significant at 6 and months;

Magnesium

-with a shift > NR in 2.7% of all subjects who received NEB;
-a shift in 3 as many subjects on NEB compared to placebo;

ALT

-a shift > NR in 5.7% of all subjects who received NEB;
-a persistent increase after long-term exposure;

AST

-a shift > NR in 3.4% of all subjects who received NEB;

Bilirubin

-a shift > NR in more than twice as many people on NEB (1.3%) compared to placebo (0.5%);

Urinary pH

-a change from baseline that was negative and the magnitude of change was greater on NEB compared to placebo;

Squamous cells in urine

-abnormal in 32.5% of all subjects on NEB;
-abnormal in twice as many subjects on NEB compared to placebo;
-a high RR across all dose levels with two dose levels statistically significantly different from placebo;

Subgroup analyses findings of laboratory abnormalities that are worth noting include:

Non-black subjects:

-uric acid: the change in mean from baseline on NEB compared to placebo became more significant;

Poor metabolizers

-total proteins: the change in mean from baseline became more prominent and statistically significant;

Older subjects

-platelet count: a more dramatic negative change in mean but no platelet count decrease was observed in this group.
-creatinine: older subjects accounted for the bulk of difference observed between NEB and placebo;

Males

-triglycerides: males accounted for most of the difference observed between NEB and placebo in the change in the mean. They accounted for the difference in incidence observed between NEB and placebo;

Other Parameters that were observed to change in long-term exposure

-Alkaline phosphatase: the magnitude in the negative change in alkaline phosphatase became 3 fold higher and statistically significant at 9 months;

-LDH: the mean change from baseline increased and became statistically significant on Day 91, and it increased further at 6 months but not in a statically significant way;

-Sodium: the mean change from baseline at 9 months became prominent and statistically significant;

Glucose: the change from baseline became statistically significant at 6 months;

MCV: the change from baseline in the mean became positive, increased in a dose response fashion and was statistically significant at 9 months

Interaction with diuretics

NEB interacted with diuretics with regard to uric acid, triglycerides, creatinine, glucose, potassium, calcium, and carbon dioxide. All these parameters were observed to shift out of normal range in a higher proportion of subjects on the combination compared to subjects on NEB alone.

5.3.1.6.2.9 Comparison to carvedilol

Unlike the experience with carvedilol, only one patient in the NEB program withdrew because of laboratory abnormalities and this was leucopenia in a subject who had a history of cancer and was treated with radiotherapy.

The parameters with mean change from baseline exceeding 5% (the value of baseline) on NEB are platelet count, creatinine, BUN, uric acid, triglycerides, AST, ALT, LDH, HDL, carbon dioxide and TSH.

Like carvedilol, NEB is associated with an alteration of the kidney and liver functions, a hint of thrombocytopenia;

Unlike carvedilol, NEB is possibly associated with:

-worsening of the lipid profile including triglycerides and HDL cholesterol;
-increase in the C-reactive proteins; increase in creatinine, uric acid, BUN;
-increase in potassium, phosphorus, chloride and magnesium;
-decrease in calcium and carbon dioxide;
-acidification of urine and presence of protein and squamous cells in urine;

5.3.1.7 Clinically significant vital sign changes

The summary of vital signs below is obtained from tabulation of results from 3 monotherapy placebo-controlled trials, NEB-202, NEB-302 and NEB-305.

5.3.1.7.1 Definition of Abnormal Vital Signs

Heart rate ≤ 49 or ≥ 2 101 bpm;
Systolic blood pressure ≤ 90 or ≥ 200 mmHg;
Diastolic blood pressure ≤ 60 or ≥ 110 mmHg;
There are two definitions of clinically significant changes in blood pressure:
--Definition 1: a reduction ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure from the third sitting to the first standing measurement;
--Definition 2: a reduction of ≥ 30 mmHg in systolic blood pressure (to a value of 90 mmHg or less), or ≥ 20 mmHg in diastolic blood pressure (to a value of 50 mmHg or less) from the third sitting to the first standing measurement;

5.3.1.7.2 Heart Rate

The incidence of clinically significant reductions in sitting heart rate (< 49 bpm) was similar (3% of all subjects on NEB) at peak and trough concentration levels of NEB.

Twenty nine and 27 subjects on NEB vs. NONE on placebo experienced a clinically significant reduction in heart rate at peak and trough respectively.

No significant reduction in heart rate was observed in doses below 5 mg.

Starting at 5 mg, a dose response effect was observed ranging from 1.0% on 5 mg to 5% on 30/40 mg at both peak and trough.

Heart rate increased > 110 bpm at peak and trough in 4 and 9 of all subjects on NEB.

PM subjects seem to experience a significant drop in heart rate at a higher proportion than EM with 4.2% vs. 2.7% at peak and 3.6% vs. 2.9% at trough.

Non-black subjects experienced a significant drop in heart rate at a slightly higher incidence than Blacks with 3.3% vs. 1.6% and 3.2% vs. 2.4% at peak and trough respectively.

Older subjects experienced a significant drop in heart rate at a greater incidence than younger subjects with 6.2% vs. 2.1% and 4.9% vs. 2.6% at peak and trough respectively.

Males experienced a significant drop in heart rate at a higher incidence than female with 3.7% vs. 1.7% and 3.7% and 2.1% at peak and trough respectively.

As the dose of NEB increased the incidence of significant drop in heart rate increased (with 0.5%, 1.2%, 2.3%, 3.3% and 5.1%) at peak (and 0%, 1.6%, 2.6%, 3.2% and 5.2%) and trough (on < 5 mg, 5 mg, 10 mg, 20 and 30/40 mg respectively).

5.3.1.7.3 Orthostatic hypotension (definition 1)

Orthostatic hypotension occurred shortly after starting NEB and led to discontinuation in 2 subjects.

Orthostatic hypotension was experienced 13% at trough and 10% at peak of all subjects on NEB while 5% exhibited orthostatic hypotension at baseline.

The rate of orthostatic hypotension at trough in the placebo-controlled trials was more prominent on placebo than on NEB; and at peak, the rate was similar in both arms, but the two highest dose levels were associated with a very slight excess (13% and 14% respectively).

Subgroup analyses showed that 17% of the PM vs. 12% of the EM experienced orthostatic hypotension at trough while they exhibited similar rates at baseline. The proportions at peak were similar, 11% and 10%.

Diabetic subjects experienced orthostatic hypotension at peak at a higher incidence than non-diabetic subjects with 14.5 vs. 9.1% respectively while they exhibited orthostatic hypotension at similar rates at baseline.

Older subjects experienced orthostatic hypotension at higher incidence compared to younger subject with 13.1% vs. 8.9% and 15.1% vs. 12.3% at peak and trough respectively.

Doses < 5 mg were associated with a slightly higher rate of orthostatic hypotension at trough (14.6%) compared to 5 mg (12%) and 10 mg (9%). It seems that there is a dose response effect with the incidence of orthostatic hypotension decreasing as the dose increases.

5.3.1.7.4 Systolic and diastolic blood pressure

Four and 0 of all subjects on NEB experienced a drop below 90 mmHg in standing blood pressure at peak and trough respectively. Sitting systolic blood pressure dropped below 90 mmHg at trough and at peak only in one of all subjects on NEB.

Six and 13 of all subjects on NEB vs. NONE at baseline exhibited an increase in sitting systolic BP > 200 mmHg at peak and at trough respectively.

Three and 7 patients on NEB vs. none on placebo experienced this increase at peak and trough respectively.

A drop in sitting diastolic blood pressure below 60 mmHg was experienced by 19 and 4 of all subjects on NEB at peak and trough respectively vs. none at baseline.

Four subjects at peak and one subject at trough compared to none on placebo had their sitting DBP < 60.

Twenty eight (1.1%) and 67 (2.8%) exhibited sitting diastolic blood pressure > 110 mmHg at peak and trough while only 0.3% did at baseline.

5.3.1.7.5 Conclusion

Nebivolol consistently and significantly caused clinically significant bradycardia at both peak and trough, and this was more prominent in older subjects, males, non-black subjects and poor metabolizers.

Orthostatic hypotension was observed with NEB at a moderate rate and the incidence at peak and trough were not significantly different.

A drop in sitting blood pressure was more observed in diastolic blood pressure.

The incidence of increasing above 200 mmHg for systolic BP and above > 110 mmHg for diastolic BP was greater than that of BP dropping below 90 and 60 for systolic and diastolic blood pressure respectively.

5.3.1.8 Exposure during Pregnancy

Three patients became pregnancy while participating in one of the NEB clinical trials.

One patient was lost to follow-up.

Patient 1553000749 (NEB-202) was a 35- year-old female completing NEB- 202 after receiving 40 mg daily for 84 days. Laboratory test results obtained during her exit examination on — revealed she was pregnant. The date of her last menstrual period was —. The patient had an ultrasound examination on —. The ultrasound report showed values for fetal measurements completed for the biparietal diameter (38.3 mm), femur length (24.1 mm), abdominal circumference (18.1 mm), and head circumference (142.3 mm). No gestational age was recorded. Based on the time of the last menstrual period, the fetus was in the embryonic growth phase, with potential exposure to nebivolol for approximately 32 days. The patient was followed throughout the pregnancy and delivered a healthy baby boy on — with no complications. Sponsor reported having contacted the patient during this review and the baby is doing fine.

Patient 2111002270 (NEB-305 and NEB-306) was a 37 year-old Hispanic female patient in the US previously enrolled in NEB-302 on 19 Feb 2002 and in NEB-306 on 12 Jun 2002 and received Nebivolol 5 and 10 mg for hypertension for a total duration of 258 days. On —

— the patient informed the site that she was pregnant and her blood was collected for the serum pregnancy assay (qualitative human chorionic gonadotropin- HCG) and study drug was discontinued. The patient also took a urine pregnancy test at the investigator's office and it was negative. The test was repeated and again the result was negative. However, on — the HCG result was reported positive. The patient's last menstrual period was on — . The patient carried the pregnancy to full term and delivered a baby girl on —, without complications. Sponsor reported having contacted the patient during this review and the baby is doing fine.

5.3.1.9 Experience with overdose

Two cases of overdose were reported with one from the postmarketing pharmacovigilance database and the other from the literature.

The first one concerns an attempt of suicide in a 61-year old female who consumed 200 mg of NEB along with cisapride, acetylsalicylic acid, diclofenac, and gallo sanol. She developed hypotension, dizziness and tiredness. The patient recovered after gastrolavage with charcoal was at the hospital.

The second one, from the literature: Heinroth KM, Kuhn C, Walper R, Busch I, Winkler M, Prondzinsky R, was also an attempted suicide through acute poisoning with nebivolol. A 17-year old normal- size (168 cm; 70 kg) German diabetic female swallowed 80- 100 tablets of nebivolol 5 mg (parent's medication), several 100- mg tablets of acetylsalicylic acid, 9 IUs of Actrapid (short- acting soluble human insulin) and 2 IUs Actraphane (insulin human recombinant). The patient was seen in the emergency room and referred to the author 8 hours after ingestion of the medication.

Eight hours after the attempt, the patient had reduced vigilance, slow motor functions, pale and sweaty skin, borderline hypotension (105/ 55 mmHg) and a sinus bradycardia of 55 beats/ min with normal cardiac function. Serum potassium and glucose were low (3.4 mEq/ L and 2.1 mmol/ L, respectively), and leucocytes were elevated at 12,200/ mcL. Capillary blood gas showed respiratory acidosis and ketone bodies and protein were detected in the urine. Other physical and laboratory findings were unremarkable. The patient was diagnosed with "acute ß1-adrenergic antagonist", hypotension, and sinus bradycardia with a normal cardiac function, respiratory global insufficiency and hypoglycemia.

The plasma level of nebivolol (by HPLC) was 480 ng/mL at the time of admission, about 8 hours after tablet ingestion (the maximum plasma concentration 2 to 4 hours after a therapeutic dose is 88- 195 ng/ mL). The levels decreased to 240 ng/mL at 18 hours, 84 ng/ mL at 26 hours and at detection threshold of 25 ng/ mL at 48 hours. The level of acetylsalicylic acid was at nontoxic level of 8.8 mcg/ mL at 8 hours. Treatment consisted of warm- water gastric lavage with charcoal and sodium sulphate (every 6 hours for 24 hours), 3L of O2 per min by nasal canula, a temporary pacemaker, arterial blood pressure monitoring, intravenous potassium with insulin and glucagon (for 14 hours). The patient recovered and was discharged after 48 hours.

5.3.1.10 Worldwide Post-Marketing Pharmacovigilance

Table 44. Post marketing reports of adverse events

Preferred Term	Received up to 4/30/03	Received 5/01/03 to 6/30/03	Received up to 6/30/04
Blood and Lymphatics	5	0	5
Hemoglobinemia	1	0	1
Iron deficiency	2	0	2
thrombocytopenia	3	0	3
Cardiovascular Disorders			
Any	135	11	146
Angina pectoris	5	0	5
Arrhythmia NOS	5		5
Bradycardia	92	4	96
Cardiac arrest	1	1	2
Cardiac failure NOS	4	1	5
Cardiogenic shock	1	1	1
Circulatory collapse	1	0	1
MI	2	0	2
Pulmonary edema	2	1	3
Tachycardia	3	2	5
Ventricular arrhythmia	1	1	1
Orthostatic hypotension	1	1	2
Hypotension NOS	13	3	16
Special Sense Disorders			
Eye Disorders	13	3	16
Any	6	1	7
Visual disturbance	6	1	7
NOS	1	0	1
Blindness transient	0	1	1
Visual acuity reduced			
Gastrointestinal Disorders			
Any	70	5	75
Constipation	10	0	10
Diarrhea	12	1	13
Dyspepsia	11	0	11
Vomiting	6	0	6
Nausea	24	2	26
General Disorders			
Any	107	5	112
Death NOS	2	0	2
Sudden death	2	0	2
Asthenia	11	1	12

Preferred Term	Received up to 4/30/03	Received 5/01/03 to 6/30/03	Received up to 6/30/04
Chest pain	8	0	8
Chest pressure sensation	3	0	3
Chest tightness	2	0	2
Condition aggravated	3	1	4
Drug interaction NOS	8	0	8
Fatigue	47	2	49
Edema peripheral	9	1	10
Malaise	7	0	7
Hepatobiliary Disorders			
Hepatic failure	1	0	1
Jaundice NOS	1	0	1
Immune system disorders			
Allergy aggravated	1	0	5
Hypersensitivity NOS	5	0	1
Infections and infestations, Any	4	0	4
Injury, poisoning			
Any	8	0	8
Overdose	3	0	3
Investigations			
Any	16	7	23
ECG			
QRS complex	1	0	1
prolonged	1	0	1
T wave inversion	2	0	2
ECG abnormal NOS	0	1	1
GGT ↗	4	2	6
Liver function tests NOS	0	1	1
abnormal	0	1	1
Prothrombin time ratio ↘			
Transaminases ↗			
Metabolism and nutrition			
Any	9	1	10
Fluid retention	1	0	1
Hyperkalemia	1	0	1
Hypokalemia	1	0	1
Hypoglycemia	5	1	6
Lipid metabolism disorder	1	0	1
NOS	1	0	1
Metabolic acidosis			
Musculoskeletal and connective tissue			

Preferred Term	Received up to 4/30/03	Received 5/01/03 to 6/30/03	Received up to 6/30/04
Myalgia	4	1	5
Neck pain	2	0	2
Peripheral swelling	1	0	1
Nervous system disorders			
Any	133	12	145
Cerebrovascular accident	3	0	3
Syncope	3	1	4
Headache	44	3	47
Dizziness	67	0	67
Dizziness postural	3	0	3
Dysgeusia	2	2	4
Hypoglycemic coma	0	2	2
Loss of consciousness	1	1	2
Parasthesia	11	1	12
Psychiatric Disorders			
Any	41	4	45
Anxiety	3	0	3
Nervousness	5	0	5
Confusional state	2	0	2
Hallucinations	1	1	2
Sleep disorders	4	0	4
Nightmares	7	1	8
Depression	8	0	8
Depression aggravated	1	0	1
Suicide ideation	0	1	1
Suicide attempt	2	0	2
Libido decreased	4	0	4
Reproductive system and breast disorders			
Any			
Amenorrhea/Metrorrhagia	1	1	2
Breast pain			
Hot flushes	0	1	1
Erectile dysfunction NOS	25	2	27
Respiratory and thoracic disorders			
Apnea	1	0	1
Asthma	2	0	2
Asthma aggravated	1	1	2
Bronchospasm	6	1	7
Bronchospasm aggravated	15	0	15
Dyspnea NOS	35	1	36

Preferred Term	Received up to 4/30/03	Received 5/01/03 to 6/30/03	Received up to 6/30/04
Dyspnea exacerbated	1	0	1
Respiratory distress	6	0	6
Respiratory failure	1	0	1
Skin and subcutaneous tissue			
Any	49	10	59
Exanthema	5	1	6
Pruritus	11	0	11
Psoriasis aggravated	5	0	5
Rash	5	1	6
Sweating increased	9	3	12
Angioedema			
Any	7		7
Edema of the mouth	1	0	1
Edema of the tongue	1	0	1
Edema of the face	2	0	2
Angioneurotic edema	3	0	3
Vascular disorders			
Flushing	4	0	4
Peripheral coldness	9	0	9
Raynaud's phenomenon	1	2	3
Shock	1	0	1

A total of 11 deaths are not listed in the above table because per the sponsor they were reported as outcome not as adverse events.

With the understanding of the limitations of spontaneous post-marketing reporting in mind, the reviewer comments on the following:

QT prolongation

Torsade de Pointes: There were two cases of sudden death listed in this table, one case of ventricular arrhythmia but no reports of Torsade de Pointes. This is somewhat reassuring, given that the wide spread understanding of the association between QT prolongation and the Torsade de Pointes.

Liver function

LFTs: the report of 6 cases of LFTs abnormalities along with the known relation of other betablockers with this adverse event substantiates the hint of an association that was observed between NEB and the effect of increasing ALT and AST in the Bertek primary program;

Blood and lymphatics

Aplastic anemia: Lack of reports of aplastic anemia while 3 cases of thrombocytopenia were reported is also somewhat reassuring given the gravity of the former and likelihood of its report had it occurred;

Thrombocytopenia: The report of the 3 cases substantiates the association of NEB with the observed effect of decreasing platelet count;

Nervous system disorders: syncope was not observed in the primary program but 4 cases are reported in postmarketing vigilance;

Respiratory disorders:

Bronchospasm: Although no confirmed cases were reported and only one case of asthma aggravated was observed in the primary program, this is believed to be a potential adverse effect of NEB because first it is mechanistically plausible and because 7 cases of bronchospasm, 4 cases of asthma/asthma aggravated, 6 cases of respiratory distress and one case of respiratory failure were reported in the postmarketing reports;

Skin and subcutaneous tissue

Angioedema: The report of 7 cases of in the post marketing program adds to the hint of a possible association as a result of the one confirmed case and the potential 4 cases in the NEB primary program.

Pruritus/rash: The reports of rash in 6, pruritus 11 and exanthema in 6 in addition to association of these events with other betablockers, substantiates the association observed in the primary program between NEB and rash and pruritus;

5.3.2 Adequacy of Patient Exposure and Safety Assessments

5.3.2.1 Description of Primary Clinical Data Sources

Seven clinical trials were initiated by Bertek to assess the efficacy and safety of nebivolol in comparison to placebo (studies 202, 302, 305 and 321); in comparison to atenolol (study 203); and in long-term exposure (studies 306 and 323).

5.3.2.1.1 For detailed description of the individual trials, please refer to Dr. Hicks Review.

5.3.2.1.2 Study type and design/patient enumeration

Table 45. Pivotal studies conducted under the Primary Program

Placebo-controlled trials						
Protocol no	**Design and type**	**Type of subjects**	**P**	**NEB**	**Days**	**Dose in mg**
NEB-202 N = 300	R, DB, PC	Blacks with HT	49	251	84	2.5, 5, 10, 20 and 40
NEB-302 N = 901	R, DB, PC	95 ≤ SDBP ≤ 109	81	251	84	1.25, 2.5, 5, 10, 20 and 30/40
NEB-305 N = 807	R, DB, PC	95 ≤ SDBP ≤ 109	75	828	84	5, 10, 20
NEB-321	R, DB, PC	95 ≤ SDBP ≤ 109	167	732	84	5, 10 and 20

N = 669						
Active-controlled trial						
Protocol N	**Design and type**	**Type of subjects**	**Atenolol N**	**NEB N**	**Days**	**Dose in mg**
NEB-203 N= 115	R, DB, AC	HT	45	70	28	5, 10 and 20
Extension trials						
Protocol N	**Design and type**	**Type of subjects**	**Treatment**			**Dose in mg Duration**
			NEB N	**NEB/ Diuret. N**	**NEB/ CCB N**	**NEB/ Other N**
NEB 306 N = 845	OL, LT	Completed NEB 202, 302, 305	607	206	21	06	5, 10, 20 mg up to 9 months
NEB 323	OL, LT	Completed NEB-306	85				5 → 10 → 20 mg up to 24 months

5.3.2.1.3 Demographics of patients in placebo-controlled trials

Table 46. Demographic and baseline medical characteristics

Patient Characteristics	Placebo N = 372	Nebivolol N = 2313
Demographic Characteristics		
Age		
Mean (SD)	53.4 (10.4)	53.7 (11.3)
(Min, Max)	(24, 80)	(19, 86)
Age Group – n (%)		
< 65	315 (84.7)	1892 (81.8)
≥ 65	057 (15.3)	0421 (18.2)
Gender – n (%)		
Male	199 (53.5)	1255 (54.3)
Female	173 (46.5)	1058 (45.7)
Race – n (%)		
Black	119 (32.0)	615 (26.6)
Other	253 (68.0)	1698 (73.4)
Genomic classification – n (%)		
Poor metabolizers	17 (4.6)	135 (5.9)
Extensive metabolizers	350 (95.4)	2168 (94.1)
BMI		
Mean (SD)	29.51 (4.32)	29.38 (4.09)

Patient Characteristics	Placebo N = 372	Nebivolol N = 2313
(Min, Max)	(14.99, 46.23)	17.37, 43.00)
Cumulative exposure (days)		
Mean (SD)	77.6 (21.27)	78.6 (20.02)
(Min, Max)	(1, 99)	(1, 112)
Medical history		
Current smoking history	85 (22.8)	526 (22.8)
Diabetic history	43 (11.6)	219 (9.5)
On Insulin therapy	29 (7.8)	132 (5.7)
Average daily dose of NEB (mg)		
Mean (SD)	NA	13.4 (10.61)
Cumulative duration of dosing (days)		
Mean (SD)	77.6 (21.27)	78.6 (20.02)
(Min, Max)	(1, 99)	(1, 112)

Although the mean age is similar in both groups, the proportion of people 65 or older is higher on NEB 18.2% vs. 15.3% on placebo.

The placebo group on the other hand has a slightly higher proportion of diabetic subjects 11.6% vs. 9.5%, and the proportion of diabetics in the placebo group on insulin therapy is also slightly higher than in the NEB group 7.8% vs. 5.7%.

5.3.2.1.4 Extent of exposure (dose/duration)

Table 47. Drug exposure in placebo-controlled trials

Duration Days	Placebo N = 373	Nebivolol mg						
		1.25 N = 83	2.5 N =133	5 N =629	10 N =631	20 N = 628	30/40 N = 217	All NEB N= 2321
≤ 14	16 4.29%	02 2.41%	6 4.51%	25 3.97%	29 4.60%	23 3.66%	9 4.5%	94 4.05%
15 - 28	10 2.68%	03 3.61%	7 5.26%	14 2.23%	15 2.38%	11 1.75%	5 2.30%	55 2.37%
29 - 56	25 6.7%	06 7.23%	7 5.26%	19 3.02%	33 5.23%	24 3.82%	8 3.69%	97 4.18%
57 - 84	89 23.86%	22 26.51%	25 18.80%	140 22.26%	150 23.77%	161 25.64%	41 18.89%	539 23.22%
>89	233 62.47%	50 64.03%	88 66.17%	431 68.52%	404 64.03%	409 65.13%	154 70.97%	1536 66.18%

Patients entering the long-term study were assigned to start NEB at 5, 10 or 20 mg daily based on the average sitting DBP, average HR and previous NEB dose. Titration was allowed for patients who did not respond to their original assigned dose level in the

feeder study. Patients received NEB either as monotherapy or in combination with other anti-hypertension medications. By the end of the study, 607 (71.8%) patients were on NEB monotherapy, 206 (24.4%) were on NEB + diuretic, 21 (2.5%) were on NEB + CCB, and 11 (1.3%) were on NEB + other medication.

Table 48. Duration of exposure in the long-term trial (days)[12]

Duration	Nebivolol N = 607 n (%)	Nebivolol + Diuretic N = 206 n (%)	Nebivolol + CCB N = 21 n (%)	Nebivolol + Other N = 11 n (%)	Total N = 845 n (%)
Mean (SD)	178.1 (96.1)	231.0 (54.1)	199.3 (65.6)	231.2 (60.3)	192.2 (89.5)
Median	203.0	256.0	203.0	247.0	221.0
Range	1.0 to 330.0	27.0 to 303.0	4.0 to 282.0	61.0 to 281.0	1.0 to 330.0
0 - 90 Days	146 (24.1)	4 (1.9)	1 (4.8)	1 (9.1)	152 (18.0)
91 - 180 Days	107 (17.6)	28 (13.6)	8 (38.1)	0 (0.0)	143 (16.9)
181 - 270 Days	171 (28.2)	83 (40.3)	7 (33.3)	7 (63.6)	268 (31.7)
271 - 360 Days	183 (30.1)	91 (44.2)	5 (23.8)	3 (27.3)	282 (33.4)
≥ 361 Days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

5.3.2.1.5 Patient Disposition

Table 49. Patient Disposition in the randomized placebo-controlled trials

Study Status	Placebo	Nebivolol
All Patients[13]		
N	372	2313
Completed – n (%)	315 (84.7)	2021 (87.4)
Discontinued – n (%)	57 (15.3)	292 (12.6)
AEs	8 (2.2)	64 (2.8)
Treatment Failure	14 (3.8)	34 (1.5)
Protocol Deviation	3 (0.8)	16 (0.7)
Loss to Follow-up	7 (1.9)	50 (2.2)
Withdrew Consent	20 (5.4)	88 (3.8)
Other	5 (1.3)	40 (1.7)
Disposition by Specific Subgroups [14]		
N	205	1811
Discontinued		
PM (P: 8; NEB: 108)	00	15 (13.9)

[12] Table completed by sponsor

[13] Data from all randomized, placebo-controlled trials

[14] Data from placebo-controlled, monotherapy trials

Study Status	Placebo	Nebivolol
EM (P: 197; NEB: 1703)	36 (18.3)	227 (13.3)
Diabetics (P: 17, NEB: 151)	2 (11.8)	31 (20.5)
Non-Diabetics	34 (18.1)	211 (12.7)
< 65 years (P: 175; NEB: 1466)	34 (19.4)	193 (13.2)
≥ 65 years (P: 30; NEB: 345)	2 (6.7)	49 (14.2)
Discontinued for AEs		
Males	1 (0.9)	19 (1.9)
Females	3 (3.1)	28 (3.4)
Black	00	9 (1.9)
Non-black	4 (3.0)	38 (2.8)
Age > 65	00	14 (4.1)
Diabetic patients	2 (1.7)	23 (3.7)
Lost to follow-up		
Blacks	01 (1.4)	20 (4.3)
Other races	2 (1.5)	24 (1.8)
< 65 years (P: 175; NEB: 1466)	3 (1.7)	43 (2.9)
≥ 65 years (P: 30; NEB: 345)	00	01 (0.3)
Treatment failure		
Black	7 (9.9)	12 (2.6)
Non-black	4 (3.0)	20 (1.5)
Withdrew Consent		
Diabetics	00	9 (6.0)
Non-Diabetics	10 (5.3)	58 (3.5)

Age: Elderly patients on NEB discontinued at a higher rate 49 (14.2%) than those on placebo 2 (6.7%), but this rate was not higher than that of younger people on NEB 193 (13.2).

Younger placebo subjects however discontinued at a higher rate 34 (19.4%) than younger subjects on NEB and 3 times higher than elderly subjects on placebo.

Diabetes: Diabetic patients on NEB discontinued at higher rate than their placebo counterpart 31 (20.5%) vs. 2 (11.8%) and than non-diabetic subjects on NEB 211 (12.7). Twenty three (3.7%) of these discontinued as a result of adverse events compared to diabetics on placebo 2 (1.7%).

Six percent (9) of the diabetic patients on NEB withdrew consent compared to none on placebo and to 3.5% (58) of non-diabetic subjects on NEB.

Genomics: Fifteen (13.9%) PM on NEB discontinued vs. none on placebo, but this is not different from the rate observed among the EM on NEB (13.3%). Also, the number of PM on placebo is small 8, which might explains why there wee no withdrawals.

Gender: Although males discontinued at a lower rate for adverse events than females, males on NEB discontinued at twice the rate of those on placebo.

Race: Blacks on NEB were more likely to be lost to follow-up compared to blacks on placebo and non-blacks on NEB, 20 (4.3%) vs. 1 (1.4%) and 24 (1.8) respectively.

Table 50. Patient disposition in the long-term trial[15]

Patient disposition	Nebivolol	Nebivolol + Diuretic	Nebivolol + CCB	Nebivolol + Other	Total N (%)
Completed	268 (44.2)	110 (53.4)	7 (33.3)	8 (72.7)	393 (46.5)
Discontinued					
Total	339 (55.8)	96 (46.6)	14 (66.7)	3 (27.3)	452 (53.5)
Adverse Event	26 (4.3)	4 (1.9)	1 (4.8)	0 (0.0)	31 (3.7)
Treatment Failure	13 (2.1)	4 (1.9)	0 (0.0)	0 (0.0)	17 (2.0)
Lost to Follow-up	32 (5.3)	6 (2.9)	0 (0.0)	0 (0.0)	38 (4.5)
Protocol Deviation	7 (1.2)	1 (0.5)	0 (0.0)	1 (9.1)	9 (1.1)
Withdrew Consent	47 (7.7)	8 (3.9)	1 (4.8)	0 (0.0)	56 (6.6)
Other	214 (35.3)	73 (35.4)	12 (57.1)	2 (18.2)	301 (35.6)

As can be seen from the table above, more than half the people on NEB discontinued from the study. Compared to subjects on the combination NEB/diuretics, subjects on NEB alone discontinued at a greater rate for all reasons except for "other" reason where the rates were similar.

5.3.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety[16]

Total of 39 studies in HTN were conducted in the Jansen program with a total of 3,840 hypertensive subjects 66% of whom received NEB. These studies were conducted in 18 countries in Europe, North America, South America, South Africa, Asia (Hong Kong) and Australia.

Most of the information in this review comes from a small proportion of these patients, especially information concerning death and SAEs. This is because no datasets were submitted for the non-IND studies, and those that were submitted for IND 33060 were done informally and the sponsor would not guarantee their accuracy.

[15] Table completed by sponsor

[16] All information on the secondary program came from Reports with no raw data to back it up

5.3.2.2.1 Secondary Program, IND 33-060 (placed on inactive status in 1994)[17]

Table 51. Hypertension Studies conducted under IND 33-060

Protocol	Dose	Duration	Design	Type of subjects	N
INT-1 USA	0.5, 1, 2.5, 5 or 10 mg	4 W	R, DB, PC	95 ≤ DBP ≤ 114 mmHg	254
USA-1	5 →10 mg	NEB 4 W Placebo 10 W	R, DB, PC & AC	95 ≤ DBP ≤ 109 mmHg	32
USA-3	30 mg	2 W	R, DB, PC	95 ≤ DBP ≤ 114 mmHg	12
USA-4	2.5, 5, or 30 mg	1 M	R, DB, PC	95 ≤ DBP ≤ 114 mmHg	180

5.3.2.2.2 Secondary Program, Dose-Finding Data

Table 52. Number of patients with dose-finding data

Trial	Duration Weeks	Number of Patient							
		Placebo	0.5 mg	1 mg	2.5 mg	5 mg	10 mg	30 mg	Total
INT-1	4	84	83	87	85	86	84	--	509
BEL-12/18	4	41	37	41	42	42	--	--	203
BEL-3/6	4	33	--	--	35	34	32	--	134
USA-4	4	46	--	--	46	44	--	44	180
CAN-3	12	20	--	20	--	20	30	--	80
Total	--	224	120	148	208	226	146	44	1106

5.3.2.2.3 Secondary Program, Therapeutic-Dose Data

Table 53. Number of patients with therapeutic-dose data

Protocol no	Duration weeks	All NEB	PC	5 mg	AC
INT-1	4	86	84	86	--

[17] Data from the secondary program is portrayed here as it was summarized in a report provided with the submission

Protocol no	Duration weeks	All NEB	PC	5 mg	AC
BEL-12/18	4	42	41	42	--
BEL-3/6	4	34	33	34	--
USA-4	4	44	46	44	--
CAN-3	12	20	20	20	20
GBR-1	4	119	124	119	119
NED-12/8	8	74	40	74	--
INT-5	12	211	--	--	211
INT-3	12	208	--	--	208
FRA-5	6	12	--	--	12
Total		932	388	419	652

5.3.2.2.4 Secondary Program, Long-term Treatment Data

Table 54. Long-treatment data in the secondary program

Phase	Time (months)	Number of patients	
		In trial	Assessed
Run-in	end	596	596
Long-term	3	686	526
	6	544	503
	9	526	410
	12	506	391
	18	480	339
	24	453	245
	30	441	258
	36	432	213

Exposure to doses of NEB in the long-term studies was 4.5% (27) to 2.5 mg, 87.2% (520) to 5 mg, 7.2% (43) to 7.5-10 mg, and 1.0% (6) to 15 to 20 mg.

Percentage of time that the 5 mg dose was taken: < 10% in 6.2%; 10-89% in 7.6%; 90-99% in 10.2% and 100% of the time in 76% of the patients.

5.3.2.2.5 Listing of trials in the SP where death and SAE information were unknown

Table 55. Enumeration of Trials in which Death and SAE information are Unknown

Protocol no	Duration	Number of patients		Exposure Treatment	SAEs	Deaths
		AC or P	NEB			
INT-1	PC: 4 W	84	425	NEB 0.5 to 10 mg:	Unk	Unk
GBR-1 UK	AC: 4 W OL: 3 years	124+121	119	Neb 5 mg Atenolol 50 mg	Unk	Unk
ITA-3	CP: 6 months	24	24	Neb mg	Unk	Unk
TCH-1/2	CP: 3 M OL phase: 3 years	73	82	NEB 5 mg OL: 97	Unk	Unk
INT-3	CP: 3M	211	208	NEB 5 mg	2	Unk
INT-4	AC, CO: 4 W OL: 36 M	35	35	NEB 5 mg d-NEB 2.5 mg l-NEB 2.5 mg	Unk	Unk
INT-7	CP: 7 M	81	82	NEB 5 mg	2	Unk
GER-12	CP: 8 W	27	41	NEB 5 mg	0	Unk
INT-5	CP: 3 M	209	211	NEB 5 mg	Unk	Unk
CAN-9	CP: 4 W	30	30	NEB 5 mg d-NEB 2.5 mg	Unk	Unk
RSA-6	CP: 14 D	21	21	NEB 5 mg	1	Unk
NED-12/8	PC: 4 W NEB solution: 2 M OL: 12-36 M	114	114	NEB 5 mg NEB solutions	Unk	Unk
NED-13/10	PC: 2 W OL: 14 W	19	19	NEB 5 mg	Unk	Unk
CAN-10	OL: 12 W		37	NEB 5 mg	0	Unk
GER-5	PC: 4 W	15	30	NEB 2.5 or 5 mg	Unk	Unk
CAN-3	AC + PC: 12 W	60	180	NEB 1, 5 or 10 mg NEB/HCT	1	Unk
CAN-6	AC: 8 W	4	30	NEB 2.5 to 10 mg	1	Unk
POR-1/5	OL: 4 W	--	133	NEB 2 – 5 mg: 81	Unk	Unk

Protocol no	Duration	Number of patients		Exposure Treatment	SAEs	Deaths
		AC or P	NEB			
	OL: 12 to 24 M					
MEX-1	SB: 1 year	--	42	NEB 5, 7.5 or 10 mg	Unk	Unk
BEL-23	OL: 1 W	--	22	NEB 10, 15, 20 mg	Unk	0
NED-4	OL: 1 W	--	12	NEB 2.5 or 7.5 mg	Unk	Unk
NED-9	OL/DI: 4 W	--	10	NEB 10, 15, 20 mg	Unk	Unk
NED-1	SB/DI: 1-2 W	--	10	NEB 2.5, 5 mg	Unk	Unk
AUS-3	DB, AC, CO 4 W	5	13	NEB 5 mg,	2	Unk
AUS-5	DB, AC & PC, CO 1 W	20	20	NEB 5 mg NEB 10 mg	0	Unk
MEX-2	DB, AC, CO 4 W	14	14	NEB 5 mg	Unk	Unk
GER-9	DB, PC	8	23	NEB 5 mg, l-NEB 2.5 mg d-NEB 2.5 mg	Unk	Unk
ARG-1	DB 8 W	15	15	MEB 5 mg	Unk	Unk
FRA-5	DB, AC, CO 4 W	12	12	NEB 5 mg	Unk	Unk
BEL-11	OL 2 years	--	37	5 mg	Unk	Unk
GER-2	OL 1 W	--	22	NEB 5 mg	Unk	Unk
BEL-10	DB, PC, CO 4 W	23	23	5 mg solution	Unk	Unk
HKG-2	DB, PC 4 W	14	18	5 mg	Unk	Unk

5.3.2.3 Other studies

Table 56. Non-IND Studies in non-hypertensive patient

Study #	Study Type	Phase	Condition	Entered	Received NEB
BEL-46	Dose-Ranging	II	Ischemic LV dysfunction	41	20
RSA-8	Dose-Ranging	II	Dilated CM	24	11
SWE-2	Dose-Ranging	II	Angina	12	12
TCH-4	Dose-Ranging	II	CHF	91	62
FRA-7	Active-control	III	Obese subjects	19	19
BEL-14	Active-control	II	History of MI	40	20
BEL-24/41	Active-control	II	History of MI	40	31
BEL-28	Active-control	II	Post CABG with altered LV	30	15
BEL-42	Active-control	II	CABG	49	49
NED-14	Active-control	II	Post MI with LV dysfunction	28	13
TCH-3	Active-control	II	LV dysfunction	20	20
GER-7	Active-control	I	CAD with stable angina	24	12
FRA-3	Placebo-control	II	CHF	12	12
ITA-1	Placebo-control	I	Exertion Angina	16	16
BEL-33	Open-Label	II	LV diastolic dysfunction	12	12
GEL-34	Open-Label	II	Acute CHF	5	5
GER-1	Open-Label	II	CHF	10	10
GER-10	Open-Label	II	Ischemic CAD	7	7
Total (18 studies)				485	346

5.3.3 Listing of Deaths

Table 57. Listing of deaths in the Primary Program

Study	Subject	age	sex	Treatment	Days	History
NEB-203	3315001384	46	M	10 mg	48	AMI
NEB_321	6813210015	75	F	5 mg	15	MI and Cardiac death

Table 58. Listing of deaths in hypertension trials under IND-33-060

Study	Subject	Age	Gender	Treatment	Trial period Days	Adverse event
USA – 4	0421	52	M	N 30 mg	DB; Ukn	Cardiovascular collapse Death[18]

Table 59. Listing of deaths in hypertension Non-IND trials

Study	Subject	Age	Gender	Treatment	Trial period; Days	Adverse event
Deaths occurring during a controlled phase of the trial[19]						
ITA-3	03	64	M	5 mg	DB; 163 days	Severe circulatory collapse
INT-8	42	68	M	5 mg	Run-out; 281	Aortic dissection
GBR-2	Unk	66	F	P[20]	CO; Unk	MI
Deaths occurring during open-label extension trials						
BEL-12/18	231	57	M	10 mg	OL; 868 days	MI
BEL-12/18	13	67	M	10 mg	OL; 445 days	CVA
BEL-12/18	216	54	F	5 mg	OL; 713	Liver cirrhosis
BEL-12/18	66	72	F	5 mg	OL; 749 days	CO poisoning
BEL-3/6	111	73	M	5 mg	OL; 643 days	Bronchial cancer

Table 60. Listing of deaths in non-hypertension, non-IND studies

Study	Subject	Age	Gender	Treatment	Trial period; Days	Adverse event
TCH-4	57	55	M	2.5 mg	DB; 34 days	Sudden death
RSA-8	19	56	M	5 mg	DB; 26 days	Sudden death
TCH-4[21]	Unk	64	M	5 mg	After TCH-4	Sudden death

[18] Redefined by reviewer as such because autopsy report does not support reported cause of death of alcohol intoxication and asphyxiation by vomit aspiration; See 5.3.6.2.1; page 95
[19] Information about death is not complete because Death data was missing in many studies (studies where death and SAEs events were reported as unknown are listed in Table 55, page 84)
[20] Patient received NEB in previous phase

Study	Subject	Age	Gender	Treatment	Trial period; Days	Adverse event
TCH-4[21]	Unk	51	M	2.5 mg	After TCH-4	Sudden death
RSA-8	Unk	24	F	P	DB; Unk	Sudden death
TCH-4	Unk	43	M	P	PRI; Unk	MI

Table 61. Listing of postmarketing deaths

Subject	Age	Gender	Dose / Duration	Indication / Condition	Cause of death
EMAD613	70	M	5 mg / 7 months	HTN	Sudden death
MENIT43883	71	M	2.5 mg / 3 days	HTN	Sudden death
EMAD7072	81	F	2.5 mg / 25 days	CHF	MI
EMA6744	75	F	5 mg / 6 days	HTN	MI
JRFBEL1191	85	M	1 mg / Unk	CHF	Basic disease
JRFBEL1193	54	F	Neb / Unk	Unk	MVA
JRFBEL1194	68	M	Neb / 416 days	CHF	??
JRFBEL1195	70	M	5 mg / Unk	HTN	Bronchial carcinoma
MENIT42428	73	M	5 mg/10 months	CHF + HTN	Sudden death
MENIT42429	74	F	5 mg/Unk	CHF + HTN	Severe bradycardia Cerebral embolism
MENIT42431	79	F	Unk/28 days	CHF	Stroke + pneumonia

5.3.4 Listing of Serious Adverse Events

Table 62. Listing of all serious adverse events in the Primary Program

Study	Subject	Age	Sex	Dose	Days	Adverse event
NEB_302	2571000714	54	M	30/40	85	ECG, ST segment abnormal
NEB_202	2203000950	52	M	30/40	17	Bladder cancer
NEB_202	2053000150	64	F	30/ 40	89	Chest pain
NEB_321	7393210001	54	M	20	55	Chest pain & angioplasty + bleeding gastric ulcer
NEB_305	7332000886	79	F	20	31	Withdrawal arrhythmia
NEB_306	7272001051	42	M	20	90	Erectile dysfunction
NEB_305	7272000566	61	M	20	85	Leucopenia
NEB_321	7193210004	62	F	20	48	Ischemic colitis
NEB_305	7102001373	51	M	20	42	Headache
NEB_305	7092000576	46	F	20	31	DVT

[21] Patients received NEB under compassionate use

Study	Subject	Age	Sex	Dose	Days	Adverse event
NEB_306	7052001753	45	M	20	323	Viral infection NOS
NEB_321	6243210022	55	F	20	84	Congestive cardiac failure
NEB_321	6213210003	60	F	20	41	Small cell lung cancer
NEB_306	2691002033	35	M	20	134	Ureteric stenosis
NEB_306	2632001686	71	M	20	108	Bradycardia
NEB_306	2571003527	74	F	20	113	Instable Angina
NEB_302	2571000326	49	F	20	85	ECG, T wave abnormal
NEB_302	1981005683	52	F	20	83	Appendicitis, perforated
NEB_302	1981005683	52	F	20	85	Staphylococcal infection NOS
NEB_305	1652004187	46	F	20	31	Orthostatic hypotension
NEB_302	1571000166	67	f	20	33	Intermittent claudication
NEB_306	1542002986	73	F	20	182	Vertigo, positional
NEB_305	1432000330	65	F	20	43	Bradycardia
NEB_302	1411008463	59	F	20	3	AMI
NEB_305	1132000282	54	F	20	8	Chest pain + NOS ECG changes
NEB_306	7052001462	82	M	10	185	Lung squamous cell carcinoma
NEB-203	3315001384	46	M	10	19	AMI[22]
NEB_306	2741000101	59	F	10	210	Breast cancer
NEB_306	2063001141	46	M	10	126	Influenza + blood pressure increased
NEB_305	1812000449	66	M	10	44	Severe bradycardia and CHF
NEB_305	1662004984	50	M	10	45	Dysphagia
NEB_305	1642003972	65	M	10	61	Rash
NEB_306	1621001629	62	M	10	242	Throat cancer
NEB_306	1621000756	71	F	10	103	Bladder diverticulum
NEB_306	1551001288	64	F	10	318	Amnesia
NEB_302	1411001285	64	M	10	8	Hepatitis A
NEB_306	1301001539	40	F	10	194	Abdominal pain, upper
NEB_305	1182001648	62	F	10	23	Shortness of Breath
NEB_306	2632000231	50	F	10	213	Colon Cancer
NEB_305	7242001376	41	M	5?	54	MI
NEB_305	7242000988	66	M	5	81	Aortic aneurysm ruptured
NEB_321	6813210015	75	F	5	3	MI and Cardiac death
NEB_321	6603210016	73	F	5	24	Bursitis infective NOS
NEB_321	6413210046	70	M	5	45	Dyspnea NOS, Wheezing
NEB_321	6323210016	57	M	5	39	SVT
NEB_306	2571002557	59	M	5	252	Gastroenteritis

[22] Reviewer reclassified this event from pericarditis to AMI; for more information see 5.3.6.1 Deaths in the Primary Program; page 95

Study	Subject	Age	Sex	Dose	Days	Adverse event
NEB_202	2203001920	46	F	5	55	Cerebral hemorrhage
NEB_202	2203001726	60	F	5	5	Road traffic accident
NEB_302	1451005249	69	M	5	65	Colon cancer
NEB_305	1232005342	55	F	5	28	ECG Q wave + ST segment elevation
NEB_202	2613000841	39	M	5	1[23]	Chest Pain
NEB_302	1981003452	46	F	2.5	86	Cholecystitis NOS
NEB_302	1971000424	36	M	2.5	34	Appendicitis
NEB_302	1611000153	52	F	2.5	48	Road traffic accident
NEB_302	1371003335	42	M	1.25	58	Unstable angina
NEB_321	7233210011	49	M	P	94	Atrial fibrillation
NEB_302	6973210017	49	F	P	70	AMI + cardiorespiratory arrest
NEB_321	6243210017	51	M	P	68	Schizo-affective disorder
NEB_305	2942001367	61	F	P		Headache
NEB_305	1662004596	52	F	P		Fatigue
NEB_305	1662003432	57	F	P		DM aggravated
NEB_302	1471000344	44	M	P	15	Back pain
NEB_305	1232002917	59	M	P		AF
NEB_202	2563000542	49	M	Run-in	-21	Prostate cancer
NEB_305	7192000786	59	M	Run-in	-10	Diverticulitis

5.3.5 Listing of adverse events that led to discontinuation

Table 63. Listing of Serious Adverse events in the Secondary Program[24]

Study	Subject	Dose	Days	Adverse event
Bel-12/18	Unk	5	Unk	MI, cardiac failure
Bel-12/18	Unk	5	Unk	Angina pectoris Coronary artery occlusion
Bel-12/18	Unk	5	Unk	Arteriosclerosis
Bel-12/18	18	unk	574	Depression
CAN-3	Unk	5	Unk	atypical chest pain Generalized edema, pruritus,
	Unk	5	Unk	Subarachnoid hemorrhage / action unknown
AUS – 3	ID Unk	Unk		Hemorrhagic stroke / action Unk
Bel-12/18	220	unk	275	Diabetic coma

[23] This patient had chest pain and convulsion during the two-hour surveillance after the first dose. The sponsor reported that it occurred 2 days pre-first dose; see 5.3.7 Narrative of Serious Adverse Events in the Primary Program; page 98

[24] Information about SAEs for many trials is missing from this table because it was reported to be unknown.

Study	Subject	Dose	Days	Adverse event
Bel-12/18	68	5	749	Femoral artery thrombosis
RSA – 6	5	Unk		Broken bone after traffic accident / discontinued
Bel-12/18	186	5	7	Fracture after fall
Bel-12/18	116	unk	369	Hysteria
AUS-3	Unk	5	Unk	Hiatal hernia with esophageal erosion
Bel-12/18	Unk	5	Unk	Hemorrhage complication of melanoma
BEL-3/6	Unk	5	Unk	Breast neoplasm
Bel-12/18	Unk	5	Unk	Hysterectomy
INT-8	3057	5	168	Injury / continued
INT-3	Unk	5	Unk	Subarachnoid hemorrhage
FRA – 6	11	20	63	Depression / discontinued
INT-3	7-710	P[25]	3	Anxiety, palpitation, paranoid reaction
INT-8	2061	P[25]	229	Cerebrovascular disorder

Table 64. Listing of adverse events associated with discontinuation in the PP

Study	Subject	Age	Sex	Dose	Days	History
NEB_302	1371002559	43	F	30/40	24	Angioneurotic edema
NEB_202	2203000950	52	M	30/40	17	Bladder cancer
NEB_202	2463000138	45	F	30/40	33	Bronchitis NOS
NEB_302	2171003754	75	M	30/40	5	Tachycardia NOS
NEB_302	1311000202	42	F	30	66	Dizziness
NEB_202	1643000453	51	F	20	1	Age indeterminate MI
NEB_302	1411008463	59	F	20	3	AMI
NEB_302	1981005683	52	F	20	83	Appendicitis, perforated, W
NEB_306	2451000171	44	m	20		Blood triglycerides increased
NEB_306	2632001686	71	M	20	108	Bradycardia + edema peripheral
NEB_306	2632000425	70	M	20	145	Bradycardia NOS
NEB_306	2632001686	71	M	20	108	Bradycardia NOS
NEB_306	2331003217	58	M	20	109	Bradycardia NOS
NEB_306	2331002344	63	M	20	117	Bradycardia NOS
NEB_305	1432000330	65	F	20	6	Bradycardia NOS

[25] Received NEB in previous phase

Study	Subject	Age	Sex	Dose	Days	History
NEB_321	6763210005	72	M	20	13	Bradycardia NOS
NEB_305	1132000282	54	F	20	8	Chest pain + NOSE ECG changes
NEB_321	6243210022	55	F	20	84	Congestive cardiac failure, W
NEB_305	2942000203	68	F	20	58	Diarrhea
NEB_302	2681000557	68	M	20	29	Dizziness
NEB_306	1682003377	60	M	20	1	Dizziness
NEB_302	1371000910	53	M	20	45	Dyspnea NOS
NEB_321	6023210002	64	M	20	26	Edema peripheral
NEB_306	7272001051	42	M	20	90	Erectile dysfunction
NEB_321	6623210002	69	F	20	1	fatigue
NEB_306	3081000330	37	M	20	55	Fatigue
NEB_	7123210002	56	M	20	1	Fatigue + headache
NEB_305	7102001373	51	M	20	42	Headache
NEB_306	1411005165	62	M	20	112	Headache
NEB_306	1981001415	76	F	20	1	Heart rate decreased
NEB-306	1232002529	59	M	20	165	Hyperkalemia
NEB_302	2151000123	75	M	20	15	Hypoventilation
NEB_302	2181002126		F	20	2	Hypoventilation
NEB_306	2571003527	74	F	20	113	Instable Angina, W
NEB_306	1451004376	48	M	20	182	Malaise
NEB_305	2662001167	74	M	20	16	Muscle weakness
NEB_302	1281000527	64	M	20	48	Nausea
NEB_305	1652004187	46	F	20	31	Orthostatic hypotension
NEB_321	6673210009	47	M	20	15	Platelet count decreased
NEB_306	2181006782	49	M	20	176	Sinus bradycardia
NEB_321	6213210003	60	F	20	41	Small cell lung cancer
NEB_305	2882000950	41	F	20	22	Somnolence
NEB_306	1542002986	73	F	20	182	Vertigo, positional
NEB_306	7292000123	65	F	20	48	Vision blurred, W
NEB_302	1411008269	40	M	10/20	113	Headache
NEB_305	7332000886	79	F	20	1	Withdrawal arrhythmia
NEB_305	1682001534	66	F	10	22	Abdominal pain

Study	Subject	Age	Sex	Dose	Days	History
NEB_302	2691001548	38	m	10	31	Aggravated headache
NEB-203	3315001384	46	M	10	19	AMI[26]
NEB_306	2711000911	47	M	10	267	Bradycardia NOS
NEB_306	1642000868	42	M	10	94	Bundle branch block
NEB_302	2801000324	56	F	10	14	Chest pain
NEB_302	1411006135	55	F	10	14	Chest pain
NEB_306	2632000231	50	F	10	213	Colon Cancer
NEB_	7222000558	10	F	10	36	cough
NEB_305	1662000813	40	M	10	60	Depression + somnolence
NEB_306	1991000757	34	M	10	?	Depression aggravated
NEB_305	1662004984	50	M	10	45	Dysphagia
NEB_306	2331002441	49	M	10	91	Dyspnea NOS
NEB_305	1182001648	62	F	10	23	Dyspnea NOS
NEB_306	3021006024	48	F	10	79	Edema aggravated
NEB_302	2781000864	55	F	10	15	Eye irritation, W
NEB_306	1642003293	41	F	10	64	Fatigue aggravated
NEB_321	6553210003	39	M	10	?	Headache
NEB_302	1411001285	64	M	10	8	Hepatitis A
NEB_306	1053003094	56	M	10		Hepatitis B
NEB_306	7052001462	82	M	10	185	Lung squamous cell carcinoma
NEB_	7052002238	65	M	10	?	Nausea + diarrhea
NEB_305	1682004056	57	F	10	2	Nausea and headache
NEB_	6763210012	64	F	10	78	Meniscus lesion
NEB_302	1961000597	64	F	10	18	Orthostatic hypotension
NEB_	2711002560	54	F	10	57	Phlebitis NOS
NEB_306	2571003236	56	F	10	DB	Proteinuria
NEB_305	1642003972	65	M	10	34	Rash NOS
NEB_305	1812000449	66	M	10	44	Severe bradycardia and CHF, w
NEB_	7143210005	41	M	10	29	Severe disorientation
NEB_302	2391000530	54	M	10	37	Skin irritation

[26] Reviewer reclassified this event from pericarditis to AMI; for more information see 5.3.6.1 Deaths in the Primary Program; page 95

Study	Subject	Age	Sex	Dose	Days	History
NEB_321	7413210008	68	M	10	50	Vertigo, W
NEB_321	6603210050	63	F	10	1	Weakness
NEB_305	7242000988	66	M	5	81	Aortic aneurysm ruptured
NEB_321	6413210024	73	F	5	24	Bursitis infective NOS
NEB_202	2203001920	46	F	5	55	Cerebral hemorrhage
NEB_202	2613000841	39	M	5	1[27]	Chest Pain, w
NEB_321	7013210005	53	F	5	38	Conjunctival hemorrhage, W
NEB_321	6523210003	71	m	5	?	Dizziness + nausea
NEB_321	6413210046	70	M	5	76	Dyspnea NOS, wheezing
NEB_305	1232005342	55	F	5	1	ECG, Q wave, ST segment elevation
NEB_306	2892000389	63	F	5	20	Fatigue
NEB_321	6073210002	76	M	5	5	Flatulence
NEB_321	7253210005	59	F	5	52	Increased BP
NEB_321	6813210015	75	F	5	3	MI and Cardiac death, W
NEB_305	7242001376	41	M	5	54	MI, W
NEB_306	2171001426	56	M	5	231	Pneumonia NOS
NEB_306	2181003193	53	F	5	273	Sinus arrhythmia
NEB_321	6323210016	57	M	5	25	SVT, W
NEB_302	1981003452	46	F	2.5	86	Cholecystitis NOS
NEB_202	3223001055	53	F	2.5	3	Edema NOS
NEB_302	2691000675	76	F	2.5	6	Gastroenteritis Viral NOS
NEB_302	1701000827	71	F	1.25	12	headache
NEB_302	1371003335	42	M	1.25	58	Unstable angina, w
NEB_302	6973210017	49	F	P	70	AMI + cardiorespiratory arrest
NEB_305	1232002917	59	M	P	15	Atrial fibrillation
NEB_302	1451000496	29	F	P	6	Chest pressure sensation
NEB_305	1662003432	57	F	P	33	Diabetes mellitus aggravated
NEB_305	1662004596	52	F	P		Fatigue
NEB_305	2942001367	61	F	P		Headache
NEB_321	6633210084	40	F	P	4	Rash NOS

[27] Patient had chest pain and convulsion during the two-hour surveillance after the first dose. The sponsor reported that it occurred 2 days pre-first dose; see 5.3.7; page 98

Study	Subject	Age	Sex	Dose	Days	History
NEB_321	6243210017	51	M	P	68	Schizo-affective disorder

5.3.6 Narrative of death events

5.3.6.1 Deaths in the Primary Program

Patient 202-3315001384

Patient was a 46-year old white male who died of an AMI seven days after discontinuation of nebivolol (10 mg) he has taken for 54 days. While still on nebivolol patient exhibited shoulder, back and sub-sternal pain, was admitted to the hospital and diagnosed with acute pericarditis of unknown etiology which was reported to have resolved one day later after hospitalization. Three days later the patient was withdrawn from the study. Seven days after discontinuation of study drug, patient experienced shortness of breath, back pain and went into cardiac arrest. He was resuscitated but without success. Autopsy results attributed the death to AMI.

Subject was a smoker, hyperlipidemic, had no history cardiovascular disease but had a family history of coronary artery disease before age 55. He was taking seldinafil for erectile dysfunction.

Patient 6813210015

This 75-year-old hypertensive female was found unconscious in the bathroom two weeks after starting nebivolol 5 m. Her husband initiated CPR but when emergency team arrived she was in ventricular fibrillation. She was pronounced dead twice by the emergency room physician, with subsequent spontaneous return of cardiac rhythm. She remained unresponsive and on life support. Her status later deteriorated and by consent from her family, life support was discontinued. Patient was not a smoker and had no family history of CAD, however, per patient's husband, patient had approximately half a dozen episodes of loss of consciousness over the past 5 to 6 years, but no information on whether the patient sought medical evaluation of her syncopal events.

5.3.6.2 Deaths in the Secondary Program

5.3.6.2.1 Deaths in the hypertension trials

USA-4[28]

Patient is a 52-year old male who was reported to have died from severe asphyxia as a result of vomiting due to alcohol abuse after 25 days of treatment with nebivolol 30 mg. The patient was found dead in his car. Autopsy findings were: pulmonary congestion and edema; focal severe segmental coronary atherosclerosis; questionable fatty change of liver, pancreatic atrophy with intervening intralobular fibrosis, strong alcohol odor about body fluids and tissues.

JAITA10548

[28] This death was reported to have resulted of alcohol intoxication and vomit aspiration. As the autopsy findings do not mention any presence of aspiration in the lungs, the reviewer reclassified this death as "circulatory collapse"

Subject was a 64 year old Caucasian male who was participating in protocol ITA-3, was apparently healthy and taking no medication when entered the study. After 163 days of starting nebivolol 5 mg, he died of cardio-circulatory collapse.

JAARG12518
Patient was a 69 year old man who was participating in NEB-INT-8 and receiving 5 mg nebivolol when he died suddenly from an aortic dissection.

aortic dissection and two surgeries. He died as a result of severe heart failure three days after admission.

JAUK9784
This 66-year-old female was participating in NEB-GBR-2 when she experienced two MIs over 5 days after about 5 weeks of double-blind study therapy. It is not sure what the patient was taking when the events occurred. The report says different things at two different sections of it (that the patient was crossed over to placebo from active therapy; the identity of the double-blind medication was not available in the J&J database).

JABEL11249
Patient is a 57-year old Caucasian male. He died of an MI 868 days after being on 10 mg of nebivolol under protocol NEB-BEL-18. Patient had a history of diabetes, arrhythmia and his BP was uncontrolled during the study. He was taking digoxin and glucophage. Adverse events reported during study were hypertension, visual disturbances and atherosclerosis.

JABEL14324
This 67-year old Caucasian male was participating in the NEB-BEL-18 where he received nebivolol 10 mg for 445 days, and died of CVA. Patient had no history of CVD and was taking ketoprofen retard for arthrosis. His lab tests showed an erythrocyte sedimentation rate that was high, and a borderline high potassium level.

JABEL12484
Caucasian female, 54 years who completed the double blind phase of the study and enrolled in the open-label phase. She was on 5 mg of nebivolol for 713 days and died of hepatic cirrhosis 19 days after discontinuing her study drug. At baseline, vertigo and trembling were present and her LFT were abnormal. Long-term follow-up visit notes checked the "No"-boxes for events leading to hospitalization and/or visits to another doctor since previous visit. Concomitant conditions and medications, except for Visit 8 where patient was prescribed Naprosyn for coxarthrosis, were not specified. At one of the last visit, cirrhosis and alcohol intake were noted. Patient's biochemistry tests revealed abnormal LFT SGOT (AST), SGPT (ALT) and total bilirubin of 73 U/L, 81U/L and 1.65 mg/100 mL respectively. The report notes that at the last visit of the open-phase, hepatic cirrhosis and alcohol abuse were noted.

Review of CRF reveals no remarkable medical history and taking no HT treatment at entry in the study. It also notes that the subject did not smoke or take alcohol.

JABEL11347
Patient was 72-year old Caucasian female who was participating in the NEB-BEL-18 protocol and she was found dead as a result of CO poisoning 749 days after being on 5 mg of nebivolol. During the trial she received medication to control severe post-menopausal symptoms. It is not known whether this was a suicide or not. The main Jansen report did not qualify this event as a suicide or accidental.

This 73 year- old man with coronary artery disease, congestive heart failure and hypertension, was treated with nebivolol 5 mg/ day for 10 months, he died suddenly while working in the garden. Concomitant medications included captopril, simvastatin, isosorbide and nifedipine.

MENIT42429

This 74 year- old woman with congestive heart failure and hypertension was treated with nebivolol 5 mg/day. Concomitant medications included digitoxin, isosorbide, thiamazole, glibenclamide, xipamide and nisoldipine. She had a syncopal episode preceded by nausea and emesis. An electrocardiogram showed a heart rate of 35 beats per minute. She was hospitalized, a pacemaker was inserted and digitoxin and Nebivolol were discontinued. Heparin was started for a suspected cerebral embolism. The patient's death was attributed to the suspected embolism.

MENIT42431

This 79 year- old woman with congestive heart failure, coronary artery disease, atrial fibrillation and hypertension, was treated with nebivolol for 28 days. The patient was hospitalized for a stroke which was complicated by pneumonia resulting in her death.

5.3.7 Narrative of Serious Adverse Events in the Primary Program

NEB-302-257000714

This 54-year-old white hypertensive male received 40 mg of nebivolol for a total of 113 days when the ECG showed changes of septal ST-T changes (described as severe and medically significant) which may be due to myocardial ischemia and bradycardia. One week later the repeated ECG showed signs of possible anterior infarct. No action was taken with regard to the study drug and the patient was entered in the extension study the same day the abnormal ECG changes were seen.

ECG was normal on the previous visit. Patient history includes hypertension, hypothyroidism, arthritis, intermittent chest pain, non specific headache and other.

NEB-302-2571000326

This 49-year-old black hypertensive female received 20 mg of nebivolol for a total of 121 days. ECG completed at the end of the double blind phase showed inferior T wave changes (described as severe and medically significant) which may be due to myocardial ischemia. A repeat ECG two weeks later showed long QT interval and non-specific T wave abnormality. The subject was enrolled in the extension trial 306.

ECG was normal on previous visit. Subject had no relevant medical history.

NEB-302-1371003335

This 42-year-old Hispanic hypertensive male received 1.25 mg of nebivolol for a total of 86 days when he had an episode of unstable angina which resolved spontaneously. The following day he presented to the emergency room complaints of worsening chest pain, shortness of breath and elevated BP. An ECG revealed PVCs. Lab tests were completed and patient was treated with nitroglycerine which relieved the chest pain, aspirin and norvasc. A stress test revealed no symptoms of ischemia and an EF of 38% and the patient was discharged with instructions to adopt a low-fat/cholesterol diet and medication including aspirin and coreg. The patient was permanently discontinued form the study.

Apart from hypertension, the patient has no relevant medical history.

NEB-302-1411001285
This 63-year-old hypertensive white male was receiving 10 mg of nebivolol for 43 days when he reported at one of his study visits that he has not been feeling well and that his urine is dark. A urine test showed a bilirubin level of 3.1 mg /dl. At the exam the patient appeared tired and jaundiced. The patient was admitted to the hospital. He was diagnosed with hepatitis A (IgM hepatitis A was positive) and his liver function tests were abnormal. The attending physician requested that patient discontinue the study drug.

NEB-202-205-3000150
This 64-year old hypertensive black female was on nebivolol 40 mg in a DB protocol for 88 days when she presented to the emergency room and was admitted for chest pain radiating to the left arm, nausea and diaphoresis. The ECG showed bradycardia and a septal infarct. Chest X-ray showed bibasilar subsegmental atelectasis. Her troponin was normal but her CK was high at 220 U/L. A stress test completed and there were no specific cardiac symptoms induced during the test. The baseline ECG for the stress test showed bradycardia, first degree AV block and evidence of an old (?) anterior septal MI. The 88th day on the study drug was the patient's last dose. The ECG report states "compatible with old ASMI – maybe lead placement or chest configuration. Needs clinical evaluation if appropriate"

The patient had a history of MI (12 years prior), and she was taking potassium chloride at the time of the event.

NEB-202-1653000453
This 52-year-old hypertensive black female received nebivolol 20 mg in a double-blind protocol for 1 day ——— when here ECG showed RWP possible posterior MI that was not seen in an earlier ECG. Patient continued with the study drug and another ECG completed ——→ showed continuing RWP, the study drug was discontinued on 11/05/02 and the event was found to have spontaneously resolved on 11/19/04.

The patient is diabetic, has a female family history of CAD before age 65, but no mention of hyperlipidemia.

NEB-202-261000841
This 39-year-old hypertensive black male received 5 mg of nebivolol in a single-blind protocol for 28 days, and on the day of randomization to the double-blind protocol ——, he complained of chest pain and shortness of breath nausea and fatigue 2 hours post study drug ECG.

The patient started to have seizures on the examination table.

In the emergency room, the patient was tachycardic, hypertensive and his CPK was 366 U/L. His blood work on —— revealed thrombocytopenia of 110 K/UL, AST of 134 U/L a CPK of 376 U/L.

Patient's chest pain continued and he was admitted for observation. His ECG of —— revealed T wave inversion. Anther ECG done —— revealed ST segment and wave abnormalities

The patient later called the study coordinator informing her that he did not take his first double-blind dose on ~~ .

Patient has a history of hyperlipidemia and was not taking any concomitant medication at the time of the event.

NEB-305-7242001376
This 41-year-old hypertensive white male received nebivolol 5 mg for 80 days when he complained of chest pain and was seen at the emergency room. An ECG showed borderline changes and he was admitted to the hospital. Cardiac enzymes were elevated and patient was diagnosed with MI. Patient was discontinued from the study.
Patient medical history except for hypertension was not remarkable.

NEB-305-1182001648
This 62-year-old hypertensive Hispanic female was receiving 10 mg of nebivolol for a total of 23 days when she presented at the office for a study visit and reported that she was admitted to the hospital for shortness of breath, chest discomfort, right arm pain and associated nausea and sweating. Cardiac enzymes tested twice were negative and ECG showed a bradycardia but no signs of ischemia. A myocardial perfusion ejection fraction study revealed a reversible distal anterior wall and apical defect consistent with myocardium at ischemic risk. Cardiac catheterization revealed normal coronary arteries. Patient was discharged, prescribed a calcium channel blocker and prednisone and was discontinued from the study.
Cardiovascular medical history except for hypertension was non-existent.

NEB-305-1812000449
This is a 66-year-old hypertensive white male who received 10 mg of nebivolol for 44 days when he presented to the emergency room with CHF. Among other CHF symptoms patient had severe bradycardia and near unresponsiveness. He was admitted, his enzymes were normal, and his ECG was abnormal for left enlargement. Left and right cardiac catheterization revealed 80% to 90% stenosis in the very proximal portion of prior to the bifurcation of the left circumflex coronary artery and mild pulmonary hypertension. Patient underwent angioplasty with A stent placement to the left circumflex coronary artery. Pulmonary consultation suggested that the patient needed home oxygen therapy. Patient was permanently discontinued from study drug.
Patient had a history of hypertension, hyperlipidemia and was taking pravastatin and hydrocodone at the time of the event.

NEB-305-7272000566
This 61-year-old hypertensive white male was receiving 20 mg of nebivolol for 121 days when he was found to have leucopenia WBC of 2.8 GI/L. WBCs completed later showed recovery of and return to normal range less than two-weeks since it started. Patient was included in the extended study 306 but was not know what and how much he was taking.
Patient has a history of nasopharyngeal carcinoma and biopsy done at the time of the event showed no signs of malignancy, and he was taking no concomitant medication.

5.3.8 Narrative of Adverse Events Leading to Withdrawal in the Primary Program

NEB-302-1411006135
This 56-year-old Hispanic female received nebivolol 10 mg for 14 days when she experienced chest pain. The study drug was discontinued and at the same time the patient was given famotidine. The event resolved two days later.

NEB-302-1961000597

This 64-year-old hypertensive white female received nebivolol 10 mg during the double blind phase for 17 days when she experienced orthostatic hypotension. The study drug was discontinued 18 days later and the event resolved one day after discontinuation.

NEB-302-2181002126

This 57-year-old hypertensive white female received 20 mg in a double-blind protocol for one day 7/23/02 when she experienced shallow breathing 7/24/02. The study drug was discontinued but the date of discontinuation was not known. The breathing problem resolved on 7/26/04 on the same date the patient was withdrawn from the study.

NEB-305-1232005342

This 55-year-old hypertensive white female was receiving 5 mg of nebivolol for 28 days when ECG changes including new Q wave and slight ST segment elevation were seen. The study drug was discontinued three days later. The events persisted and the patient was withdrawn from the study 20 days later.

Medical history beside hypertension include a heart murmur, and patient was taking simvastatin, supplemental nutrients and vitamins, replacement hormonal therapy, antihistamines and nasal steroid spray.

NEB-305- 1662004984

This 50-year-old hypertensive white male received nebivolol 10 mg for 45 days when he started experiencing difficulty swallowing, discontinued the study drug eleven days after the beginning of this symptom which resolved three days after study drug discontinuation.

Except for hypertension, the patient has no relevant medical history and was taking no concomitant medication. Other AEs reported included shortness of breath and flushing.

Neb-302-1371002559

This 43-year-old Hispanic female was on 30/40 mg of NEB for 24 days when she develop angioedema, was discontinued from the study, and the event resolved spontaneously. Patient was not taking any concomitant medications.

NEB-305- 7222000558

This 58-year-old hypertensive white female received 10 mg of nebivolol for 36 days when she experienced cough (bronchospasm). She was treated with salbutamol inhalation, simple inctus and prednisolone. The study drug was discontinued 6 days later and the cough resolved the following day.

NEB-305- 1132000282

This 54-year-old hypertensive Hispanic female received nebivolol 20 mg for 8 days when she experienced "chest pain non cardiac" and long QT intervals (per adverse event form). The study drug was discontinued five days later and the pain resolved spontaneously one week later.

Patient has a history of hypercholesterolemia, abnormal ECG (T wave changes of equivocal significance), and she was taking no concomitant medication.

NEB-305- 1432000330

This 65-year-old, hypertensive white female received nebivolol for 6 days experienced bradycardia five days after the study drug was discontinued. The event resolved spontaneously 15 days later.

Patient has a history of thyroidectomy, von Willebrand's disease, degenerative arthritis. She was taking levothyroxine, alendronate, calcium and glucosamine at the time of the event. Diplopia entered in the AE form on the same day that was entered for drug discontinuation.

NEB-305- 1652004187

This 46-year-old hypertensive white female received 20 mg of nebivolol for 31 days when she experience orthostatic hypotension, fatigue, palpitations and dizziness, study drug was discontinued 3 days later and the event resolved one day after discontinuation. She also experienced blood hematology and chemistry test abnormalities.

Patient has a history of hyperlipidemia and a number of other health problems.

NEB-305- 2942000203

This 68-year-old hypertensive female received 20 mg for 58 days when she was found to have ST-T changes in I and aVL. The narrative reports severe worsening of diarrhea as the reason for study drug discontinuation which took place 12 days after the worsening of the diarrhea.

The patient had a history high cholesterol, anxiety, irritable bowel syndrome, DVT, hysterectomy. She was taking paroxetine, acetaminofen and Imodium.

NEB-305- 7332000886

This 79-year-old hypertensive white female received nebivolol for 31 days when she experienced atrial fibrillation. The patient was treated with antiarrhythmics and anticoagulants the study drug was discontinued, but the fibrillation persisted.

Patient had a history of DM type 2 and first degree AV block. She was taking paracetamol.

NEB-306-2181006782

This 50-year-old white male experienced moderate sinus bradycardia 176 days after being on 10/20 mg of NEB. ECG obtained showed a heart rate of 49 bpm. The study drug was discontinued.

NEB-306-2331002344

This 63-year-old white male was on NEB 20 mg for 117 days when she experienced moderate bradycardia exacerbation and she was withdrawn.

NEB-306-2331002441

This 50-year-old white male was on 10 mg for 91 days when she experienced mild shortness of breath, the study drug was discontinued and event resolved spontaneously.

NEB-306-2331003217

This 58-year-ld white male experienced mild bradycardia exacerbation after been on NEB for 109 days. NEB was discontinued but the event persisted.

NEB-306-2451000171

This 44-year-old white male experienced moderate elevated triglyceride which was ongoing from the previous NEB-302 study. Study drug was discontinued but the elevated triglycerides persisted.

NEB-306-2571003236

This 56-year-old white female received 20 mg in the NEB-302 and on the first day of her participation in the extension trial the test showed mild proteinuria that was ongoing from the previous trial. The drug was discontinued and the proteinuria resolved the same day.

NEB-306-2632000425

This 70-year-old white male was on 20 mg of NEB in the NEB-03 and continued onto the NEB-306 for 145 days when he experienced mild bradycardia that resolved spontaneously after drug discontinuation.

NEB-306-2711000911
This 48-year-old black male was on 10/20 mg of NEB + 25 mg HCT for a total of 267 days, in addition to what he received in NEB 302, when he experienced mild bradycardia. The study drug was discontinued but the bradycardia persisted.

NEB-321-6243210022
This 55-year-old white female was on NEB 20 mg for 51 days when she experienced mild CHF that resolved one day after study drug discontinuation and treatment.

NEB-321-6413210046
This 70-year-old black male was on 5 mg of NEB for 76 days when he experienced moderate wheezing and shortness of breath that resolved after discontinuation of the study drug and treatment.

NEB-321- 6673210009
This 47-year-old white male was on 20 mg of NEB for 15 days when he experienced a further decline in his platelet count, from 107,000/mm^3 to 75,000/ mm^3. The study drug was discontinue, but the platelet count continued to decline to 70, 000 two weeks after withdrawal and 38,000 four months later.

NEB-321- 6763210005
This 72-year-old white male patient was on NEB 20 for 13 days when he experienced moderate bradycardia which resolved without treatment after discontinuation.

NEB-321- 6973210005
This 54-year-old Hispanic male was on 5 mg of NEB for 13 days when he experienced moderate hypotension (BP unknown) that resolved spontaneously one day after it started, but the study drug was not discontinued until three days later. Patient was taking valsartan/hydrochorthiazide at the same time.

NEB-321- 7013210005
This 53-year-old black female was on 5 mg of NEB for 38 days when she experienced subconjunctival hemorrhage that resolved spontaneously 5 days later. The study drug was not discontinued until 4 days after the event had resolved and it is not known why it was withdrawn since the event resolved. (lying regarding concomitant meds).

NEB-302-2151000123
This 57-year-old white female was on 20 mg of NEB for one day when she experienced shallow breathing which resolved two days later. It is not known when the study drug was discontinued but the patient was withdrawn from the study the same day the event resolved.

NEB-306-2632001686
This 72-year-old black male who was previously enrolled in NEB-305 was on NEB 20 mg for 23 days in the extended study when he was hospitalized for bradycardia and pedal edema. His heart rate was in the forties and his blood pressure was 212/126. The patient was treated with furosemide, potassium, valsartan and amlodipine which resulted in good control of blood pressure and resolution of the edema. At discharge from the hospital both events of bradycardia and edema were considered resolved.

NEB-306-1981001415
This 76-year-old female participated in the NEB-302 was enrolled to participate in the extension trial and he experienced a decrease in heart rate 1 day after being on 20 mg. the study drug was discontinued but the event persisted and he was withdrawn from the study two days after experiencing the decrease in heart rate.

NEB-302-1371000910
This 53-year-old Hispanic male was on NEB 20 for 45 days when he experienced mild shortness of breath which resolved spontaneously after the NEB was discontinued. He also experienced an increase in SGPT, glucose and CRP. He was taking no concomitant medication.

NEB-306-1642000868
This 42-year-old white male was on 10 mg of NEB for 94 days in the extended trial when he experienced BBB which resolved spontaneously after discontinuation of study drug.

NEB-306-2181003193
This 53-year-old white female was on NEB 5/10 mg fro 186 days when she experienced worsening of sinus arrhythmia which resolved spontaneously after withdrawal. Patient was taking placebo in the NEB-306 study.

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/s/

Salma Lemtouni
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MEDICAL OFFICER

1/31/05

CLINICAL REVIEW

Application Type	NDA
Submission Number	21,742
Submission Code	000
Letter Date	April 29, 2004
Stamp Date	May 4, 2004
PDUFA Goal Date	February 28, 2005
Reviewer Name	Karen A. Hicks
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Established Name	Nebivolol
(Proposed) Trade Name	~~~~
Therapeutic Class	Selective ß1 blockade
Applicant	Bertek Pharmaceuticals, Inc.
Priority Designation	S
Formulation	PO
Dosing Regimen	2.5 mg, 5 mg, 10 mg
Indication	Hypertension
Intended Population	Adults

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