Study	Subject	Age	Sex	Dose	Days	History
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 + cardio-respiratory 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
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 substernal 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 Three days later the patient was withdrawn from the study.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.

10548

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.

12518

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.

9784

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).

11249

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.

14324

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.

12484

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,

[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"

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.

—— 11347

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.

—— 12484

Subject is a 73 year-old Caucasian male who was participating in NEB-BEL-3-6 and was receiving 5 mg of nebivolol for 643 days when he died from broncho-pulmonary cancer. Except for angina, patient medical history was non-remarkable and he was taking no medication at the inclusion in the study. No CRF was available but it was reported that the patient had a history of mining and suffered from broncho-emphysema.

5.3.6.2.2 Death occurring in the post marketing phase

—— 2001000613

This 70 year- old man with hypertension was treated with nebivolol 5 mg/ day for seven months, died suddenly and no postmortem examination was preformed.

—— 43883

This 71 year- old man with diabetes, obesity, hypercholesterolemia, coronary artery disease and severe hypertension was treated with nebivolol 2.5 mg/ day for 3 days. Concomitant medications included Vaseretic, candesartan cilexetil, amitriptyline, gliclazide, pravastatin, and aloxiprin. He died suddenly (further details were requested).

—— 2001007072

This 81 year- old woman with coronary artery disease, heart failure, aortic valvular disease atrial fibrillation and hypertension was taking nebivolol 2.5 mg/ day for 25 days. Concomitant medications included furosemide, phenprocoumon, and isosorbide. The patient had a sudden collapse and was diagnosed by an ER physician as having a myocardial infarction.

—— 2001006744

This 75 year- old woman with coronary artery disease and hypertension was treated with nebivolol 5 mg/ day for 6 days when she was found dead at home. The reporting physician presumed the cause of death to be myocardial infarction. Concomitant medications included Diazide and memantine hydrochloride.

—— 1999001191

This 85 year- old man with congestive heart failure and hypertension was treated with nebivolol 1 mg/ day for an unspecified period of time. The reporting physician was contacted for additional information and reported that the patient died of " basic disease" not felt to be related to Nebivolol.

1999001193

This 54 year- old woman died in an accident that her physician thought was not related to nebivolol.

1999001194

This 68 year- old man with congestive heart failure and hypertension, was treated with nebivolol for 416 days. He died 2 weeks after his last dose of nebivolol.

1999001195

This 70 year- old man with hypertension and bronchial carcinoma, was treated with nebivolol 5 mg a day. He died due to his preexisting carcinoma.

42428

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.

42429

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.

42431

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 on —— 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
3/10/05 07:50:14 AM
MEDICAL OFFICER

2/23/05

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 23, 2005

FROM: Abraham Karkowsky, M.D., Ph.D.; Group Leader Division of Cardio-Renal Drug, Products HFD-110

TO: Robert Temple, M.D.; Office Director ODE-1

SUBJECT: Approvability of Nebivolol Tablets; NDA 21-742, Bertek Pharmaceuticals.

This memo outlines the rationale for the approvability recommendation for Nebivolol Tablets (Nebivolol), a relatively selective β1-selective adrenergic blocker for the treatment of hypertension. There is adequate information to assure that nebivolol at a dose range of 1.25 to 40 mg once daily is effective in the treatment of essential hypertension. There is adequate information that nebivolol is useful for the treatment of hypertension in both Caucasian and black patients.

An approval recommendation, however, will be dependent on demonstrating that the Leydig cell tumors that were observed in male mice at a dose of 40 mg/kg are not a relevant risk to humans. Although endoreduplicaton and polyploidy were observed in chromosomal aberration studies, these phenomena that do not appear to be risk factors for cell-transformation. Nebivolol, therefore, does not appear to directly provoke tumor formation. The sum of evidence strongly suggests that the tumors observed in mouse are a consequence of disruption of the hypothalamic-pituitary-endocrine axis.

Since other beta blockers do not induce Leydig cell tumors, and since such tumors in rodents are usually endocrine-based, the consequence of any secondary unwanted endocrine effects of nebivolol, should they occur in humans, would be sufficient basis to recommend non-approval. In the absence of a mechanistic explanation for the etiology of the mice tumors and also a demonstration that the mechanism by which the tumors are generated is irrelevant at the doses and exposure proposed for humans, the drug should not be approved.

There are other suggestions that nebivolol exerts endocrine-related effects during reproduction and differs from other ß-blockers. Nebivolol is unique among ß-blockers in that reproductive toxicity was observed at safety margins of approximately 1.25-fold the proposed human exposure. Safety margin for other ß-blockers is generally 10-fold higher than the upper portion of their proposed dosing regimen. Dystocia, delayed parturition and cannibalism were prominent features of reproductive toxicology studies with nebivolol, not described in current approved labeling for other ß-blockers (see Dr. Hausner's listing in a memo dated 11 February

2005). Of particular concern, was, a decrease in pup fertility (F1 generation) was noted after treatment of the F0 generation through pregnancy with nebivolol.

Approval also awaits the satisfactory completion of the inspection of the drug substance facilities. The inspection is scheduled to occur February 6-16, 2005.

There are additional issues that will likely be shortly resolved. For completeness, these issues should be included in the decision letter and are described below.

Dr. Mittal's review notes that — impurities — of nebivolol are all of sufficiently high concentration as impurities to require qualification. The information pertinent for qualification of the impurities was recently received (3 February 2005) and is under review by Dr. Hausner. Approval awaits qualification of these impurities as acceptable for the usable nebivolol dose range.

The chemistry section is still deficient in some aspects of specifications and controls. (e.g., allowed water content) and stability protocols for the 2.5, 5 and 10 mg tablets.

Labeling recommendations are currently being circulated through the reviewers of each of the disciplines. Labeling recommendation will be transmitted separately.

The following is a list of reviews referenced in the construction of this memo.

- Chemistry review by Ramasharan D. Mittal dated 15 February 2005.
- Biopharmaceutic review by Elena V. Mishina, Ph.D., and Robert Kumi, Ph.D., dated 31 January 2005.
- Pharmacology/toxicology reviews by Elizabeth Hausner; D.V.M., dated 21 December 2004; 21 December 2004 and 10 January 2005.
- Statistical review of efficacy by Jasmine Choi, M.S., dated 16 December 2004.
- Inspection report by Karen M. Storms and Leslie K. Ball, M.D., dated 1 February 2005.
- DDMAC label review by Lance McLeroy, dated 9 February 2005.
- Medical officer review-efficacy by Karen Hicks, M.D., dated 31 January 2005.
- Medical officer review-safety by Salma Lemtouni, M.D., dated 9 February 2005.
- Consult response DRUDP by Harry Handelsman, D.O., and Mark S. Hirsch, M.D., dated 4 February 2005.
- Consult response DMEDP by Bruce V. Stadel, M.D., M.P.H., dated 31 January 2005.
- Executive CAC minutes; Jeri El Hage, Chair, dated 3 August 2004.
- DMETS review by Carol Holquist R.Ph. dated 11 August 2004.
- Statistical review of carcinogenicity by Jasmine Choi M.S., dated 21 July 2004.
- Minutes of teleconference between Bertek and Elizabeth Hausner dated 25 January 2005.
- EDR files of NDA 21-742.

Administrative:
Trade name:

The DMETS reviewer recommended that the proposed Trade name for nebivolol " ——— " not be approved. There were two rationales. The first is that the name is unusually "fanciful". Although I agree that the name is overly fanciful, my rationale differs from that of DMETS. DMETS interpreted the —— portion of the name as modifying the term ———— '. That is, somehow nebivolol completely mitigates any —— effect. My view is that the suffix implies that nebivolol has some additional properties by generating nitric oxide, a potent vasodilator. As shown below, there does not appear to be a demonstrated beneficial effect of nebivolol other than its beta blockade effect. Any interaction with the nitric oxide system has not been demonstrated as a meaningful effect in humans. Furthermore, the interaction of nebivolol with the nitric oxide generating system in animals is only observed at orders of magnitude higher concentrations than generated in humans *in vivo*.

The second reason that DMETS expressed concern was that the name ' —— could be orthographically or phonetically mistaken for drugs such as Betimol, betaxolol (Kerlone) or Lovinox.

Betimol is an intraocular beta blocker, for use in the treatment of increased intraocular pressure, and is dispensed as a solution of different strengths ranging from 0.25% to 0.5%. DMETS notes that the symbol for % and that for mg dose could be misread and interchanged. If a 0.25% Betamil prescription is sloppily written, the order could be interpreted as 25 mg of ——— (the only dose where percent and mg overlap in the dose range). Mix-up with Lovinox appears to be less problematic. Its route of administration, frequency of dosing and indications is sufficiently different for nebivolol to make any confusion unlikely.

Both betaxolol and nebivolol are oral beta blockers with overlapping dose ranges. Confusion and medical errors appear likely. In my opinion, the consequence, however, of any error would be modest since the pharmacological properties of the two drugs are similar.

In summary, I agree that the TRADENAME ——— is unduly "fanciful" and the potential for confusion either orthographically or phonetically with Betimol and betaxolol make the name —— unsuitable.

Pediatric studies:

In a letter dated 7 July 2004, the Division granted a deferral for three years for the requirement to conduct pediatric studies. Given the uncertainties relative to safety of nebivolol in adults, the granting of a deferral is appropriate.

Financial Disclosure:

The sponsor submitted FDA form 3454 asserting no investigator in the listed pivotal studies had a financial interest, requiring disclosure. The documentation appears adequate.

Inspections:

As of the writing of this review, the recommendation by the Office of Compliance has not been received for the drug-substance manufacturing facilities (Janssen Pharmaceutica). The inspection is scheduled between the dates of February 6-16, 2005.

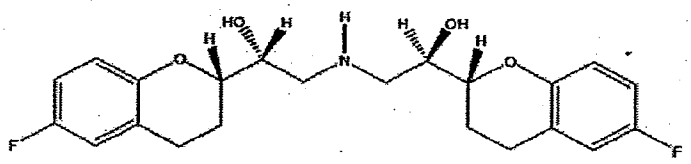
DSI reviews.

DSI evaluated the quality of the data at three investigator sites. The conclusion of the report was that there were no deficiencies in the data collected, of sufficient magnitude, to question the integrity of the data.

Chemistry:

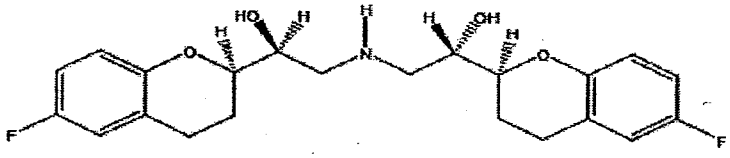
The structure of Nebivolol is shown below. Nebivolol contains four asymmetric carbons. The product is a mixture of the RSSS and SRRR isomers with the stereochemistry designated in the asymmetric carbons starting on the left and proceeding to the right. Although there appears to be symmetry on the flat representation of the molecule, the two sides of the molecule are not equivalent. Functionalization of either the hydroxyl group or aromatic chain results in different compounds based on which side of the molecule is altered.

Figure 1: Nebivolol structure and name



• HCl

SRRR – or d-nebivolol hydrochloride



• HCl

RSSS – or l-nebivolol hydrochloride

Chemical Name*: (±)-[2R*[R*[R*(S*)]]]- α,α'-[iminobis-(methylene)] bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride

For the racemate Nebivolol (RSSS + SRRR) : [2R[R*[R*(S*)]]]

Although the sponsor has studied doses of nebivolol ranging from 1.25 to 40 mg daily, the sponsor plans to market only dose strengths of 2.5, 5 and 10 mg. The 2.5 mg dose is apparently not scored.

Expiration date:

Dr. Mittal recommends an expiration date of — nonths for the 2.5, 5 and 10 mg nebivolol tablet strengths.

Biopharmaceutics:

Only the highlights of Drs. Mishina's and Kumi's review are summarized below.

Pharmacokinetics:

The absolute bioavailability of nebivolol has not been determined. Nebivolol's pharmacokinetics is dependent on the genomic characteristics of the CYP2D6 gene. Subjects are classified as either extensive metabolizers (EM) or poor metabolizers (PM). In the Caucasian, Black and Asian population the frequency of PM is 7%, 2% and 2%, respectively.

After a single 10- mg dose, peak nebivolol concentrations are measured between 1.5 and 4 hours post dose. The pharmacokinetic profile appears to be independent of food. There was modest accumulation of d- and l- nebivolol upon multiple-day dosing (14 days) for EM. There

was however substantial accumulation for the PM patients after 14 days of treatment for l-nebivolol.

Table 1: C_{max} at day 1 and day 14 after a 10-mg dose to extensive and poor metabolizers

	Extensive metabolizers		Poor metabolizers	
	d-nebivolol	l-nebivolol	d-nebivolol	l-nebivolol
Day 1 (ng/ml)	1.1 ± 48	2.1 ± 42	4.3 ± 19	5.7 ± 26
Day 14 (ng/ml)	1.2 ± 47	2.3 ± 38	6.5 ± 14	25.9 ± 24

The pharmacokinetics of nebivolol as a single dose in the range of 2.5 to 20 mg was linear for C_{max} for both EM and PM subjects. AUC measurements (either to infinity or to last measurable value) approximated dose-proportionality for the EM subjects in considering the d- and l-nebivolol isomer concentrations. For the PM subjects linearity was limited to the measurements of the concentration of the d-isomer; there was greater than dose proportionate increases in AUC measurements for the l-nebivolol isomer.

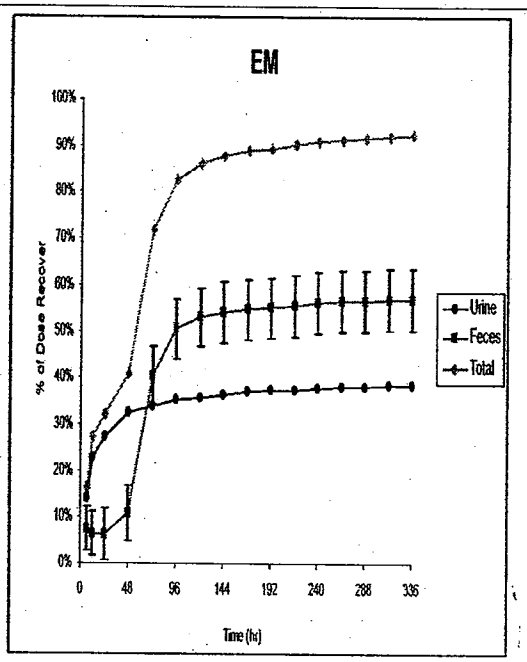
Both isomers of nebivolol are bound to an approximately 98% to human plasma proteins.

With respect to the fate of nebivolol, studies NEBI-136 and NEBI-142 were the most informative. In the two studies six subjects (3 EM and 3 PM) received, as a single dose, approximately 15 mg nebivolol as a solution containing 100 uCi of ^{14}C-labeled nebivolol (labeled on the methylene carbon) of the R-S (or S-R) portion of the molecule. Blood samples were collected for up to 168 hours post dose; urine and feces were collected for up to 336 hours post-dose in the three EM patients and up to 432 hours in the three PM subjects. Study NEB-136 quantified the amount and routes of excretion. Study NEB-142 analyzed the radioactivity with respect to the specific entities excreted.

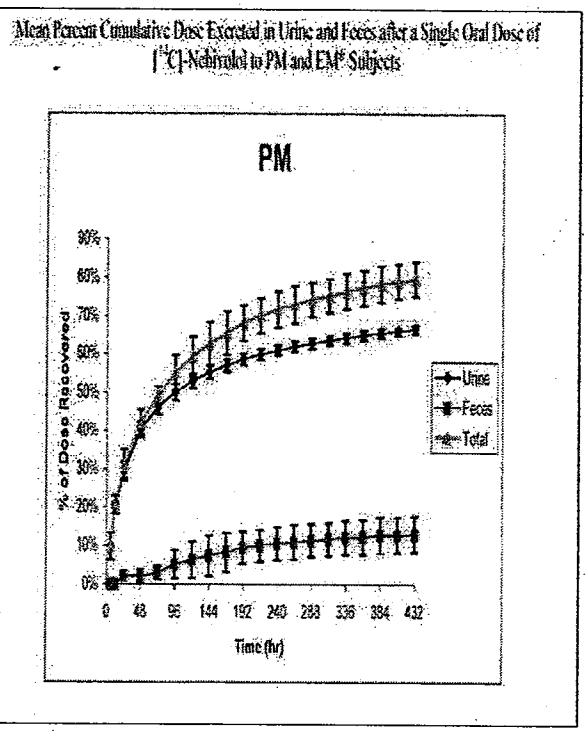
There were differences in the excretion pattern of nebivolol radioactivity comparing PM and EM subjects. For the three PM subjects, approximately 75% of the dose was excreted in 432 hours (18 days); with 66% of the radioactivity excreted in urine and 13% in feces.

For the EM subjects the vast majority of radioactivity was excreted over a much shorter time period (96 hours; 4 days) with some additional radioactivity trickling out over the next 240 hour. Forty four % of the dose was excreted in feces and 38% in urine. The long tail indicates that there are metabolites that have long half-lives for both the EM and PM subjects. The time course of excretion is shown below.

Figure 2: Total excretion of ^{14}C-labeled nebivolol and excretion in urine and feces after a single 15 mg dose



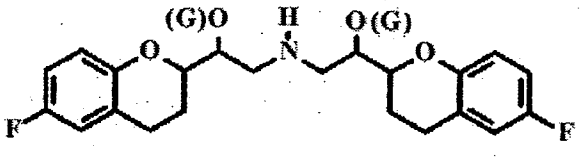
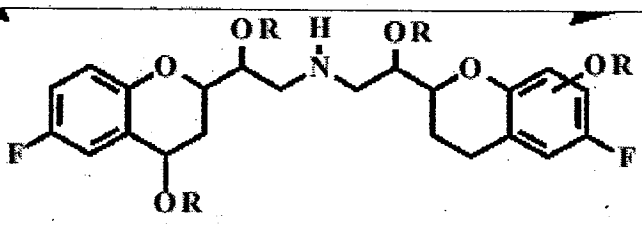
*The percent of dose data of EM feces and total were mean of Subjects 1 and 3.



At least 10 metabolites for which the skeletal structure of nebivolol was altered were isolated from feces, urine and plasma. Additional metabolites included glucuronides conjugates of both nebivolol and the above noted metabolites. The distribution of metabolites differed in the EM and PM subjects. The major metabolite among the three EM subjects was the dihydroxy- metabolite and its corresponding glucuronides. This metabolite (and glucuronides) accounted for approximately 25% of the administered radioactivity. This metabolite was not detectable in the poor metabolizers. The major metabolite for the PM was the conjugated nebivolol and it accounted for 34% of the radioactivity in the PM and 2% in the EM. A scheme for the metabolism and excretion of nebivolol is presented by the sponsor and is included in the pharmacokinetic review, but not reproduced here.

Appears This Way
On Original

Figure 3: Major metabolites in poor and extensive metabolizers

	Nebivolol glucuronides(s) accounted for approximately 44% in the PM subjects. In EM it accounted for only 2% of the metabolic product identified
	Dihydroxy-nebivolol, this metabolite accounted for approximately 25% of the excreted radioactivity in EM subjects with either R= H or the mono-glucuronide. For PM subjects this metabolite was not detected either in plasma, urine or feces.

In vitro P450 studies:

Metabolism of d- and l- nebivolol is primarily through glucuronides conjugation and through CYP2D6 with some contribution by CYP3A4. Three methods were used to assess the contribution of the CYP enzymes. The studies are summarized in the table below

Table 2: Methodology and results of CYP450 assessment for nebivolol

Method	Results
Correlation of nebivolol metabolism with metabolism of model substrate	Sixteen human liver samples had the activity of disappearance of nebivolol correlated to the metabolism of CYP-specific model substrates. The metabolism of Nebivolol was correlated with activity of dextromethorphan O-demethylase a CYP2D6 model activity (r =0.932 for d-nebivolol and 0.925 for l-nebivolol).
Inhibition of nebivolol metabolism by monoclonal antibodies	Monoclonal antibodies to CYP2D6 inhibited the metabolic conversion of d- and l-nebivolol to 4-hydroxy-nebivolol by 73% and 75% respectively. Monoclonal antibodies to CYP3A4/5 inhibited the metabolism of d- and l- nebivolol by 16% and 20%, respectively.
Metabolism of nebivolol by cloned human CYP450	Nebivolol appears to be a competitive inhibitor of several CYP450 enzymes. The K_i for CYP2D6 was 0.37 uM with Dextromethorphan as the substrate and O-demethylation as the reaction. Nebivolol appears to be a mixed competitive/noncompetitive inhibitor of CYP3A4/5 with testosterone (6-B-hydroxylation) with a Ki 13 uM. The inhibitory constants for the other CYP450 enzymes as assessed by model substrate were > 40 uM.

Drug-Drug interactions;

The pharmacokinetics of nebivolol (single dose at 10 mg) was compared before and after Fluoxetine (a substrate of CYP2D6) at a dose of 20 mg, at steady state in 12 patients who were all EM. AUC and C_{max} were increased by approximately 8 and 3.5 fold, respectively, for d-nebivolol and approximately 4 and 2 fold, respectively for l-nebivolol.

There was no apparent interaction with the following substrates with nebivolol at doses of 10 mg in some cases as a single dose and in other cases after 10 days of nebivolol dosing:

hydrochlorothiazide, digoxin, warfarin, spironolactone, ramipril, losartan and charcoal (when administered repeatedly after four hours when nebivolol was administered).

In summary, the in vitro data are the most informative in indicating that the metabolism of nebivolol in considering the CYP450 system is most dependent on CYP2D6 and to a much lesser extent with CYP3A4.

Special populations:

Hepatic failure NEBI-124: Single dose of 5 mg nebivolol when administered to 8 patients with moderate hepatic failure (child-Pugh classification) was compared to matched healthy individuals. All enrolled were genetically EM. Both C_{max} and AUC were increased by several-fold for both the d- and l- nebivolol isomers. Both C_{max} and AUC for the glucuronides conjugates were increased but to a lesser extent. The steady state consequences of moderate hepatic failure at steady state are likely to amplify the decreased clearance of this drug. The effect is likely to be magnified in more severe degrees of hepatic failure. The effects of any degree of hepatic failure in PM patients on the kinetics of nebivolol are unknown.

Renal failure NEBI-125: Single dose of 5 mg nebivolol when administered to 20 patients, all characterized as EM, with normal renal function (creatinine clearance > 80 ml/min; n=4), mild (creatinine clearance 50-80 ml/min; n=7), moderate (creatinine clearance 30-50 ml/min; n= 9) or severe (creatinine clearance < 30 ml/min; n= 5) degrees of renal dysfunction as calculated by the Cockroft-Gault equation. The only substantial changes to nebivolol concentrations were in the moderate and severely compromised patients. The greatest effect was in the severely compromised renal function group with several fold increases in AUC and Cmax of d-nebivolol and less so for l-nebivolol. Nebivolol glucuronide conjugates were also increased.

Since there were substantial effects on kinetics even after only a single dose of nebivolol and unknown steady state consequences on the administration of nebivolol in hepatic failure and renal failure (of moderate or severe magnitude i.e. a calculated creatinine clearance of < 50 ml/min), caution should be exercised in any recommendation for dosing.

Dissolution:

The biopharmaceutic reviewer suggested dissolution specifications —— in 15 minutes; the sponsor's proposal was for —— in 60 minutes. The conditions include dissolution apparatus II, 900 ml, 0.1 N HCl with a paddle speed of 50 rpm.

Pharmacology/Toxicology:

D-Nebivolol binds relatively selectively to cloned and expressed in E-coli human β_1- and β_2- adrenergic receptors. Nebivolol had an approximately 12-fold higher selectivity for the β_1-receptor relative to the β_2-receptor. L-Nebivolol was bound to the β_1 receptor with less affinity than the d-isomer. d,l- Nebivolol was bound to the β_1 receptor of rabbit lung with a K_i of approximately 10^{-9} M. The binding to the β_2 adrenergic receptor of rat lung was approximately 50-fold less potent than for the ß1-receptor. Shift of the isoprenaline ß1-adrenergic response in guinea pig right atrium, the ED_{50} for nebivolol was approximately 10^{-9} M.

There does not appear to be compelling evidence that other properties of nebivolol contribute to its blood pressure effect. Although the sponsor suggests that nebivolol has additional vasodilatory properties related to its ability to generate nitric oxide, the relevance of this phenomenon to humans at therapeutic doses is unclear. Concentrations at which nitric oxide-related effects were observed in *in vitro* animal models (10^{-5} to 10^{-6} M) do not appear to be in the range of nebivolol achievable during therapy.

With respect to the ability of animal preparations to generate nitric oxides, high concentrations of nebivolol (approximately 10^{-5} M) were able to induce relaxation in pig coronary arteries pre-contracted with prostaglandin $F2_{\alpha}$ only in arteries with intact endothelium. The relaxation could be abolished by the addition of nitro-l-arginine, an inhibitor of nitric synthetase. Similar effects were observed in canine coronary artery but not in rat aortic ring. The concentrations at which effects were observed are perhaps 3 or more orders of magnitude greater than the concentrations of nebivolol observed *in vivo* in humans and even less when corrections are made for *in vivo* protein binding. Although the finding of an interaction with the nitric oxide system is of theoretic interest, it is unlikely based on the concentrations of nebivolol required to elicit this effect, that this effect is of clinical consequence.

Toxicology:
Genetic Toxicology:

Nebivolol was negative as a mutagen in an Ames assay and in an in vitro mammalian cell gene mutation assay (L5178Y/TK+/-). There did not appear to be a signal for increase in micronucleus formation at the doses of nebivolol administered which were toxic in mice.

The results of chromosomal aberration lymphocyte assay showed no increase in what the sponsor defined as chromosomal aberrations, nevertheless, reproducible polyploidy (of unknown significance) were observed with nebivolol (with and without microsomal activation). Endoreduplication[1] were seen in one study with and without microsomal activation, but not in a repeat assay. Pulverized chromosomes were seen in one metaphase cell only with nebivolol after of microsomal activation.

With respect to general toxicology, in rodents, nebivolol affected spleen, red blood cell mass, adrenal gland and reproductive tract; in beagle dogs, spleen and adrenals were target organs.

At the highest dose of 40 mg /day, nebivolol treatment was associated with an increase in Leydig cell tumors in Albino Swiss mice. The data shown in the table below indicate not only an increase in hyperplasia and adenomas but also the occurrence of carcinomas in the studied mice. The Executive CAC has determined that that the Leydig cell tumors are drug related. No increased in incidence of neoplastic changes were found in rats at a dose of 40 mg/kg/day. The dose in mice reflect approximately 19 times the 10 mg dose, but only 5 times should the highest studied and useful doses (40 mg/day) to be approved.

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[1] Endoreduplication is a process whereby multiple uniform copies of chromosomes (nuclear polyploidization) are made usually in terminally differentiated tissues with high metabolic activity.
Larkin BA, Dilkes BP, Dante RA,Coelho CM, Woo Y, Liu Y; Journal of Experimental Botany ;2001, 52: 355 183-192.

Table 3: Carcinogenicity effects of nebivolol in Swiss Albino mice

Dose	Control	Vehicle	Nebivolol Dose (mg/kg)		
		ß-clclodextran	2.5 mg	10 mg	40 mg
Number of mice/group	50	50	50	50	50
Negative for hyperplasia and neoplasia	44	43	46	44	23
Interstitial-cell neoplasia present	1	2	0	3	17
Interstitial cell adenoma, unilateral, single	1	2	0	2	9
Interstitial cell adenoma, unilateral, multiple	0	0	0	1	1
Interstitial cell adenoma, bilateral, single	0	0	0	0	7
Interstitial cell carcinoma, unilateral, single	0	0	0	0	2
Interstitial-cell hyperplasia, present	5	6	4	3	16
Interstitial-cell hyperplasia, unilateral, focal	0	0	2	0	11
Interstitial-cell hyperplasia, unilateral, multifocal	1	1	0	0	1
Interstitial-cell hyperplasia, unilateral, diffuse	0	2	0	0	0
Interstitial-cell hyperplasia, bilateral, multifocal	1	1	1	0	2
Interstitial-cell hyperplasia, bilateral, diffuse	3	2	1	3	2

Reproductive toxicology indicate that nebivolol decreased litter size, birth weights, number of live pups at a dose of 1.25 mg/kg/day in rats (~1.25 times the high dose range). The safety margin for other ß-blockers is generally 10-fold higher than their useful dosing range. Dystocia, delayed parturition and cannibalism were prominent features of reproductive toxicology studies with nebivolol, these effects are not described in current approved labeling for other ß-blockers (see Dr. Hausner's listing in a memo dated 11 February 2005). Of particular concern was that, unique to nebivolol, a decrease in pup fertility (F1 generation) was observed. First generation effects are unusual.

The Leydig cell tumors in mice and the effects seen in reproductive toxicology studies are suggestive of a disruption by nebivolol of the hypothalamic-pituitary-endocrine axis. The sharp dose-response effect to the generation of these tumors is also consistent with an endocrine-based mechanism of action. The specific disruption of the axis has yet to be determined.

Clinical:

Efficacy of nebivolol is supported by three placebo-controlled, dose-ranging monotherapy studies and one placebo controlled, dose-ranging study as add-on treatment to other antihypertensive agents. Each of the trials is described, followed by a tabulation of the patient disposition, the demographics and the blood pressure effects.

Study NEB-302:

The study was a randomized, multi-center, placebo-controlled dose-ranging study in patients with mild-moderate hypertension (sitting diastolic blood pressure of 95 to 109 mm Hg, inclusive). Patients were randomized to receive placebo or nebivolol at a dose of 1.25, 2.5, 5, 10, 20 or 40 mg in a ratio of placebo 1: nebivolol 1:2:2:2:2:2 for 12 weeks. Those randomized to the 40 mg dose group received two weeks of nebivolol at a dose of 30 mg. If the sitting trough heart rate was greater than 55 BPM, the dose was increased to the 40 mg target dose. The primary metric of the study was the change in sitting diastolic blood pressure at the end of the 12-week randomized period. Other measurements collected and analyzed included: tough sitting systolic blood pressure, trough supine and standing, systolic and diastolic blood pressures and peak measurements of systolic and diastolic blood pressure in sitting, supine and standing positions.

The primary analytic population was the ITT population, with a last observation carried forward approach for missing data. The statistical plan called for an ANCOVA with treatment as the factor and the following covariates: baseline blood pressure, CYP2D6 status (PM/EM), diabetes status (yes/no), gender, race (black/non-black), and age (≥ 65 or < 65) . The primary analytic test was a dose-response trend test including placebo and all doses up to 20 mg. If that test was found significant, the test was repeated with the highest dose excluded. This procedure was continued until the test was no longer significant.

There were a total of 909 patients enrolled. The patients were allocated to placebo or nebivolol of 1.25: 2.5: 5: 10 20 and 40 mg was placebo 81: nebivolol 83: 82: 165: 166: 166: 166. Of those enrolled the mean age $\pm$ SD was 55 $\pm$ 12, 79% were less than or equal to 65 years, 57% of those enrolled were male. Among those enrolled 14 % were classified as black, 70 % as Caucasian, 14% as Hispanic and 2% as Asian or Other. Poor metabolizers were 6.5% of those enrolled.

There was convincing evidence from this study that nebivolol in the dose range 1.25 to 20 mg was effective in the treatment of hypertension. Although not part of the statistical plan the 40 mg dose appears to be an effective antihypertensive.

Study 305

The study was a randomized, multi-center, placebo-controlled dose-ranging study in patients with mild-moderate hypertension (sitting diastolic blood pressure of 95 to 109 mm Hg, inclusive). Patients were randomized to receive either placebo or nebivolol at a dose of, 5, 10 or 20 mg in a ratio of placebo 1: nebivolol 3: 3: 3 for 12 weeks. The primary metric of the study was the change in sitting diastolic blood pressure at the end of the 12-week randomized period. Other measurements that were made and analyzed were sitting trough systolic blood pressure

and trough systolic and diastolic measurements in the supine and standing position. Peak systolic and diastolic measurements were also analyzed in the sitting, supine and standing positions.

The primary analytic population was the ITT population with a last observation carried forward. The statistical plan called for an ANCOVA with treatment as the factor and the following covariates: baseline blood pressure, CYP2D6 status (PM/EM), diabetes status (yes/no), gender, race (black/non-black), and age (≥ 65 or < 65) . The primary analytic test was a dose-response trend test including placebo and all nebivolol doses up to 20 mg. If that test was found significant, the test was repeated with the highest dose excluded. This procedure was continued until the test was no longer significant.

There were a total of 807 patients enrolled. The patients were allocated to placebo or nebivolol at a dose of 5: 10 and 20 mg was placebo 75: nebivolol 244: 244: 244, respectively. Of those enrolled the mean age $\pm$ SD was 53 $\pm$11; 82% were less than or equal to 65 years old; 54% of those enrolled were male. Among those enrolled 13 % were classified as "Black", 79 % as Caucasian, 7% as "Hispanic" and 2% as Asian or "Other". Poor metabolizers were 6.2% of those enrolled. Patients with diabetes were approximately 5% of those enrolled.

There was convincing evidence from this study that nebivolol in the dose range of to 20 mg was effective in the treatment of hypertension. The data is tabulated below.

Study 202

The study was a randomized, multi-center, placebo-controlled dose-ranging study limited to Black patients with mild-moderate hypertension (sitting diastolic blood pressure of 95 to 109 mm Hg, inclusive). Patients were randomized to receive for 12 weeks allocated in equal proportion to receive either placebo or nebivolol at a dose of, 2.5, 5, 10 , 20 or 40 mg once daily in equal proportion. The primary metric of the study was the change in sitting diastolic blood pressure at the end of the 12-week randomized period. Additional measurements collected for analysis were sitting systolic at trough, as well as supine and standing measurements of blood pressure at trough. Peak measurements blood pressures were also analyzed in the sitting supine and standing positions.

The primary analytic population was the ITT population with a last observation carried forward. The statistical plan called for an ANCOVA with treatment as the factor and the following covariates: baseline blood pressure, CYP2D6 status (PM/EM), diabetes status (yes/no), gender, and age (≥ 65 or < 65). The primary analytic test was a dose-response trend test including placebo and all nebivolol doses up to 40 mg. If that test was found significant, the test was repeated with the highest dose excluded. This procedure was continued until the test was no longer significant.

There were a total of 300 patients enrolled. The number of patients who were allocated to placebo or nebivolol of 2.5: 5: 10: 20 and 40 mg was placebo 49: nebivolol 49: 50: 51: 50 and 51, respectively. Of those enrolled the mean age $\pm$ SD was 51 $\pm$ 10; 88 % were less than or equal to 65 years old; 45% of those enrolled were male. Patients with diabetes were

approximately 14% of those enrolled. The fraction of patients classified as poor metabolizers was 2%. The mean baseline sitting blood pressure was 152.3/100.2 mm Hg.

There was convincing evidence from this study that nebivolol in the dose range of up to 40 mg in black patients was effective in the treatment of hypertension. The data is tabulated below.

Study 321

This was a multi-center, randomized, placebo-controlled, dose-ranging study in patients who, despite current use of one or two classes of antihypertensive medication at stable doses, still had sitting diastolic blood pressure of between 90 to 109 mm Hg, inclusive. Patients were randomized in equal proportions to receive for 12 weeks either placebo or nebivolol at a dose of, 5, 10 or 20 mg once daily on top of their standard medications. The primary metric of the study was the change in sitting diastolic blood pressure at the end of the 12-week randomized period. Additional measurements collected for analysis were sitting systolic blood pressure at trough, standing and supine diastolic and systolic blood pressures at trough and peak measurements in the standing, sitting and supine positions for diastolic and systolic blood pressure.

The primary analytic population was the ITT population with a last observation carried forward. The statistical plan called for an ANCOVA with treatment as the factor and the following covariates: baseline blood pressure, CYP2D6 status (PM/EM), diabetes status (yes/no), gender, race (black/non-black), and age ($\geq$ 65 or < 65) . The sponsor used observed case and worse case analysis for the primary efficacy end point. Hochberg's step up procedure was used for paired comparison between treatment groups. This procedure was continued until the test was no longer significant.

There were a total of 669 patients enrolled. The number of patients who were allocated to placebo or nebivolol of 5: 10 and 20 mg was placebo 167: nebivolol 168: 168 and 166, respectively. Of those enrolled the mean age $\pm$ SD was 54 $\pm$ 11; 85 % were less than or equal to 65 years old; 55% of those enrolled were male; 29% were black. Patients with diabetes were approximately 14% of those enrolled. The fraction of patients classified as a poor metabolizer was 5.4% (their metabolizer status of 2% was not defined). Of the patients, 49% were taking ACE-inhibitors, 32% were taking angiotensin receptor blocker, and 44 % were taking diuretics. Mean sitting baseline blood pressure was 146/96.3 mm Hg.

There was convincing evidence that Nebivolol at a dose of 5-20 mg on top of other therapies is active in further reducing blood pressure.

Description of patient disposition:

The disposition of patients for the four pivotal studies is shown below. In considering the 4 pivotal studies the percentage of patients ranged from 86-90%, compared to 81-87% for placebo. The major reason for not completing the study was "withdrew consent".

Table 4: Disposition of patients in NEB-302, NEB-305, NEB-202 and NEB-321

	Placebo	Nebivolol Dose						All nebivolol
		1.25	2.5	5	10	20	40	
Study 302								
ITT	81	83	82	165	166	166	166	828
Completed	67 (83%)	68 (82%)	68 (83%)	148 (90%)	133 (80%)	144 (87%)	149 (90%)	710 (86%)
Discontinued	14 (17%)	15 (18%)	14 (17%)	17 (10%)	33 (20%)	22 (13%)	17 (10%)	118 (14%)
Adverse event	1 (1%)	3 (4%)	2 (2%)	0	7 (4%)	7 (4%)	3 (2%)	22 (3%)
Treatment failure	4 (5%)	4 (5%)	1 (1%)	3 (2%)	5 (3%)	1 (1%)	1 (1%)	15 (2%)
Lost to follow up	2 (2%)	1 (1%)	2 (2%)	4 (2%)	5 (3%)	4 (2%)	5 (3%)	21 (2%)
Protocol Deviation	1 (1%)	3 (4%)	1 (1%)	0	1 (1%)	2 (1%)	0	7 (1%)
Withdrew consent	5 (6%)	3 (4%)	5 (6%)	9 (6%)	12 (7%)	7 (4%)	7 (4%)	43 (5%)
Other	1(1%)	1 (1%)	3 (4%)	1 (1%)	3 (2%)	1 (1%)	1 (1%)	10 (1%)
Study 305								
ITT	75			244	244	244		732
Completed	61 (81%)			218 (89%)	206 (84%)	217 (89%)		641 (88%)
Discontinue	14 (19%)			26 (11%)	38 (16%)	27 (11%)		91(12%)
Adverse event	4 (5%)			3 (1%)	9 (4%)	8 (3%)		20 (3%)
Treatment failure	3 (4%)			3 (1%)	5 (2%)	3 (1%)		11 (1%)
Lost to follow up	0			4 (2%)	8 (3%)	3 (1%)		15 (2%)
Protocol Deviation	1 (1%)			0	3 (1%)	0		3 (<1%)
Withdrew consent	4 (5%)			8 (3%)	4 (2%)	7 (3%)		19 (3%)
Other	2 (3%)			8 (3%)	9 (4%)	6 (3%)		23 (3%)
Study 202								
ITT	49		49	50	51	50	51	251
Completed	41 (84%)		42 (86%)	41 (82%)	47 (92%)	45 (90%)	43 (84%)	218 (87%)
Discontinued	8 (16%)		7 (14%)	9 (18%)	4 (8%)	5 (10%)	8 (16%)	33 (13%)
Adverse event	0		1 (2%)	2 (4%)	0	1 (2%)	2 (4%)	6 (2%)
Treatment failure	4 (8%)		1 (2%)	2 (4%)	0	1 (2%)	2 (4%)	6 (2%)
Lost to follow up	1 (2%)		2 (4%)	4 (6%)	1 (2%)	0	1 (2%)	8 (3%)
Protocol Deviation	1 (2%)		0	0	2 (4%)	1 (2%)	1 (2%)	4 (2%)
Withdrew consent	1 (2%)		2 (4%)	1(2%)	0	0	1 (2%)	4 (2%)
Other	1 (2%)		1 (2%)	1(2%)	1 (2%)	2(4%)	0	5 (2%)
Study 321								
ITT	167			168	168	166		502
Completed	146 (87%)			152 (90%)	150 (89%)	150 (90%)		452(90%)
Discontinued	21 (13%)			16 (10%)	18 (11%)	16 (10%)		50 (10%)
Adverse event	4 (2%)			9 (5%)	5 (3%)	7 (4%)		21 (4%)
Treatment failure	3 (2%)			0	0	2 (1%)		2 (<1%)
Lost to follow up	4 (2%)			0	5 (3%)	1 (1%)		6 (1%)
Protocol Deviation	0			0	1 (1%)	1 (1%)		2 (< 1%)
Withdrew consent	10 (6%)			7 (4%)	7 (4%)	3 (2%)		17 (3%)
Other	0			0	0	2 (1%)		2 (<1%)
Studies NEB-302. NEB305, NEB-202 and NEB-321								
ITT	372	83	131	627	629	626	217	2313
Completed	315 (85%)	68 (82%)	110 (83%)	559 (89%)	536 (85%)	556 (89%)	192(90%)	2021 (87%)
Discontinued	57 (15%)	15 (18%)	21 (16%)	68 (11%)	19 (3%)	70 (11%)	25 (10%)	292 (13%)
Adverse event	9 (2%)	3 (4%)	3 (2%)	14 (2%)	21 (3%)	23 (4%)	5 (2%)	69 (3%)
Treatment failure	14 (4%)	4 (5%)	2 (1%)	8 (1%)	10 (2%)	7 (1%)	3 (1%)	34 (2%)
Lost to follow up	7 (2%)	1 (1%)	4 (3%)	12 (2%)	19 (3%)	8 (1%)	6 (3%)	46 (2%)
Protocol Deviation	3 (1%)	3 (4%)	1 (1%)	0	7 (1%)	4 (1%)	1 (<1%)	16 (1%)
Withdrew consent	20 (5%)	3 (4%)	7 (5%)	25 (4%)	23 (4%)	17 (3%)	8 (4%)	83 (4%)
Other	4 (1%)	1 (1%)	4 (3%)	10 (2%)	13 (2%)	11 (2%)	1 (< 1%)	40 (2%)

Demographics:

The demographic characteristics for each study for age gender race and genomic status is shown below. Each of the dose groups within each study and each of the studies appeared well balanced.

Table 5: Demographic characteristics of studies NEB-302, NEB-305, NEB-202 and NEB-321

		Nebivolol Dose					
	PBO	1.25	2.5	5	10	20	40
Study							
Age (mean ± SD)							
302	56 ± 12	56 ± 12	53 ± 12	55 ± 12	55 ± 13	54 ± 12	54 ± 12
305	51 ± 10			54 ± 11	54 ± 11	53 ± 11	
202	50 ± 9		50 ± 10	52 ± 11	51 ± 11	51 ± 11	52 ± 12
321	54± 10			54 ± 11	54 ± 11	3 ± 11	
Age > 65 (%)							
302	21%	22%	17%	20%	25%	19%	23%
305	11 %			18 %	19%	18%	
202	11%		8 %	12%	12%	10 %	18%
321	16 %			16%	15%	15%	
Gender (% Female)							
302	43 %	45 %	35%	42%	44%	45%	45%
305	48 %			46%	46%	46%	
202	53%		47%	56%	57 %	58 %	57 %
321	46 %			44%	45%	45 %	
Race %Caucasian/% Black/% Hispanic/% Other [* categorized as non-black/black]							
302	75/14/11/0	72/15/12/1	73/16/11/0	73/14/13/1	68/15/152	68/15/15/2	68/15/15/2
305	80/15/5/0			78/13/8/2	79/12/8/1	78/13/7/1	
202	0/100/0/0		0/100/0/0	0/100/0/0	0/100/0/0	0/100/0/0	0/100/0/0
321*	71/29			70/30	70/30	71/29	
Metabolic profile number % poor metabolizers)							
302	4 (5%)	5 (6%)	6 (7%)	10 (6%)	11 (7%)	12 (7%)	11 (7%)
305	4 (5%)			9 (4%)	12 (5%)	12 (5%)	
202	0		1 (2%)	1 (2%)	2 (4%)	1 (2%)	2 (4%)
321*	9 (5%)			10 (6%)	9 (5%)	8(5%)	

Sitting trough diastolic blood pressure:

Below is a summary of the effects for each of the pivotal studies for sitting diastolic blood pressure, the primary metric of each of the studies.

Table 6: LS mean placebo-subtracted effect for trough sitting diastolic blood pressure.

	Nebivolol dose					
	1.25	2.5	5.0	10	20	40
Study 302	-5.1*	-5.6*	-5.5*	-6.3*	-6.9*	-8.3*
Study 305			-2.8*	-3.9*	-4.5*	
Study 202		-2.9#	-4.9*	-6.1*	-6.0*	-5.5*
Study 321			-3.2*	-3.3*	-4.7*	

P-value reflects trend test or Hochberg adjusted p-values. *$P < 0.01$; #$0.1 < p < 0.05$

All studies were significant by their primary endpoint. There was a clear dose response trend test for all studies. The dose range of 1.25 to 40 mg daily appears to have reasonable effects, particularly for a general hypertension population.

Supportive measurements at trough:

Additional measurements collected at trough (Table 7) are shown below (LS mean). The results are similar to the pivotal endpoints. The results for peak measurements (Table 8) in all positions are qualitatively similar to the primary study endpoint results.

Table 7: LS mean placebo-subtracted effect for trough blood pressure measurement

		Nebivolol dose					
		1.25	2.5	5.0	10	20	40
Sitting trough SBP	Study 302	-6.6	-8.5	-8.1	-9.2	-8.7	-11.7
	Study 305			-3.5	-3.1	-6.3	
	Study 202		-1.5	-2.6	-6.0	-7.3	-6.8
	Study 321			-5.7	-3.7	-6.2	
Standing trough DBP	Study 302	-4.5	-6.4	-5.2	-6.6	-7.3	-9.1
	Study 305			-3.2	-3.5	4.4	
	Study 202		-0.8	-3.6	-4.6	-4.3	-5.0
	Study 321			-3.6	-3.5	-4.6	
Standing trough SBP	Study 302	-6.8	-10.1	-8.0	-9.1	-8.9	-12.4
	Study 305			-4.4	-3.0	-6.4	
	Study 202		0	-3.2	-3.2	-5.2	-6.2
	Study 321			-3.7	-2.2	-5.1	
Supine trough DBP	Study 302	-3.0	-5.1	-4.9	-5.4	-5.9	-7.6
	Study 305			-4.4	-4.3	-5.0	
	Study 202		-3.3	-3.8	-5.7	-5.2	-5.1
	Study 321			-3.5	-3.5	-4.2	
Supine Trough SBP	Study 302	-5.3	-8.9	-8.2	-7.7	-7.8	-11.5
	Study 305			-4.6	-3.2	-7.0	
	Study 202		+0.2	-0.1	-4.3	-2.1	-4.3
	Study 321			-4.9	-2.9	-4.5	

Table 8: LS mean placebo-subtracted effect for peak blood pressure

		Nebivolol dose					
		1.25	2.5	5.0	10	20	40
Sitting peak DBP	Study 302	-3.8	-4.7	-5.4	-6.2	-7.8	-8.5
	Study 305			-3.5	-4.6	-5.2	
	Study 202		-4.8	-6.8	-8.5	-7.1	-7.6
	Study 321			-3.2	-4.0	-4.3	
Sitting peak SBP	Study 302	-4.5	-5.0	-6.5	-7.9	-10.0	-10.9
	Study 305			-3.1	-4.9	-6.0	
	Study 202		-4.8	-7.6	-8.5	-9.2	-9.2
	Study 321			-5.7	-5.6	-5.9	
Standing peak DBP	Study 302	-3.2	-4.7	-5.4	-6.9	-8.1	-9.3
	Study 305			-3.8	-5.4	5.5	
	Study 202		-3.0	-6.1	-6.9	-5.4	-5.9
	Study 321			-3.5	-3.9	-3.1	
Standing peak SBP	Study 302	-2.8	-4.7	-6.7	-7.4	-8.4	-10.7
	Study 305			-5.0	-6.2	-7.6	
	Study 202		-4.0	-8.5	-7.5	-7.5	-7.7
	Study 321			-5.1	-4.4	-5.5	
Supine peak DBP	Study 302	-2.8	-4.4	-4.7	-5.1	-6.5	-7.7
	Study 305			-10.8	-11.0	-11.4	
	Study 202		-4.3	-5.3	-6.5	-6.3	-6.3
	Study 321			-3.4	-3.6	-3.2	
Supine peak SBP	Study 302	-3.2	-5.6	-6.0	-7.5	-8.1	-10.2
	Study 305			-7.5	-7.8	-9.3	
	Study 202		-4.6	-6.8	-8.7	-8.7	-8.5
	Study 321			-5.2	-4.9	-5.9	

Inter-dosing interval:

The once-daily dose regimen is appropriate based on the retention of substantially effect comparing the placebo-subtracted peak measurements (2-3 hours post dose) to trough (24 $\pm$ 2 hours) supine measurements. The peak to rough ratio for the various pivotal studies based on dose is shown below. No regimens other than once daily were studied.

Table 9: Peak to trough ratios for trough measurements of sitting diastolic blood pressure

Study	Nebivolol dose					
	1.25	2.5	5	10	20	40
302	1.4	1.2	1.0	1.0	0.9	1.0
305			1.1	1.2	1.1	
202		1.7	1.4	1.4	1.2	1.4
321			1.0	1.2	0.9	

Dose range:

The development program for nebivolol explored the dose range of 1.25 to 40 mg daily. There was a consistent and dose-related effect on blood pressure for the entire dose range. Side effects that appear to limit dose are generally extensions of its β- blockade mechanism of action.

Time to establish effect:

Measurement at several time points during therapy in study NEB-302, NEB-305 and NEB-202 demonstrate that by 14 days the effect at steady state seems to be present (see Figures 10, 14 and 15 of Dr. Hick's review). Dose titration for inadequate response can be recommended at two-week intervals.

Subgroup efficacy

Race:

Study NEB-202 was performed in a Black population. Nebivolol at doses ranging from 2.5 mg to 40 mg appeared to have a reasonable magnitude in sitting diastolic blood pressure effects. There were too few black subjects in other studies to be able to determine whether the effect in Caucasians and Blacks are equivalent.

Age, Gender and CYP2D6 phenotypic status

Subgroup analyses per sponsor for Age (≤ 65 or > 65), Gender and metabolizer status for the three monotherapy studies are shown below. The general dose response relationship appears to be similar across the demographic characteristics. There are, however, modest number of subjects greater than 65 and modest number who are poor metabolizers. For the geriatric section the paragraph A wording still seems the most appropriate. The labeling should be mute on the effect on poor metabolizers since there is inadequate information to either establish similarities or differences between PM and EM subjects.

Table 10: Subgroup analysis for the three monotherapy studies NEB-302, NEB-305 and NEB-202.

Parameter	PBO	Nebivolol daily dose					
		1.25	2.5	5	10	20	40
Age							
≤65	-4.0 ±0.6 n=175	-7.1 ±1.1 n= 65	-8.0 ± 0.9 n= 113	-8.6 ± 0.7 n=375	-9.4 ± 0.7 n=367	-10.0 ± 0.7 n= 376	-11.2 ± 0.4 n=170
>65	-6.2 ± 1.7 n=30	-7.7 ± 2.1 n=18	-7.1 ± 2.1 n=18	-10.0 ±1.2 n=84	-11.5 ± 1.3 n=94	-11.5 ± 1.3 n=75	-9.9 ± 1.4 n=97
Gender							
Male	-3.8 ± 1.0 n=108	-7.1 ± 1.4 n= 46	-8.2 ± 1.1 n= 79	-8.8 ± 0.9 n=249	-9.4 ± 0.9 n= 246	-9.7 ± 0.8 n= 244	-11.5 ± 1.0 n=114
Female	-4.9 ± 1.1 n=97	-7.0 ± 1.5 n=37	-7.1 ± 1.3 n=52	-8.8 ±0.9 n=210	-9.8 ± 0.9 n=215	-10.8 ± 0.9 n=216	-9.1 ± 1.1 n=114
Metabolizer status							
PM	-3.4 ± 4.7 n=8	-7.5 ±5.1 n= 5	-14.0 ±1 n= 7	-10.7 ± 0.9 n=26	-12.3 ± 3.7 n= 28	-11.4 ± 3.7 n= 20	-10.0 ± 3.7 n=13
EM	-4.3 ± 0.7 n=197	-7.0 ± 1.0 n=78	-7.4 ± 0.8 n=124	-8.7 ±0.5 n=433	-9.5 ± 0.5 n=433	-10.1 ± 0.5 n=431	-10.3 ± 0.6 n=204

Long-term efficacy:

There is inadequate information to conclude that the antihypertensive effects persist for the duration of the open-label extension. Patients who completed the monotherapy efficacy studies (NEB-302, NEB-305, NEB-202) were eligible for enrollment into a 9-month follow-up study (NEB-306). During this phase additional antihypertensive medications were allowed for blood pressure control. A total of 845 subjects entered the long-term follow-up study. Of these patients 393 completed the study, of which 268 remained on nebivolol monotherapy. The large fraction of patients who discontinued coupled with the frequent co-administration of additional antihypertensive medication make the persistence of any blood pressure effects difficult to interpret.

Twenty eight subjects who completed this open-label extension were randomized in a 2:1 ratio of placebo: continued nebivolol dose. The effect after one to four weeks of withdrawal showed a small and unconvincing blood pressure increase for the placebo relative to those who remained on therapy (3-4 mm Hg); with the blood pressure effect between the two groups overlapping. Neither the baseline comparison because of the confounding dropouts and concomitant treatments nor the randomized withdrawal study is convincing that the effect of nebivolol persists during chronic dosing.

Safety:

Primary safety was derived from the current US-development program. This program consisted of 4 placebo-controlled dose-ranging studies (NEB-302, NEB-305, NEB-202 and NEB-321) each lasting for 12-weeks and one positive controlled study (NEB-203), comparing nebivolol to atenolol. One of the placebo-controlled studies NEB-321 was on top of other anti-hypertensive medications. These medications included ACE-inhibitors, angiotensin receptor

blockers or diuretics. Patients who successfully completed one of the four placebo-controlled studies could be entered into an open-label extension study (NEB-306) in which patients could be treated for up to an additional 9 months.

In addition to the current database, a second database generated by Janssen Pharmaceutica, the original IND holder for nebivolol, which was the sole support for approval of nebivolol in Europe. The Janssen database consisted of 2874 patients enrolled in 65 nebivolol studies. In these studies 2570 were treated for hypertension, 144 for CHF and 144 for ischemic heart disease. The doses used in these studies were, in general, less than 10 mg. Neither case report forms nor adequate documentation for the Janssen database are available. An accurate assessment and description of adverse events would contain some uncertainty. The Janssen database, however, was not needed to support either efficacy or safety conclusion of this review. The fact that the Janssen database was the safety basis for approval of the drug in Europe strongly suggest no safety signal of sufficient magnitude is missed by not having the data currently available for review.

Exposure in U.S.-database:

The placebo-controlled, dose-ranging trials were all 12-week in duration. Study NEB-203 was a small positive controlled study (atenolol) that is not included in the above table, during which patients were exposed for 4 weeks. Study NEB-203 randomized 115 patients 45 to atenolol and 70 to nebivolol. The nebivolol patients were equally allocated to 5, 10 and 20 mg daily doses.

In addition, to the controlled data base, subjects who completed the monotherapy controlled studies (NEB-302, NEB-305 and NEB-202) were eligible for entry into the open-label 9- month extension study.

Disposition and demographics:

The disposition of patients and the demographic characteristics of patients are tabulated above in Table 4 and Table 5, respectively.

Deaths/Dropouts Discontinuation

There were two deaths in the current nebivolol database. One patient a 75 year-old female died after a myocardial infarction following one day of nebivolol treatment. The second patient, a 46- year old male, was treated with nebivolol for 12 days and had a resolving episode of pericarditis. The patient died from cardiac arrest apparently 3 days after resolution of the pericarditis. Among other medications the patient was taking sildenafil.

The listing of adverse events leading to discontinuation is shown below. The table only includes the number of events in the major system category and those events for which more than one subjects in any of the nebivolol doses had an event.

The percentage of patients with such events ranged from 1.5% in the 2.5 mg dose to 3.5% in the 20 mg dose. The most common events in the nebivolol treatment group were bradycardia, nausea, headache and fatigue.

Table 11: List of reason for discontinuation in placebo-controlled, dose-ranging study (NEB-302, NEB-305, NEB-202 and NEB-321).

Event	PBO	Any Nebivolol	Nebivolol					
			1.25	2.5	5	10	20	40
Number /group	372	2313	83	131	627	626	626	217
Any (%)	9(2.4%)	64 (2.7%)	2 (2.4%)	2 (1.5%)	13 (2.1%)	20 (3.2%)	22 (3.5%)	5 (2.4%)
Cardiac disorder (Any)	2	13	1	0	2	2	8	1
Bradycardia	0	4	0	0	0	0	4	0
Cardiac failure congestive	0	2	0	0	0	1	1	0
Gastrointestinal (any)	0	11	0	0	2	5	4	0
Nausea	0	4	0	0	1	2	1	0
Diarrhea	0	2	0	0	0	1	1	0
Nervous system (any)	1	10	1	0	2	4	2	1
Headache	1	6	1	0	0	3	2	0
Dizziness	0	2	0	0	1	0	0	1
General disorders and administrative site conditions (any)	2	9	0	1	2	2	4	0
Fatigue	1	3	0	0	1	0	2	0
Chest pain	0	2	0	0	0	1	1	0
Respiratory, thoracic and mediastinal disorders (any)	0	3	0	1	2	2	0	5
Vascular disorders (any)	0	5	0	0	2	2	1	0
Orthostatic hypotension	0	2	0	0	0	1	1	0
Investigations (any)	0	3	0	0	2	0	1	0
Skin and subcutaneous tissue disorder	1	0	0	0	0	2	0	1
Eye disorders (any)	0	2	0	0	1	1	0	0
Infections and infestations (Any)	0	2	0	0	0	1	0	1
Neoplasms: benign, malignant and unspecified	0	2	0	0	0	0	1	1
Psychiatric disorders (any)	1	2	0	0	0	2	0	0
Ear and labyrinth disorders (any)	0	1	0	0	0	1	0	0
Hepatobiliary disorder (any)	0	1	0	1	0	0	0	0
Injury, poisoning and procedural complications	0	1	0	0	0	1	0	0
Musculoskeletal and connective tissue								

disorder (any)	0	1	0	0	0	0	1	0
Immune system disorder (any)	1	0	0	0	0	0	0	0
Metabolism and nutrition disorders (any)	1	0	0	0	0	0	0	0

Serious Adverse:

Serious adverse events occurring in more than one nebivolol patients are shown below. There was no glaring sign of a specific serious adverse event in the nebivolol treated subjects.

Table 12: Serious adverse events by system and specific events observed in more than one nebivolol patient dose-ranging study (NEB-302, NEB-305, NEB-202 and NEB-321).

Event	PBO	Any Nebivolol	Nebivolol					
			1.25	2.5	5	10	20	40
Number /group	372	2313	83	131	627	626	626	217
Any	4	26	1	3	8	3	8	3
Cardiac Disorder (any)	2	4	1	0	1	1	1	0
Gastrointestinal (any)	0	4	0	1	1	0	2	0
General disorders and administrative site conditions (any) Chest pain	0 0	3 2	0 0	0 0	2 1	0 0	0 0	1 1
Infections and infestations (any)	0	3	0	0	1	1	1	0
Neoplasms: benign, malignant and unspecified	0	3	0	0	1	0	1	1
Vascular disorders (any)	0	3	0	0	1	0	2	0
Injury, poisoning and procedural complications Road traffic accident	0 0	2 2	0 0	1 1	1 1	0 0	0 0	0 0
Investigations (any)	0	2	0	0	0	0	1	1
Blood and lymphatic system disorder (any)	0	1	0	0	0	0	1	0
Heptobiliary disorder (any)	1	0	0	1	0	0	0	0
Nervous system (any)	1	1	0	0	1	0	0	0

Respiratory, thoracic and mediastinal disorder (any)	0	1	0	0	0	1	0	0
Musculoskeletal and connective tissue disorder (Any)	1	0	0	0	0	0	0	0
Psychiatric disorder (Any)	1	0	0	0	0	0	0	0

Additional serious events of concern:

Angioedema:

As Dr. Lemtouni's review notes there was one subject during the clinical trials that developed angioedema and was discontinued from nebivolol. The subject was not on concomitant ACE-I or angiotensin II blockers. There were four additional cases of either tongue or facial edema not leading to discontinuation.

Liver dysfunction:

Dr. Lemtouni notes that there were three subjects who suffered clinically significant hepatic disease.

- One patient apparently developed acute hepatitis A (positive IGM).
- One patient had persistent right upper quadrant pain with a liver biopsy showing scarred, necrotic and proliferative changes. The pain apparently resolved while still treated with nebivolol.
- One patient developed a viral syndrome prior to entering into the clinical trial. His liver abnormalities began near the end of the extension phase. The sponsor claims that the enzymes were decreasing by the end of the study.

General adverse events:

Adverse events occurring in > 1% of nebivolol patients during the randomized clinical studies are shown below. There was a dose-response trend to adverse events. Thirty-nine percent of those randomized to placebo and 49% of the high-dose nebivolol group had adverse events. Infections and infestations, nervous system disorders (headache and dizziness), gastrointestinal disorders (diarrhea), general disorders and administrative site conditions (fatigue) and investigations (CRP-increased) were the most common adverse events.

Table 13: Events by general classification and those events most frequent in that class and those > 1 % dose-ranging studies (NEB-302, NEB-305, NEB-202 and NEB-321).

Event	PBO	Any nebivolol	Nebivolol Dose (mg/day)					
			1.25	2.5	5	10	20	40
Number /group	372	2313	83	131	627	626	626	217
Any event	144 (39%)	1008 (44%)	29 (35%)	56 (43%)	258 (41%)	266 (43%)	292 (47%)	107 (49%)
Infections and infestations (Any)	42 (11%)	300 (13%)	7 (8%)	13 (10%)	86 (14%)	61 (10%)	90 (14%)	43 (20%)
Nasopharyngitis	11(3%)	68 (3%)	2 (2%)	5 (4%)	21 (3%)	12 (2%)	22 (4%)	6 (3%)
Upper respiratory tract infections	8 (2%)	46 (2%)	0 (0%)	2 (2%)	13 (2%)	9 (1%)	15 (2%)	7 (3%)
Urinary tract infections	8 (2%)	41 (2%)	1 (1%)	2 (2%)	16 (2%)	5 (1%)	13 (2%)	4 (2%)
Sinusitis	3 (1%)	30 (1%)	1(1%)	0 (0%)	8 (1%)	9 (1%)	7 (1%)	5 (2%)
Nervous system disorders (Any)	33 (9%)	257 (11%)	7 (8%)	17 (13%)	69 (11%)	62 (10%)	71 (12%)	31 (14%)
Headache	16 (4%)	153 (7%)	6 (7%)	8 (7%)	49 (8%)	39 (6%)	34 (6%)	17 (8%)
Dizziness	7 (2%)	65 (3%)	1 (1%)	4 (3%)	12 (2%)	15 (2%)	23 (4%)	10 (5%)
Gastrointestinal disorders (Any)	27 (7%)	188 (8%)	4 (4%)	11 (9%)	42 (7%)	52 (8%)	59 (9%)	20)9%)
Diarrhea	7 (1%)	54 (2%)	1 (1%)	2 (2%)	14 (2%)	10 (2%)	19 (3%)	8 (4%)
Nausea	3 (1%)	39 (2%)	0 (0%)	3 (3%)	6 (15)	16 (3%)	12 (2%)	2 (1%)
General disorders and administration site conditions	18 (5%)	174 (7%)	3 (3%)	11 (9%)	36 (6%)	44 (7%)	63 (10%)	17 (8%)
Fatigue	7 (2%)	83 (4%)	1 (1%)	6 (5%)	17 (3%)	16 (3%)	33 (5%)	10 (5%)
Investigations (any)	22 (6%)	237 (10%)	3 (3%)	10 (8%)	42 (7%)	52 (8%)	44 (7%)	11 (5%)
C-RP increased	1 (< 1%)	22 (1%)	1 (1%)	5 (4%)	3 (<1%)	4 (1%)	5 (1%)	4 (2%)
Musculoskeletal and Connective tissue (any)	18 (5%)	123 (5%)	3 (3%)	7 (5%)	34 (5%)	35 (6%)	30 (5%)	14 (6%)
Arthralgia	6 (2%)	31 (1%)	0 (0%)	3 (2%)	8 (15)	11 (2%)	5 (1%)	4 (2%)
Respiratory and mediastinal disorders (any)	14 (4%)	107 (5%)	6 (6%)	8 (6%)	29 (5%)	28 (5%)	31 (5%)	5 (2%)
Cough	5 (1%)	24 (1%)	3 (3%)	3 (2%)	7 (1%)	8 (1%)	3 (<1%)	0 (0%)
Cardiac disorders (any)	8 (2%)	60 (3%)	2 (2%)	2 (2%)	15 (2%)	11 (2%)	24 (4%)	6 (3%)
Bradycardia	1 (< 1%)	17 (1%)	0 (0%)	0 (0%)	2 (<1%)	3 (<1%)	11 (2%)	1 (<1%)
Psychiatric disorders (any)	3 (1%)	58 (3%)	2 (2%)	4 (3%)	2 (<1%)	14 (2%)	23 (4%)	3 (1%)
Insomnia	1(<1%)	25 (1%)	0 (0%)	3 (2%)	4(1%)	6 (1%)	11 (2%)	1 (<1%)
Injury poisoning and procedural complications (any)	15 (4%)	56 (2%)	2 (2%)	3 (2%)	12 (2%)	16 (3%)	14 (2%)	9 (4%)
Back injury	1 (<1%)	9 (<1%)	0 (0%)	0 (0%)	2 (<1%)	5 (1%)	0 (0%)	2 (1%)
Skin and subcutaneous tissue disorders (any)	10 (3%)	56 (2%)	1 (1%)	4 (3%)	10 (2%)	19 (3%)	15 (2%)	7 (3%)
Rash	3 (1%)	18(1%)	1 (1%)	3 (2%)	1(<1%)	7 (1%)	5 (1%)	1 (<1%)

Metabolism and nutrition disorders (any) hyperlipidemia	8 (2%) 1 (<1%)	47 (2%) 8 (<1%)	2 (2%) 1 (1%)	1 (1%) 0 (0%)	8 (1%) 2(<1%)	15 (2%) 2 (<1%)	16 (3%) 2 (<1%)	2 (1%) 1 (<1%)
Eye disorder (Any) Vision blurred	0 (0%) 0 (0%)	30 (1%) 12 (5%)	1 (1%) 0 (0%)	3 (25) 2 (2%)	8 (1%) 3(<1%)	10 (2%) 4 (1%)	8 (1%) 3(<1%)	0 (0%) 0 (0%)
Reproductive system and breast disorders (any) Dysmenorrhea	7 (2%) 0 (0%)	24 (1%) 5 (<1%)	0 (0%) 0 (0%)	2 (2%) 0 (0%)	4(1%) 1(<1%)	9 (1%) 1 (<1%)	5(1%) 2 (<1%)	4 (2%) 1 (<1%)
Renal and urinary disorders (any) Hematuria	6 (2%) 0 (0%)	22 (1%) 7 (<1%)	1 (1%) 0 (0%)	0 (0%) 0 (0%)	11 (2%) 3(<1%)	7 (1%) 3 (<1%)	2(<1%) 0 (0%)	1 (<1%) 1(<1%)
Ear and labyrinth disorders (any) Ear pain	3 (1%) 0 (0%)	21 (1%) 9 (<1%)	0 (0%) 0 (0%)	0 (0%) 0 (0%)	5 (1%) 2(<1%)	8 (1%) 3 (<1%)	7 (1%) 4 (1%)	1 (<1%) 0 (0%)
Vascular disorders Flushing	6 (2%) 0 (0%)	19 (1%) 1 (<1%)	1 (1%) 0 (0%)	0 (0%) 0 (0%)	3 (<1%) 2 (<1%)	5 (1%) 1 (<1%)	10 (2%) 0 (0%)	9 (4%) 4 (2%)
Blood ad lymphatic system disorders (any) Anemia aggravated	2 (1%) 0 (0%)	13 (1%) 0 (0%)	0 (0%) 0 (0%)	1 (1%) 1 (1%)	4 (1%) 1(<1%)	4 (1%) 0 (0%)	4 (1%) 1(<1%)	0 (0%) 0 (0%)
Neoplasms, benign, malignant and unspecified (any) Breast lump	1 (< 1%) 0 (0%)	13 (1%) 3 (< 1%)	0 (0%) 0 (0%)	1 (1%) 1 (1%)	3(<1%) 0 (0%)	2(<1%) 1(<1%)	6 (1%) 1 (<1%)	1 (<1%) 0 (0%)
Immune system disorders (Any) Hypersensitivity	3 (1%) 2(1%)	12 (<1%) 5 (<1%)	0 (0%) 0 (0%)	0 (0%) 0 (0%)	1(<1%) 1(<1%)	4(1%) 1(<1%)	4(1%) 2 (<1%)	3 (1%) 1(<1%)
Hepatobiliary disorders (Any) Cholecystitis	0(0%) 0(0%)	3 (< 1%) 0 (0%)	0 (0%) 1 (1%)	1 (1%) 0 (0%)	0 (0%) 0 (0%)	0 (0%) 0 (0%)	1(<1%) 0 (0%)	1 (<1%) 0 (0%)
Surgical and medical procedures Bunion operation	1 (<1%) 0 (0%0	1 (< 1%) 1 (< 1%)	0 (0%) 0 (0%)	0 (0%) 0 (0%)	1(<1%) 1(<1%)	1 (<1%) 0 (0%)	0 (0%) 0 (0%)	1 (<1%) 0 (0%)

Adverse events

Adverse events during the open-label study and other databases:

Dr. Lemtouni's review describes the safety from the Janssen's database as well as the post-marketing database. Most of the adverse events noted by Dr. Lemtouni are difficult to interpret either because of the heterogeneity of types of study during which patients received nebivolol in the Janssen's database (patients were enrolled in either placebo-controlled, positive controlled or open-label extensions) and the uncontrolled nature of the open-label extension database. The usefulness of this database is predominantly to capture rare and serious events.

There were one additional patients who developed some evidence or frank angioedema while treated with nebivolol during the marketing survey.

Labs:

Below are the changes in laboratory values at the last available measurement for the patient during the controlled studies relative to baseline. The number for which the values were collected varied.

Table 14: Change in laboratory parameters clinical placebo-controlled studies (NEB-302, NEB-305, NEB-202 and NEB-321).

Parameter Units	PBO	All nebivolol	Nebivolol dose (mg/day) 1.25	2.5	5	10	20	40
Hemoglobin G/DL	-0.04 ± 0.04 (N= 358)	-0.03 ± 0.02 (n=2184)	0.20 ± 0.08 (n=78)	-0.04 ± 0.06 (n=121)	-0.02 ± 0.03 (n=593)	-0.05 ± 0.03 (n=594)	-0.06 ± 0.03 (n=595)	-0.02 ± 0.05 (n=203)
Hematocrit %	0.10 ± 0.12 (N= 358)	-0.09 ± 0.05 (n=2183)	0.27 ± 0.26 (n=78)	-0.04 ± 0.06 (n=121)	-0.02 ± 0.03 (n=593)	-0.05 ± 0.03 (n=594)	-0.06 ± 0.03 (n=595)	-0.02 ± 0.05 (n=203)
Platelet count X $10^3/mm^3$	-3.3 ± 1.8 (n=358)	-13.4 ± 0.8 (n = 2174)	-9.9 ± 3.9 (n=77)	-11.9 ± 3.5 (n= 120)	-12.3 ± 1.4 (n=590)	-12.1 ± 1.5 (n= 592)	-15.2 ± 1.4 (n=592)	-17.8 ± 2.5 (n=203)
WBC count X $10^3/uL$	0.07 ± 0.7 (n=358)	0.13 ± 0/03 (n=2180)	0.01 ± 0.13 0.02 (n=78)	0.60 ± 0.78 (n=123)	-0.68 ± 0.33 (n=596)	-0.76 ± 0.34 (n=597)	-0.41 ± 0.34 (n=596)	0.13 ± 0.08 (n=203)
Chemistry								
Sodium mEq/L	0.1 ± 0.14 (n=361)	0.0 ± 0.05 (n=2203)	0.1 ± 0.3 (n=77)	0.1 ± 0.20 (n=124)	-0.1 ± 0.1 (n=596)	0.0± 0.1 (n=602)	0.0 ±0.1 (n=600)	-0.1± 0.20 (n=204)
Potassium mEq/L	-0.03 ± 0.02 (n=357)	0.05 ± 0.01 (n=2202)	0.07 ± 0.04 (n=77)	0.05 ± 0.03 (n=124)	0.06 ± 0.02 (n=601)	0.03 ± 0.02 (n=600)	0.04 ±0.02 (n=600)	0.04 ± 0.03 (n=204)
Chloride mEq/L	-0.1 ± 0.13 (n=361)	0.3 ± 0.06 (n=2204)	0.0± 0.13 (n=77)	0.2 ± 0.2 (n=124)	0.3 ± 0.11 (n=597)	0.3± 0.11 (n=602)	0.2 ±0.10 (n=600)	0.3 ± 0.21 (n=204)
Carbon dioxide mEq/L	-0.1 ± 0.19 (n=359)	-0.2 ± 0.07 (n=2203)	-0.1 ± 0.41 (n=77)	0.6 ± 0.3 (n=124)	0.0 ± 0.14 (n=596)	-0.2± 0.14 (n=602)	-0.6 ±0.13 (n=600)	-0.6± 0.25 (n=204)
Calcium Mg/dL	-0.06 ± 0.18 (n=359)	-0.02 ± 0.01 (n=2202)	-0.09 ± 0.40 (n=77)	-0.07 ± 0.03 (n=124)	0.03 ± 0.016 (n=596)	-0.01± 0.016 (n=601)	-0.01 ±0.016 (n=600)	-0.02± 0.03 (n=204)
Phosphorus mg/dL	0.03 ± 0.03 (n=361)	0.06 ± 0.01 (n=2203)	-0.1 ± 0.058 (n=77)	0.08 ± 0.04 (n=124)	0.04 ± 0.02 (n=597)	0.07± 0.02 (n=601)	0.08 ±0.02 (n=600)	0.13± 0.05 (n=204)
Magnesium mEq/L	-0.01 ± 0.01 (n=361)	-0.02 ± 0.00 (n=2204)	0.01 ± 0.01 (n=77)	-0.02 ± 0.01 (n=124)	-0.0 2± 0.01 (n=597)	-0.02± 0.01 (n=602)	-0.02 ±0.01 (n=600)	-0.04± 0.01 (n=204)

BUN Mg/dL	0.2 ± 0.19 (n=361)	0.5 ± 0.08 (n=2204)	0.5 ± 0.47 (n=77)	0.5 ± 0.3 (n=124)	0.3 ± 0.16 (n=597)	0.8± 0.16 (n=602)	0.7 ±0.15 (n=600)	0.1± 0.26 (n=204)
Creatinine Mg/dL	0.0 ± 0.01 (n=361)	0.02 ± 0.00 (n=2204)	0.01 ± 0.02 (n=77)	0.01 ± 0.01 (n=124)	0.02 ± 0.01 (n=597)	0.02± 0.01 (n=602)	0.02 ±0.01 (n=600)	0.01± 0.01 (n=204)
Total cholesterol Mg/dL	-3.6 ± 1.5 (n=361)	-2.7 ± 0.6 (n=2204)	-3.8 ± 3.3 (n=77)	0.2 ± 2.2 (n=124)	-4.3 ± 1.2 (n=597)	-1.4± 1.3 (n=602)	-2.4 ±1.1 (n=600)	-4.1± 2.0 (n=204)
HDL cholesterol Mg/dL	0.5 ± 0.5 (n=316)	-2.1 ± 0.2 (n=1916)	-1.8 ± 1.0 (n=65)	-1.1 ± 0.9 (n=105)	-2.4 ± 0.4 (n=508)	-1.8± 0.4 (n=526)	-2.3 ±0.4 (n=531)	-2.5± 0.7 (n=181)
LDL cholesterol Mg/dL	-3.6 ± 1.5 (n=299)	-2.6 ± 0.6 (n=1793)	-2.5 ± 3.3 (n=62)	-0.6 ± 2.0 (n=97)	-2.6 ± 1.02 (n=476)	-2.6 ± 1.1 (n=490)	-2.4 ±1.7 (n=492)	-3.6± 0.1.7 (n=176)
Triglycerides Mg/dL	2.7 ± 3.8 (n=360)	16.1 ± 2.8 (n=2204)	7.9 ± 10.3 (n=77)	17.7 ± 12.3 (n=124)	6.2 ± 5.2 (n=597)	27.7± 6.4 (n=602)	15.6 ±4.8 (n=600)	14.5± 8.4 (n=204)
Uric acid Mg/dL	-0.02 ± 0.04 (n=360)	0.17 ± 0.02 (n=2203)	-0.07 ± 0.04 (n=77)	0.1 ± 0.09 (n=124)	0.17 ± 0.03 (n=597)	0.18± 0.04 (n=601)	0.22 ±0.04 (n=600)	0.16± 0.06 (n=204)
Alk Phosphatase U/L	-0.0 ± 0.6 (n=361)	-1.8 ± 0.2 (n=2204)	-0.0 ± 1.3 (n=77)	1.2 ± 0.95 (n=124)	-1.7 ± 0.45 (n=597)	-1.6± 0.6 (n=602)	-2.5 ±0.4 (n=600)	-3.3± 0.95 (n=204)
SGOT U/L	-0.1 ± 0.45 (n=359)	0.1 ± 0.25 (n=2203)	1.5 ± 0.9 (n=77)	-1.2 ± 0.8 (n=124)	-0.1 ± 0.4 (n=596)	0.5± 0.46 (n=602)	0.3 ±0.6 (n=600)	-0.8± 0.77 (n=204)
SGPT U/L	-0.3 ± 0.6 (n=361)	0.2 ± 0.26 (n=2204)	2.4 ± 1.3 (n=77)	-1.5 ± 0.96 (n=124)	0.2 ± 0.5 (n=597)	0.8± 0.46 (n=602)	0.1 ±0.49 (n=600)	-0.2± 0.9 (n=204)
LDH U/L	-0.5 ± 1.4 (n=359)	-0.2 ± 0.57 (n=2201)	-1.3 ± 2.9 (n=77)	-3.8 ± 3.9 (n=124)	-0.8 ± 1.13 (n=596)	1.2± 1.07 (n=600)	-0.1 ±0.96 (n=600)	-0.2± 1.7 (n=204)
Total Protein G/dL	-0.09 ± 0.02 (n=361)	-0.07 ± 0.01 (n=2204)	-0.02 ± 0.42 (n=77)	-0.7 ± 0.04 (n=124)	-0.06 ± 0.01 (n=597)	-0.06± 0.015 (n=602)	-0.08 ±0.014 (n=600)	-0.08± 0.027 (n=204)
Glucose Mg/dL	3.5 ± 1.22 (n=361)	2.0 ± .6 (n=2202)	3.0 ± 2.3 (n=77)	4.2 ± 4.0 (n=124)	1.7 ± 1.0 (n=597)	2.4± 1.00 (n=601)	2.0 ±1.02 (n=599)	0.3± 1.7 (n=204)

Of note was a dose-related decrease in platelet count for clinical hematology. For chemistry there were apparent dose related increases in serum K+, uric acid, and triglycerides. There were dose-related decreases in serum chloride, alkaline phosphatase and HDL.

ECG.

The effects of nebivolol on ECGs are derived from two databases. The first database is the routinely collected ECGs that were measured during the 4 placebo controlled dose ranging studies (NEB-305, NEB-302, NEB-202 and NEB-321). In general, ECGs were collected at trough, at the final visit during the 12-week efficacy portion of the study. The measurements were compared to the corresponding baseline ECG. In study NEB-202 ECGs were also to be collected at peak (2-3 hours post-dose) but unfortunately these ECGs were collected in < 40 % of those enrolled. The dose related ECG-effects at trough are shown below. I have also included the QTcF effects of nebivolol for those who are poor metabolizers who were entered in the monotherapy dose-response studies (NEB-302, NEB-305, NEB-202).

Table 15: ECG changes during monotherapy clinical studies (NEB-302, NEB-305 and NEB-202)

Parameter	Placebo						
		1.25	2.5	5	10	20	40
N=	324	75	119	550	560	574	200
Δ HR bpm	-0 ± 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
Δ QRS msec	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
Δ RR msec	2.3 ± 8.3	49 ± 13	58 ± 11	101 ± 7	132 ± 7	143 ± 6	170 ± 11
ΔQT msec	1.1 ± 1.9	10.3 ± 2.1	6.4 ± 2.7	14 ± 1.2	20 ± 1.4	23 ± 1.4	27 ± 1.8
Δ QTcB msec-1/2	-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
ΔQTcF msec-1/3	-3.9 ± 5.0	0.2 ± 2.3	-5.2 ± 3.0	-18 ± 6.9	-17 ± 5.4	-7.5 ± 1.4	-11.3 ± 4.6
Poor metabolizer in study NEB-302,NEAB-305 and NEB-202.							
N=	8	5	6	24	23	28	10
ΔQTcF msec-1/3	0.8 ± 6.0	13.2 ± 5.6	12.0 ±9.4	1.5 ± 4.0	3.4 ± 4.2	-1.0 ± 4.1	3.6 ± 3.8

The observed dose-related effects are consistent with β-blockade. Heart rate decreased, and R-R interval increased. QTcF for the main population (nearly all EM subjects) was not increased at trough. There was relatively modest data in poor metabolizers at trough.

A second set of information was study NEB-122. In this stgudy 281 subjects were randomized to one of four treatments: placebo, atenolol, moxifloxacin and nebivolol. Patients in the atenolol and nebivolol groups received half the maximal dose for three days and then were titrated to the target dose if trough heart rate was > 51 bpm and PR interval was < 220 msec. Only three of the subjects in the nebivolol allocated group were PM. For moxifloxacin the dose was 400 mg daily, for atenolol the initial dose was 100 mg daily to be raised to 200 mg daily if tolerated. For nebivolol the dose was 20 mg to be increased, if tolerated to 40 mg daily. The primary metric of the study was ECG at day 7 of dosing compared to the same measurement at baseline. The results at day 7 showed an increase in QTcF for moxifloxacin. The effect of nebivolol on QTcF did not differ from either atenolol or placebo, but did qualitatively differ from moxifloxacin (see figure 50 of Drs. Mishia/Kumi's review.

The sum of the two databases appears to be adequate to suggest that nebivolol does not appear to be a risk for prolonging repolarization, with the following caveats.

- The ECGs collected during the clinical trials corresponded to trough nebivolol concentrations. The effects on repolarization at peak are unknown.
- Study NEB-122 did not extend the dose range beyond the usable 40-mg dose. For definitive QT studies the dose range is usually extended far above the proposed regimen.
- The duration of treatment in study NEB-122 was too short to attain steady state. In study NEB-122, patients received maximum dose for only 4 days; the first three days of dosing were with the 20 mg dose. The excretion of radioactivity after a single ^{14}C-labeled nebivolol dose (NEB-136) was far from complete at 96 hours for the EM and even less so for the PM subjects, the long time to clear a single dose, would suggest that much longer treatment durations than 4 days are needed to define steady state effects.
- There were only 3 PM subjects enrolled into Study NEB-122. There were also relatively few PM subjects in the hypertension database. The description of the effect of nebivolol on repolarization in the PM population is marginal.

Vital signs:

Blood pressures were collected as the primary efficacy outcome; the table below captures the changes from baseline the trough sitting heart rate.

Table 16: Mean change in heart rate from baseline at trough and peak heart rates, monotherapy studies (NEB-302, NEB-305, NEB-202 and NEB-321).

Study	PBO	Nebivolol daily dose					
		1.25	2.5	5	10	20	40
Trough heart rates							
202	-3.3 ± 2.6		-2.7 ± 2.6	-2.9 ± 2.5	-6.8 ± 2.5	-5.6 ± 2.5	-7.1 ± 2.6
302	2.8. ± 1.1	-1.1 ± 1.1	-1.8 ± 1.1	-4.1 ± 0.9	-4.6 ± 0.9	-6.9 ± 0.9	-7.8± 0.9
305	-0.2 ± 1.2			-5.6 ± 1.0	-6.6 ± 1.0	-7.5 ± 1.0	
321*	-1.8 ± 0.9			-5.9 ± 0.9	-6.6 ± 0.9	-7.8 ± 0.9	
Peak heart rates							
202	3.5 ± 2.8		1.6 ± 2.8	-0.4 ± 2.7	-2.2 ± 2.6	-1.9 ± 2.6	-3.1 ± 2.7
302	3.2. ± 1.1	-1.4 ± 1.1	-1.6 ± 1.1	-4.9 ± 1.0	-5.4 ± 1.0	-6.6 ± 0.9	-8.6± 0.9
305	-2.0 ± 1.2			-6.6 ± 0.9	-8.3 ± 0.9	-9.0 ± 0.9	
321*	-0.4 ± 1.1			-6.8 ± 1.0	-8.0 ± 1.0	-10.3 ± 1.1	

* sitting

There were clear dose-related effects on heart rate for each study, with somewhat greater effects for peak measurements.

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/s/

Abraham Karkowsky
2/23/05 07:21:23 PM
MEDICAL OFFICER
Secondary nebivolol review

TABLE OF CONTENTS

1 LIST OF TABLES

2 ABBREVIATIONS

Abn	abnormal
AC	active-controlled
AC:	Active-controlled
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm:	beats per minute
CCB:	Calcium channel blocker
CHF	congestive heart failure
CRF	case report form
CRP	C-reactive protein
CVA:	cerebrovascular accident
CVD	cardiovascular disease
DBP:	diastolic blood pressure
DM	diabetes mellitus
DVT	deep venous thrombosis
EM	extensive metabolizers
GGT	gamma-glutamyl transferase
HCG	human chorionic gonadotropin
HDL	high density lipoprotein
HR	heart rate
HTN	hypertension
IGM	immunoglobulin M
ITT	intent to treat
LDH	lactic dehydrogenase
LDL	low density lipoprotein
LFT:	Liver Function Test
LT:	Long Term
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MI	myocardial infarction
msec	millisecond
MVA	motor vehicle accident
NEB	Nebivolol
NOS:	Not Otherwise Specified
NR	normal range
NR:	Normal range
NSAIDs	non-steroid anti-inflammatory drugs
NUL:	Normal Upper Limit
OL:	Open Label
PC	placebo-controlled

PC:	Placebo-controlled
PM	poor metabolizers
PP	per protocol
PVC	premature ventricular contraction
QTc (B):	QT corrected by the Bazzet method
QTc (F):	QT corrected by the Fridirecia method
RBC	red blood cells
RDW	red cell distribution width
RR	relative risk
SAE	serious adverse event
SBP:	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SP	secondary program
SVT	supraventricular tachycardia
TSH	thyroid stimulating hormone
Unk:	Unknown
UTI	urinary tract infection
WBC	white blood cell
WCC	white cell count

3 EXECUTIVE SUMMARY OF SAFETY

The nebivolol primary program included a total of 2313 patients who were exposed for an average of 12 weeks in three placebo-controlled and one active-controlled trial to doses ranging between 1.25 and 40 mg. Of these subjects, 845 participated in the one-year long-term, open label trial and 85 participated in the 2-year follow-up trial.

This program was designed to evaluate the efficacy of NEB and as a result it was underpowered to assess the association of NEB with the many adverse events that were observed. The conclusions drawn with regard to the safety of NEB rely on the comparison with safety results of the review of carvedilol, the labels of carvedilol and metoprolol succinate and on the foreign post marketing data of nebivolol.

Compared to carvedilol, the experience of death with NEB does not seem to be out of line.

The incidence of SAEs on NEB was slightly higher on NEB in the monotherapy trials compared to placebo, and on the 20 mg dose level. Adverse events that led to discontinuation were more common on 10 and 20 mg. All bradycardia cases that led to discontinuation but one occurred on 20 mg. Other cardiac reasons that led to discontinuation were observed in twice as many patients on NEB compared to placebo. The 6 cases of dyspnea that led to discontinuation were observed solely on NEB.

A slight excess of all neoplasms on NEB compared to placebo was observed.

Compared to carvedilol, the experience of SAEs adverse and events leading to discontinuation on NEB in the controlled trials was not different.

In this program's study population, NEB seems to increase the risk of myocardial ischemia, and promote and/or aggravate the cardiovascular lipid profile in both placebo-controlled and long-term exposure trials.

QT evaluation was less than accurate because both correction (Bazzet and Fridericia) methods overcorrected and consequently led to shortening of QT on NEB. Despite this overcorrection, QT prolongation was observed. The incidence of QT prolongation was higher among poor metabolizing subjects on NEB compared to their counterparts on placebo and compared to extensive metabolizing subjects on NEB.

Nebivolol seems to cause significant and consistent bradycardia that was shown to be of the same magnitude at peak and trough levels of NEB. Bradycardia and edema led to hospitalization in one case. It might even have helped precipitate the few cases of cardiac failure and circulatory collapse that were observed in the secondary program.

NEB potentially interacts with alcohol in further aggravating bradycardia, especially at high doses.

The increased potassium, sodium, chloride and phosphorus + decreased carbon dioxide, calcium and urine Ph + increased BUN, creatinine and uric acid + presence of squamous epithelial cell in urine all point to a tendency of NEB to compromise the renal function. Two cases of nephritic syndrome were reported in the post marketing data.

Nebivolol was associated in few instances with hyperuricemia, gout and aggravated gout, and urinary stones in this study population.

One case of pancreatitis and one case of hepatic cirrhosis (attributed to alcohol) were observed in the secondary program, and one case of hepatic failure was reported post marketing.

The pancreatitis was secondary to multi-microcholecystolithiasis for which the subject underwent cholecystectomy.

The hepatic failure led to hospitalization in a 37-year old subject who was treated with NEB 5 mg and was receiving at the same time phenprocoumon which was co-suspected, and both drugs were discontinued. Serology for other causes was negative. Liver function continued to deteriorate and a liver transplant was necessary.

Five cases of angioedema including one which was diagnosed as such and led to discontinuation, 3 cases of face edema and one case of tongue edema were observed.

The adverse events that were observed on NEB but NOT on placebo and were not described in the label of carvedilol include C-reactive protein increase, ECG T wave and ST segment abnormalities, QT prolongation, angioedema and dysmenorrhea.

With regard to the adverse events observed and quantitatively described in the label of carvedilol including chest pain, dyspnea, fatigue, dizziness and insomnia, their association with NEB seems to be stronger than with carvedilol.

On the other hand, the association of NEB with bradycardia, hypertriglyceridemia, thrombocytopenia and peripheral edema seems to be less strong than that with carvedilol.

Other adverse events that were observed in excess on NEB compared to placebo, and with NO or NOT enough data in the carvedilol label and/or review for comparison, include bronchitis, influenza, viral gastroenteritis, viral infections NOS, sinusitis NOS, sinus congestion, nasal congestion, pharyngolaryngeal pain, paresthesia, and palpitations.

The adverse events that were associated with NEB in a dose response fashion include bradycardia, fatigue, dizziness, diarrhea, sinusitis, insomnia, bronchitis, chest pain, influenza, dyspnea, viral gastroenteritis, somnolence, and depression.

Adverse events that are known to be associated with other beta-blockers were observed with NEB and these include:

-Suspicion of bronchospasm which led to discontinuation in 5 subjects on NEB.

-Liver function

AST abnormalities were observed consistently: 10 subjects on NEB $\geq$ 3 x ULN and 2 subjects $\geq$ 5x ULN; a shift above NR in > 5% of all subjects on NEB and in 9 subjects on NEB compared to none on placebo; a positive change from baseline in the mean on NEB was also observed;

ALT abnormalities were seen consistently: 3 subjects experiencing $\geq$ 3 x ULN on NEB; a shift above normal range in > 3% of all subjects on NEB and in 9 NEB subjects vs. no placebo;

Alkaline phosphatase > 3 x ULN in one subject;

AST or ALT $\geq$ 5x ULN in 2 subject;

AST or ALT + bilirubin abnormal in 2 subjects;

-Hematology

Decrease in platelet count;

Some adverse events were observed at higher incidence in some demographic groups.

Younger non-black males of this study population were more likely to experience something akin to the metabolic syndrome while exposed to NEB.

Younger subjects of this study population were more likely to experience myocardial ischemia and an increase in C-reactive proteins;

Younger males of this study population were more likely to experience LFTs and hematologic abnormalities.

Younger black subjects were more likely to experience swelling of the face;

Females were more likely to experience chest pain, palpitations, clinically significant QT prolongation and decrease in heart rate;

NEB interacted with CYP2D6 with regard to chest pain, headache and influenza. In the long-term trial, NEB interacted with diuretics with regard to all, musculoskeletal, gastrointestinal, general and respiratory adverse events. The numbers were too small for assessing an interaction for specific adverse event.

The information available from the secondary program, to some extent, supports some of the above findings. Data from the secondary program was used for approval of nebivolol in over 45 countries in Europe where they were supposedly reviewed and the safety of nebivolol evaluated.

4 RECOMMENDATION ON REGULATORY ACTION

There three issues that are of concern to the reviewer and these are nebivolol's potential myocardial ischemic effect, its lipid metabolism effects, its seemingly compromising effect of the renal function, and its potential interaction with alcohol.

5 SUMMARY OF SAFETY FINDINGS

5.1 Introduction and Background

The following review uses data from the primary program, the secondary program and worldwide post marketing reporting.

Data from the primary program was generated from four randomized placebo-controlled (PC) studies (NEB 202, 302, 305, and 321), one active-control study (NEB 203), one open-label (OL) extension study (NEB 306), and from clinical pharmacology studies.

A total of 2464 patients who were treated with nebivolol at doses ranging from 1.25 mg to 40 mg for mild to moderate hypertension were followed-up, and 2257 of these were from the US. The duration of treatment ranged from 84 days in the randomized, PC trials to 12 months in the OL extension trial. Another OL extension study is still ongoing and only partial safety data from this study contributed to the evaluation of this submission. Placebo-controlled comparisons involved 372 placebo and 2313 NEB patients, and atenolol-controlled comparisons involved 45 atenolol and 70 NEB patients.

Clinical pharmacology studies involved 71 placebo, 139 active-control and 367 NEB subjects.

Data from the secondary program consisted of study result reports:

-summarizing incomplete information on all kinds of safety parameters including death and SAE;

-summarizing information inconsistently;

-with unclear information regarding randomized numbers, sample sizes and denominators used for analyses;
-with very little summarization comparing adverse events in treatment arms especially that there are ample data to complete this comparison given the number of comparative studies conducted;

The reviewer, therefore, tried to make sense of the all the information and capture what appeared to be relevant especially deaths, serious adverse events, events that led to discontinuation and frequencies of some events that were available.

Data from post marketing reports with an estimated 3.5 million person-years use through September 2004, in more than 45 countries where NEB was approved for the treatment of hypertension, are referred to.

5.2 Data Sources, Review Strategy, and Data Integrity

5.2.1 Review Strategy

Extensive amounts of electronic tabulated data were reviewed for relevant safety information and used to compile informative frequencies, means and incidence. Narratives and/or CRFs of a selection of adverse events were reviewed to complete adverse event profiles, reclassify adverse events, or to confirm or dispute a diagnosis.

5.2.2 Data Quality and Integrity

The primary program data are extensive and encumbering.. And looking for relevant information was very difficult.

The use of data from the secondary program was limited despite its apparent abundance because there were no raw data to confirm or dispute information in the submitted reports. Putting together a comprehensive picture of safety from the reports submitted was very difficult for a reason concerning denominators. These were missing in many analyses, were sometimes inconsistent across different analyses, and they were difficult to compute because the information on randomization schemes was missing.

5.3 Integrated Review of Safety

5.3.1 Methods and Findings

5.3.1.1 List of trials, and disposition and demographic characteristics by trial

5.3.1.1.1 Primary Program

Table 1. List of trials and number of patients used for the evaluation of safety

Studies	Nebivolol	Placebo	Active-control
Clinical Pharmacology			
	367	71	139
All Studies Phase 2/3 Studies Randomized Controlled Studies			

Studies	Nebivolol	Placebo	Active-control
NEB-202	251	49	--
NEB-203	70	--	45
NEB-302	828	81	--
NEB-305	732	75	--
NEB-321	502	167	--
NEB-306	845	--	--
NEB-323	85	--	--
Total exposed to NEB[1]	2468		

Table 2. Patient disposition in the NEB-202 study

End of Study Status Discontinuation Reason	Placebo n (%)	Nebivolol mg					Total n (%)
		2.5 n (%)	5 n (%)	10 n (%)	20 n (%)	40 n (%)	
ITT	49	49	50	51	50	51	251
Completed	41(83.7)	42(85.7)	41(82.0)	47(92.2)	45(90.0)	43(84.3)	218(86.9)
Discontinued							
Total	8 (16.3)	7 (14.3)	9 (18.0)	4 (7.8)	5 (10.0)	8 (15.7)	33 (13.1)
Adverse Event	0 (0.0)	1 (2.0)	2 (4.0)	0 (0.0)	1 (2.0)	2 (3.9)	6 (2.4)
Treatment Failure	4 (8.2)	1 (2.0)	2 (4.0)	0 (0.0)	1 (2.0)	2 (3.9)	6 (2.4)
Lost to Follow-up	1 (2.0)	2 (4.1)	3 (6.0)	1 (2.0)	0 (0.0)	2 (3.9)	8 (3.2)
Protocol Deviation	1 (2.0)	0 (0.0)	0 (0.0)	2 (3.9)	1 (2.0)	1 (2.0)	4 (1.6)
Withdrew Consent	1 (2.0)	2 (4.1)	1 (2.0)	0 (0.0)	0 (0.0)	1 (2.0)	4 (1.6)
Other	1 (2.0)	1 (2.0)	1 (2.0)	1 (2.0)	2 (4.0)	0 (0.0)	5 (2.0)

Table 3. Patient characteristics in the NEB-202 study

Parameter	Placebo N = 49 n (%)	Nebivolol mg					Total N = 300 n (%)	p-value
		2.5 N = 49 n (%)	5 N = 50 n (%)	10 N = 51 n (%)	20 N = 50 n (%)	40 N = 51 n (%)		
Age (years)								
Mean (SD)	49.7 (9.1)	49.9 (9.6)	51.6 (10.5)	50.5 (10.5)	51.3 (10.8)	52.3 (12.0)	50.9 (10.4)	0.800
Median	49.0	49.0	51.0	49.0	51.5	51.0	50.0	
Range	34.0 to	33.0 to	26.0 to	29.0 to	28.0 to	28.0 to	26.0 to	

[1] The total number exposed does not match the added total of subjects exposed in each study because all subjects exposed in NEB-306 and NEB-323 were exposed in the randomized controlled trials.

Parameter	Placebo N = 49 n (%)	Nebivolol mg 2.5 N = 49 n (%)	5 N = 50 n (%)	10 N = 51 n (%)	20 N = 50 n (%)	40 N = 51 n (%)	Total N = 300 n (%)	p-value
	70.0	75.0	77.0	79.0	74.0	79.0	79.0	
Age Group								
< 65	44 (89.8)	45 (91.8)	44 (88.0)	45 (88.2)	45 (90.0)	42 (82.4)	265 (88.3)	0.762
≥ 65	5 (10.2)	4 (8.2)	6 (12.0)	6 (11.8)	5 (10.0)	9 (17.6)	35 (11.7)	
Gender								
Male	23 (46.9)	26 (53.1)	22 (44.0)	22 (43.1)	21 (42.0)	22 (43.1)	136 (45.3)	0.890
Female	26 (53.1)	23 (46.9)	28 (56.0)	29 (56.9)	29 (58.0)	29 (56.9)	164 (54.7)	
Diabetes Status								
Yes	6 (12.2)	7 (14.3)	8 (16.0)	6 (11.8)	7 (14.0)	9 (17.6)	43 (14.3)	0.961
No	43 (87.8)	42 (85.7)	42 (84.0)	45 (88.2)	43 (86.0)	42 (82.4)	257 (85.7)	
EM or PM Classification								
Poor	0 (0.0)	1 (2.0)	1 (2.0)	2 (3.9)	1 (2.0)	2 (3.9)	7 (2.3)	0.796
Extensive	49 (100.0)	48 (98.0)	49 (98.0)	49 (96.1)	49 (98.0)	49 (96.1)	293 (97.7)	
< 30	21 (42.9)	26 (53.1)	26 (52.0)	26 (51.0)	25 (50.0)	20 (39.2)	144 (48.0)	0.672
≥ 30	28 (57.1)	23 (46.9)	24 (48.0)	25 (49.0)	25 (50.0)	31 (60.8)	156 (52.0)	

Table 4. Patient disposition in the NEB-203 study

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

Table 5. Patient characteristics in the NEB-203 study

Parameter	Atenolol mg		Nebivolol mg			Total N = 115 n (%)	p-value
	50 N = 24 n (%)	100 N = 21 n (%)	5 N = 23 n (%)	10 N = 23 n (%)	20 N = 24 n (%)		
Age (years)							
Mean (SD)	51.1 (13.8)	51.8 (11.1)	48.2 (9.0)	51.3 (11.9)	51.0 (9.7)	50.7 (11.1)	0.841
Median	51.0	51.0	49.0	50.0	52.5	50.0	
Range	(29.0, 79.0)	(34.0, 74.0)	(33.0, 72.0)	(21.0, 76.0)	(35.0, 69.0)	(21.0, 79.0)	
Age Group							
< 65	19 (79.2)	17 (81.0)	22 (95.7)	21 (91.3)	22 (91.7)	101 (87.8)	0.340
≥ 65	5 (20.8)	4 (19.0)	1 (4.3)	2 (8.7)	2 (8.3)	14 (12.2)	
Gender							
Male	17 (70.8)	16 (76.2)	18 (78.3)	17 (73.9)	17 (70.8)	85 (73.9)	0.972
Female	7 (29.2)	5 (23.8)	5 (21.7)	6 (26.1)	7 (29.2)	30 (26.1)	
Race							
Black	4 (16.7)	2 (9.5)	4 (17.4)	4 (17.4)	3 (12.5)	17 (14.8)	0.928
Non-Black	20 (83.3)	19 (90.5)	19 (82.6)	19 (82.6)	21 (87.5)	98 (85.2)	
Caucasian	17 (70.8)	16 (76.2)	19 (82.6)	19 (82.6)	19 (79.2)	90 (78.3)	
Asian	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	
Hispanic	1 (4.2)	1 (4.8)	0 (0.0)	0 (0.0)	1 (4.2)	3 (2.6)	
Other	1 (4.2)	2 (9.5)	0 (0.0)	0 (0.0)	1 (4.2)	4 (3.5)	
Diabetes Status							
Yes	2 (8.3)	1 (4.8)	1 (4.3)	1 (4.3)	2 (8.3)	7 (6.1)	0.947
No	22 (91.7)	20 (95.2)	22 (95.7)	22 (95.7)	22 (91.7)	108 (93.9)	
EM or PM Classification							
Poor	1 (4.2)	1 (4.8)	1 (4.3)	1 (4.3)	1 (4.2)	5 (4.3)	>0.999
Extensive	23 (95.8)	20 (95.2)	22 (95.7)	22 (95.7)	23 (95.8)	110 (95.7)	
BMI (kg/m^2)							
< 30	15 (62.5)	13 (61.9)	14 (60.9)	14 (60.9)	15 (62.5)	71 (61.7)	>0.999
≥ 30	9 (37.5)	8 (38.1)	9 (39.1)	9 (39.1)	9 (37.5)	44 (38.3)	

Table 6. Patient disposition in the NEB-302 study

Disposition	Placebo	Nebivolol mg						Total (%)
		1.25 n (%)	2.5 n (%)	5 n (%)	10 n (%)	20 n (%)	30/40 n (%)	
ITT	81	83	82	165	166	166	166	909
Completed	67(82.7)	68 (81.9)	68 (82.9)	148 89.7)	133 80.1)	144(86.7)	149 (89.8)	777(85.5)
Discontinued	14(17.3)	15 (18.1)	14 (17.1)	17 (10.3)	33 (19.9)	22 (13.3)	17 (10.2)	132(14.5)
Adverse Event	1 (1.2)	3 (3.6)	2 (2.4)	0	7 (4.2)	7 (4.2)	3 (1.8)	23 (2.5)
Treatment Failure	4 (4.9)	4 (4.8)	1 (1.2)	3 (1.8)	5 (3.0)	1 (0.6)	1 (0.6)	19 (2.1)
Lost to FU	2 (2.5)	1 (1.2)	2 (2.4)	4 (2.4)	5 (3.0)	4 (2.4)	5 (3.0)	23 (2.5)
Protocol Deviation	1 (1.2)	3 (3.6)	1 (1.2)	0	1 (0.6)	2 (1.2)	0	8 (0.9)
Withdrew Consent	5 (6.2)	3 (3.6)	5 (6.1)	9 (5.5)	12 (7.2)	7 (4.2)	7 (4.2)	48 (5.3)
Other	1 (1.2)	1 (1.2)	3 (3.7)	1 (0.6)	3 (1.8)	1 (0.6)	1 (0.6)	11 (1.2)

Table 7. Baseline characteristics of patients in the NEB-302 study

Parameter	Placebo N = 81 n (%)	Nebivolol mg						Total N=909 n (%)	p-value
		1.25 N = 83 n (%)	2.5 N = 82 n (%)	5 N=165 n (%)	10 N=166 n (%)	20 N=166 n (%)	30/40 N=166 n (%)		
Age (years)									
Mean (SD)	56.0 (11.6)	55.5 (11.5)	53.4 (2.3)	54.9 (1.8)	55.2 (2.5)	54.1 (11.6)	54.3 (11.6)	54.7 (11.8)	0.790
Median	57.0	56.0	54.0	54.0	54.5	54.0	54.0	54.0	
Range	24.0 - 80.0	28.0 - 84.0	24.0 - 81.0	25.0 - 82.0	23.0 - 83.0	22.0 - 82.0	26.0 - 78.0	22.0 - 84.0	
Age Group									
< 65	64 (79.0)	65 (78.3)	68 (82.9)	132 (80.0)	125 (75.3)	134 (80.7)	128 (77.1)	716 (78.8)	0.827
65	17 (21.0)	18 (21.7)	14 (17.1)	33 (20.0)	41 (24.7)	32 (19.3)	38 (22.9)	193 (21.2)	
Gender									
Male	46 (56.8)	46 (55.4)	53 (64.6)	96 (58.2)	93 (56.0)	92 (55.4)	92 (55.4)	518 (57.0)	0.865
Female	35 (43.2)	37 (44.6)	29 (35.4)	69 (41.8)	73 (44.0)	74 (44.6)	74 (44.6)	391 (43.0)	
Black	11 (13.6)	12 (14.5)	13 (15.9)	23 (13.9)	23 (13.9)	25 (15.1)	25 (15.1)	132 (14.5)	>0.999

Parameter	Placebo N = 81 n (%)	Nebivolol mg						Total N=909 n (%)	p-value
		1.25 N = 83 n (%)	2.5 N = 82 n (%)	5 N=165 n (%)	10 N=166 n (%)	20 N=166 n (%)	30/40 N=166 n (%)		
Non-Black	70 (86.4)	71 (85.5)	69 (84.1)	142 (86.1)	143 (86.1)	141 (84.9)	141 (84.9)	777 (85.5)	
Caucasian	61 (75.3)	60 (72.3)	60 (73.2)	120 (72.7)	114 (68.7)	112 (67.5)	113 (68.1)	640 (70.4)	
Asian	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	2 (1.2)	1 (0.6)	6 (0.7)	
Hispanic	9 (11.1)	10 (12.0)	9 (11.0)	21 (12.7)	24 (14.5)	25 (15.1)	25 (15.1)	123 (13.5)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	2 (1.2)	2 (1.2)	8 (0.9)	
Diabetes Status									
Yes	7 (8.6)	9 (10.8)	10 (12.2)	11 (6.7)	17 (10.2)	14 (8.4)	20 (12.0)	88 (9.7)	0.683
No	74 (91.4)	74 (89.2)	72 (87.8)	154 (93.3)	149 (89.8)	152 (91.6)	146 (88.0)	821 (90.3)	
EM or PM Classification									
Poor	4 (4.9)	5 (6.0)	6 (7.3)	10 (6.1)	11 (6.6)	12 (7.2)	11 (6.6)	59 (6.5)	0.995
Extensive	77 (95.1)	78 (94.0)	76 (92.7)	155 (93.9)	155 (93.4)	154 (92.8)	155 (93.4)	850 (93.5)	
BMI (kg/m^2)									
< 30	44 (54.3)	43 (51.8)	45 (54.9)	91 (55.2)	102 (61.4)	101 (60.8)	84 (50.6)	510 (56.1)	0.389
30	37 (45.7)	40 (48.2)	37 (45.1)	74 (44.8)	64 (38.6)	65 (39.2)	82 (49.4)	399 (43.9)	

Table 8. Patient disposition in the NEB-305 study

Disposition	Placebo	Nebivolol mg			Total n (%)
		5 n (%)	10 n (%)	20 n (%)	
ITT	75	244	244	244	807
Completed	61 (81.3)	218 (89.3)	206 (84.4)	217 (88.9)	702 (87.0)
Discontinued	14 (18.7)	26 (10.7)	38 (15.6)	27 (11.1)	105 (13.0)
Adverse Event	4 (5.3)	3 (1.2)	9 (3.7)	8 (3.3)	24 (3.0)
Treatment Failure	3 (4.0)	3 (1.2)	5 (2.0)	3 (1.2)	14 (1.7)
Lost to follow-up	0 (0.0)	4 (1.6)	8 (3.3)	3 (1.2)	15 (1.9)
Protocol Deviation	1 (1.3)	0 (0.0)	3 (1.2)	0 (0.0)	4 (0.5)
Withdrew Consent	4 (5.3)	8 (3.3)	4 (1.6)	7 (2.9)	23 (2.9)
Other	2 (2.7)	8 (3.3)	9 (3.7)	6 (2.5)	25 (3.1)[c]

Table 9. Baseline patient characteristics for study NEB-305

Parameter	Placebo N=75 n (%)	Nebivolol mg			Total N=807 N (%)	p-value
		5 N=244 n (%)	10 N=244 n (%)	20 N=244 n (%)		
Age (years)						
Mean (SD)	51.2 (10.0)	53.9 (11.1)	53.8 (11.2)	53.4 (11.1)	53.4 (11.0)	
Median	50.0	54.0	53.0	53.0	53.0	
Range	27.0 to 73.0	23.0 to 79.0	22.0 to 82.0	28.0 to 80.0	22.0 to 82.0	
Age Group						
< 65	67 (89.3)	199 (81.6)	197 (80.7)	197 (80.7)	660 (81.8)	0.357
65	8 (10.7)	45 (18.4)	47 (19.3)	47 (19.3)	147 (18.2)	
Gender						
Male	39 (52.0)	131 (53.7)	131 (53.7)	131 (53.7)	432 (53.5)	0.994
Female	36 (48.0)	113 (46.3)	113 (46.3)	113 (46.3)	375 (46.5)	
Race						
Black	11 (14.7)	31 (12.7)	33 (13.5)	30 (12.3)	105 (13.0)	0.947
Non-Black	64 (85.3)	213 (87.3)	211 (86.5)	214 (87.7)	702 (87.0)	
Caucasian	60 (80.0)	190 (77.9)	191 (78.3)	192 (78.7)	633 (78.4)	
Asian	0 (0.0)	4 (1.6)	2 (0.8)	3 (1.2)	9 (1.1)	
Hispanic	4 (5.3)	19 (7.8)	17 (7.0)	19 (7.8)	59 (7.3)	
Other	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)	
Diabetes Status						
Yes	4 (5.3)	9 (3.7)	12 (4.9)	12 (4.9)	37 (4.6)	0.881

Parameter	Placebo N=75 n (%)	Nebivolol mg 5 N=244 n (%)	Nebivolol mg 10 N=244 n (%)	Nebivolol mg 20 N=244 n (%)	Total N=807 N (%)	p-value
No	71 (94.7)	235 (96.3)	232 (95.1)	232 (95.1)	770 (95.4)	
EM or PM Classification						
Poor	4 (5.3)	15 (6.1)	15 (6.1)	16 (6.6)	50 (6.2)	0.985
Extensive	71 (94.7)	229 (93.9)	229 (93.9)	228 (93.4)	757 (93.8)	
BMI (kg/m^2)						
< 30	48 (64.0)	152 (62.6)	145 (59.4)	137 (56.4)	482 (59.9)	0.473
30	27 (36.0)	91 (37.4)	99 (40.6)	106 (43.6)	323 (40.1)	
Missing	0	1	0	1	2	

Table 10. Patient Disposition in the NEB-321 study

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

Table 11. Patient characteristics in the NEB-321 study

Variable	Placebo N=167 n(%)	Nebivolol mg 5 N=168 n(%)	Nebivolol mg 10 N=168 n(%)	Nebivolol mg 20 N=166 n(%)	Total N=669 n(%)	p-Value
Age (years)						
Mean (SD)	54.3 (9.83)	53.5 (10.92)	54.0 (10.59)	52.6 (10.82)	53.6 (10.54)	0.467
Median	54.0	54.0	54.0	52.0	53.0	
Range (Min, Max)	(25.0, 78.0)	(19.0, 80.0)	(26.0, 86.0)	(24.0, 76.0)	(19.0, 86.0)	
< 65	140 (83.8%)	142 (84.5%)	143 (85.1%)	141 (84.9%)	566 (84.6%)	
>= 65	27 (16.2%)	26 (15.5%)	25 (14.9%)	25 (15.1%)	103 (15.4%)	
Gender						

Variable	Placebo N=167 n(%)	Nebivolol mg			Total N=669 n(%)	p-Value
		5 N=168 n(%)	10 N=168 n(%)	20 N=166 n(%)		
Male	91 (54.5%)	94 (56.0%)	92 (54.8%)	91 (54.8%)	368 (55.0%)	0.994
Female	76 (45.5%)	74 (44.0%)	76 (45.2%)	75 (45.2%)	301 (45.0%)	
Race						
Black	48 (28.7%)	50 (29.8%)	51 (30.4%)	48 (28.9%)	197 (29.4%)	0.987
Non-Black	119 (71.3%)	118 (70.2%)	117 (69.6%)	118 (71.1%)	472 (70.6%)	
Diabetes Status						
Yes	26 (15.6%)	24 (14.3%)	22 (13.1%)	22 (13.3%)	94 (14.1%)	0.910
No	141 (84.4%)	144 (85.7%)	146 (86.9%)	144 (86.7%)	575 (85.9%)	
Metabolism of Nebivolol						
Poor	9 (5.4%)	10 (6.0%)	9 (5.4%)	8 (4.8%)	36 (5.4%)	0.972
Extensive	153 (91.6%)	154 (91.7%)	155 (92.3%)	156 (94.0%)	618 (92.4%)	
Missing	5 (3.0%)	4 (2.4%)	4 (2.4%)	2 (1.2%)	15 (2.2%)	

Table 12. Patient disposition in the NEB-306 study

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

Table 13. Patient characteristics in the NEB-306 study

Parameter	NEB N = 607 n (%)	NEB + Diuretic N = 206 n (%)	NEB + CCB N = 21 n (%)	NEB + Other N = 11 n (%)	Total N = 845 n (%)
Age Group					
< 75	591 (97.4)	203 (98.5)	21 (100.0)	10 (90.9)	825 (97.6)
≥ 75	16 (2.6)	3 (1.5)	0 (0.0)	1 (9.1)	20 (2.4)

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

5.3.1.1.2. Secondary Program

This program was conducted mostly in Europe, except for one study that was conducted under an IND in this country, and was the base for approval first in the Netherlands, then Germany and other countries with a total of 45 countries.

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Table 14. Overview of the total patient sample[2]

	nebivolol			placebo			reference*			TOTAL**		
	n***	nE	nS	n	nE	nS	n	nE	nS	n	nE	nS
hypertension												
8 pivotal trials	1391	1386	1391	354	352	353	581	580	581	2246	2238	2245
12 supportive trials	647	644	647	201	199	201	238	235	238	973	970	973
10 pilot trials	220	183	220	53	40	53	59	59	59	239	202	239
12 pharm.dyn. ****	240	236	238	141	138	141	144	143	143	282	278	280
5 special populations	72	59	72				15	15	15	87	74	87
subtotal	2570	2508	2568	749	729	748	1037	1032	1036	3827	3762	3824
no hypertension												
10 cor. artery disease	144	142	144	16	16	16	145	139	145	269	263	269
7 cong. heart failure	144	143	143	79	79	79	10	10	10	227	226	226
1 special populations	16	16	16				16	15	16	32	31	32
subtotal	304	301	303	95	95	95	171	164	171	528	520	527
TOTAL: 65 trials	**2874**	2809	2871	844	824	843	1208	1196	1207	**4355**	4282	4351

n = number randomized;
nS = number in safety analysis;
nE = number in efficacy analysis;
* = active control drugs or d- or l-nebivolol;

Table 15. Number of patients with dose-finding data[2]

Phase	Time	Number of patients							
		placebo	neb (0.5 mg)	neb (1 mg)	neb (2.5 mg)	neb (5 mg)	neb (10 mg)	neb (30 mg)	Total
Run-in	start	224(a)	120	148	208	226	136	44	1106
	week 2	214	115	139	192	221	134	44	1059
	week 4	198	112	132	178	196	120	44	980
	end	223	120(b)	148	208(b)	226	136	44	1105
Double-blind	week 2	222	115	145	201	220	133	44	1080
	week 4	202	113	143	192	218	131	43	1042
	end	223	118	148	207	226	136	44	1102

[2] Tables from the secondary program report

Table 16. Number of patients with therapeutic dose data[2]

Trial [Reference]	Duration of treatment (weeks)	Number of patients				
		All neb patients	Placebo-controlled			Active-controlled
			placebo	neb (5 mg)	Total	neb (5 mg)
INT-1 [1]	4	86	84	86	170	
BEL-12/18 [2]	4	42	41	42	83	
BEL-3/6 [3]	4	34	33	34	67	
USA-4 [4]	4	44	46	44	90	
CAN-3 [5]	12	20 *	20	20	40	20
GBR-1 [6]	4	119 *	124	119	243	119
NED-12/8 [7]	8	74	40	74	114	
INT-5 [11]	12	211				211
INT-3 [9]	12	208				208
TCH-1/2 [8]	12	82				82
FRA-5 [13]	6	12				12
Total		932	388	419	807	652

5.3.1.2 Deaths

5.3.1.2.1 Deaths in the Primary (Bertek) program

There were two deaths in the Bertek development program both of which were observed in controlled trials and were due to MI. One death occurred in a 46 year old male after being on 10 mg for 12 days and the other in a 75-year old female after being on 5 mg for only one day.

5.3.1.2.2 Deaths in the Secondary (Jansen) Program[3]

Death in the hypertension program was reported as unknown in 32 studies in which 2114 subjects received NEB. The 9 deaths that were described came from 6 studies with a total of 404 subjects receiving NEB. There were 6 additional deaths which occurred in subjects studied for non-hypertension illnesses.

Four of the 9 deaths in the hypertension component of the secondary program were observed in double-blind protocols and the other 5 in long-term uncontrolled follow-up protocols. One of the deaths in hypertensive subjects occurred under IND 33060 and the other 8 occurred under non-IND protocols.

Three of the 4 subjects that died during a double-blind protocol were on NEB and the 4th patient died of an MI after crossing over from NEB to placebo.

Deaths in the double-blind protocols included one possible cardiocirculatory collapse on 30 mg that resulted possibly from the combination of alcohol and NEB, one confirmed severe circulatory collapse on 5 mg, one aortic dissection on 5 mg, and one AMI on placebo.

Deaths in the long-term protocols included one MI, one CVA, one liver cirrhosis (reported to be alcoholic), one CO poisoning and one bronchial cancer;

Deaths in the non-hypertension trials were five, 3 in double-blind protocols and two under compassionate use. All five deaths were characterized as sudden.

5.3.1.2.3 Post marketing deaths

Eleven deaths observed since nebivolol was marketed and these included 3 sudden deaths, 2 MIs, and one each preexisting carcinoma, cerebral embolism secondary to severe bradycardia, pneumonia, MVA, and basic disease.

[3] Reviewer relied on reports compiled by previous sponsors to summarize Information in this section because raw data were missing

5.3.1.2.4 Comparison to Carvedilol

Table 17. Comparison of NEB and Carvedilol with regard to the events that led to death in hypertension trials

Death Events	Nebivolol Overall Program			Carvedilol Overall Program		
	Overall Program N = 2925[4]	Controlled Trials		Overall Program N = 3857	Controlled Trials	
		NEB N = 2645	Control N = 515		Carvedilol N = 1142	Placebo N = 462
All Deaths	9 (0.3)[5]	6 (0.2)	1 (0.2)[6]	23 (0.6)	5 (0.4)	0
MI	3	2	1	6	2	--
Sudden	1	1	--	4	2	--
Cardiac Failure	--	--	--	3	--	--
Severe circulatory collapse	--	2	--	--	--	--
Cerebrovascular	1	--	--	2	--	--
Ruptured aneurysm	1	1	--	--	--	--
Suicides	--	--	--	2	1	--
Traffic Accident	--	--	--	2	--	--
Malignant Neoplasm	1	--		--	--	--
Hepatic cirrhosis	1	--	--	--	--	--
CO poisoning	1	--	--	--	--	--

Twenty three deaths were observed in the carvedilol hypertension program seventeen of which died while on treatment. The 23 deaths included 6 MIs, 4 sudden deaths, 3 cardiac failures, 2 CVA and 1 subdural hematoma, 2 suicides, 2 traffic accidents, and one each coronary occlusion, cerebral tumor and pulmonary edema.

5.3.1.2.5 Conclusion

Data on death are very limited but the experience of deaths in the NEB controlled program does not seem to be different from the experience with carvedilol.

5.3.1.3 Other Serious Adverse Events

5.3.1.3.1 Other SAEs in the Primary Program

[4] Number includes the denominator from the PP + denominators of studies in which deaths occurred in the SP.

[5] Number is not reflective of the incidence of deaths in the secondary program because data were missing for a denominator of 2114 subjects.

[6] This patient received NEB in the previous phase.

Table 18. Summary of SAEs and events that led to discontinuation in the primary program

Adverse Events	Controlled Trials								Extension Trials NEB	All Trials
	Monotherapy PC		Adjunct-therapy PC		Active-control		All Placebo-controlled			
	P 205	NEB 1811	P 167	NEB 502	Atenol 45	NEB 70	P 372	NEB 2313	930	2464
SAEs	1 (0.49)	21 (1.2)	3 (0.6)	5 (1.4)	00	01	04 (1.1%)	26 (1.1%)	18 (1.9%)	42 (1.7)
AE led to Discont.	5 (2.4)	43 (2.4)	4 (2.4)	21 (4.2)	00	01 (1.43)	9 (2.4)	64 (2.8)	31 (3.3)	96 (3.9)

5.3.1.3.1.1 Serious Adverse Events

Table 19. SAEs in the primary program

Events	NEB N=2464	Events	NEB
AMI	3	Appendicitis	2
Angina unstable	2	Colitis ischemic	1
Chest pain + chest pressure	2	Gastric Ulcer	1
ECG abnormal ST segment or T wave abnormal	2	Gastroenteritis NOS	1
Leucopenia	1	Abdominal pain	1
Cardiac failure	1	Hepatitis A	1
Bradycardia	1	Cholecystitis	1
Cerebral Hemorrhage	1	Viral infection	1
Aortic Aneurysm	1	Staphylococcal infection	1
Intermittent claudication	1	Bursitis	1
Edema peripheral	1	Erectile dysfunction	1
DVT	1	Ureteric stenosis	1
Dyspnea NOS	1	Bladder cancer	1
Amnesia	1	Colon cancer	2
Vertigo	1	Small cell lung cancer	1
Road traffic accident	1	Lung squamous cell cancer	1
Influenza	1	Throat cancer	1

Serious adverse events were observed in 42 patients in all trials combined, and the majority of these were cardiovascular events (9 events in 7 patients), neoplasms (7 events in 7 patients), infections (6 events in 6 patients) and gastrointestinal events (5 events in 5 patients).

Twenty six subjects on NEB and 4 subjects on placebo experienced SAEs in all placebo-controlled trials, but when monotherapy trials were considered separately, a higher proportion of people on NEB experienced serious adverse event 21 (1.16%) compared to placebo 1 (0.49%) with a relative risk RR = 2.38.

5.3.1.3.1.2 Events that led to Discontinuation

Table 20. Adverse events that led to discontinuation in the in the primary program

Events	NEB n	Event	NEB n
Headache	09	Dyspnea NOS	04
Bradycardia	09	Nausea	05
Fatigue/malaise	07	Dizziness	03
AMI	03	Diarrhea + aggravated	03
Chest pain	03	Somnolence	02
Angina unstable	02	Vertigo	02
Cardiac failure	02	Edema peripheral	02
Orthostatic hypotension	02	Hepatitis A	01
ST segment or T wave abn	02	Hepatitis B	01
Cardiac death	01	Dysphagia	01
Age indeterminate MI	01	Edema NOS	01
Hypotension NOS	01	Edema aggravated	01
Blood pressure increased	01	Appendicitis perforated	01
Heart rate decreased	01	Cholecystitis	01
Bundle branch block	01	Abdominal pain	01
Cerebral Hemorrhage	01	Flatulence	01
Aortic Aneurysm, ruptured	01	Rash NOS	01
Withdrawal arrhythmia	01	Skin irritation	01
Tachycardia NOS	01	Angioneurotic edema	01
SVT	01	Sweating decreased	01
Hypoventilation	01	Conjunctival hemorrhage	01
Cough	01	Eye irritation	01
Wheezing	01	Vision blurred	01
Bronchitis NOS	01	Weakness	01
Pneumonia NOS	01	Muscle weakness NOS	01
Disorientation	01	Phlebitis NOS	01
Depression, aggravated	01	Meniscus lesion	01
Tremor	01	Bladder cancer	01
Nightmares	01	Colon cancer	01
Erectile dysfunction	01	Small cell lung cancer	01
Blood triglycerides ↗	01	Lung squamous cell cancer	01

Events	NEB n	Event	NEB n
Proteinuria	01	Platelet count ↘	01

Of all subjects exposed to NEB, 3.9% (96) discontinued because of adverse events.

In all placebo-controlled trials combined and in the monotherapy trials, the overall events that led to discontinuation occurred at similar rates in both treatment groups, but in the adjunctive therapy trials there was an excess of events that led to discontinuation on NEB (RR = 1.7) compared to placebo.

Table 21. Frequency of events that led to study drug discontinuation by dose level

Events	P N=372 n(%)	Nebivolol mg						All NEB N=2313 n(%)
		1.25 N=83 n(%)	2.5 N=131 n(%)	5 N=627 n(%)	10 N=629 n(%)	20 N=626 n(%)	30/40 N=216 n(%)	
Events that led to discontinuation								
Total events	8 (2.2)	2 (2.4)	3 (2.3)	16 (2.6)	33 (5.2)	42 (6.7)	06 (2.8)	102 (4.4)
Bradycardia	00	00	00	00	1	11 (1.8)	00	
Other cardiac	1 (0.3)	1	00	7 (1.1)	2	3	1	14 (0.6)
Dyspnea	00	00	00	1	2	3	00	
Headache	1	1			1	3	00	
nausea	00	00	00	00	2	1	00	
Serious adverse events								
Total	8 (2.2)	1 (1.2)	3 (2.3)	11 (1.2)	14 (2.2)	22 (3.5)	3 (1.4)	54 (2.3)

As can be seen from the tabulation above, the incidence of discontinuation on the 10 and 20 mg dose levels were 2 and 3 times higher than that on placebo. Bradycardia accounted for a quarter of these.

5.3.1.3.1.3 Other significant adverse events

Bronchospasm

One subject treated with 10 mg with no history of asthma or bronchospasm was hospitalized for shortness of breath that occurred at two occasions and tests ruled out a cardiovascular origin. She was discontinued from the study.

Five subjects treated with NEB 5 to 20 mg discontinued because of symptoms suggestive of bronchospasm. Four of these patients had no history of respiratory disease and the fifth had a history of sleep apnea. These symptoms occurred between 6 and 8 weeks of treatment in 3 patients, during the extension trial after increasing the dosage from 5 to 10 mg in the fourth patient, and after one day of treatment in the fifth patient.

Liver function

Three people experienced hepatic events suggestive of clinical hepatic injury:

-The first case developed significant increase in liver enzymes and bilirubin that were related to hepatitis A by IGM antibody testing.

-The second case experienced right upper quadrant pain two months after initiation of NEB which continued for several months and into the extension trial. Liver biopsy showed scar, necrotic and proliferative abnormalities. The upper quadrant pain resolved while the patient was still taking NEB.

-The third case developed symptoms of a viral infection and an increase in liver enzymes 4 weeks before the end of his participation in the extension phase. His symptoms resolved and liver enzymes started decreasing by three weeks after the end of the study.

Leucopenia

-One case of leucopenia was observed in a patient who had a history nasopharyngeal carcinoma with radiation treatment. His WBC increased without treatment and he continued NEB in open-label.

Urinary stones

Two cases of urinary stones were observed.

-The first one diagnosed in a subject who received 20 mg of NEB in the double-blind phase and shortly after the start of NEB-306. The patient had a history of stones at baseline and was taking a carbonic anhydrase inhibitor that is believed to promote urinary stones.

-The second case had a stone that was found by X-ray while he was taking 2.5 mg in the double-blind phase of the study for two months. Patient was treated for right kidney infection 3 days prior to the discovery of the stone.

Heart failure

One subject was hospitalized for bradycardia and edema consistent with CHF shortly after enrolling in the extension trial NEB-306 and being on NEB for 108 days. He was discontinued from the study.

QT prolongation

Four cases of QT prolongation were observed on NEB.

5.3.1.3.2 Other serious adverse events in the SP

5.3.1.3.2.1 Serious adverse events

Information regarding SAEs is missing from many clinical trials with an approximate denominator of 1482 subjects, and the cases summarized below are by no means reflective of the experience of SAEs in the secondary program.

-One case of "pancreatitis Surgical procedure" was reported to have been observed in a long-term period of a trial and on an unknown dose of NEB with 49 'Days in phase to withdrawal". This was reported under the adverse events that led to withdrawal but not under SAEs.
-One case of hepatic cirrhosis that led to death was reported to be alcoholic in an open-label period on 5 mg for 713 days;
-one severe circulatory collapse on 5 mg for 163 days that led to death in a double-blind protocol;
-Other events worth mentioning include:
One malignant breast neoplasm on 5 mg for an unknown duration in an unknown period of a trial;

Two MIs that led to death, one on 10 mg in an OL trial period for 868 days; the other on 5 mg for an unknown duration in an unknown period of a trial;
One aortic dissection, one angina and one atypical chest pain on 5 mg in unknown periods and unknown durations of treatment.

5.3.1.3.2.2 Adverse Events that led to Discontinuation

Adverse events that led to discontinuation and are worth mentioning include the following:

-Respiratory disorder in 2 subjects, one in an open-label period of a trial on 7.5 mg for an unknown duration and the other in a long-term period of a trial on 5 mg for 872 days;
-Dyspnea observed after short-term exposure in 4;
-Dyspnea observed in long-term (176 days and 846 days) exposure in 2;
-Dyspnea observed after unknown time of exposure in 3;
-Asthma in one subject in open-label period on 2.5 mg for 13 days;
-Wheezing in one subject in DB, on 5 mg for 10 days;
-Bronchospasm in one subject in open-label period on 2.5 mg for 13 days;
-Chest pain in 4;
-Angina in 3;
-MI in 3;
-Cardiac failure in 2;
-Nocturnal dyspnea in one subject in double-blind period on 5 mg for unknown period;
-Menstrual disorders in one subject in long-term period of a trial on 5 mg for unknown duration;
-Malignant breast cancer in 2 subjects, one in unknown trial period after unknown duration on 5 mg, and the other in long-term-period of trial on 5 mg for 546 days;
-Bladder papilloma in a long-term period of a trial on 5 mg for 122 days;
-Malignant lymphoma in 2 subjects in unknown periods of long-term trials after 84 and 778 days of unknown doses;
-Bronchial cancer leading to death in one subject in an open-label phase on 5 mg for 643 days;
-Malignant melanoma in double-blind period of a trial on 5 mg for 98 days;
-AST and ALT increased (severity unknown) in a double-blind phase on 5 mg reported to be on Day 0 in phase to withdrawal;
-Pruritus in one;

5.3.1.3.3 Conclusion on SAEs and events that led to discontinuation

Serious adverse events were observed on NEB at twice the incidence on placebo in the monotherapy trials of the primary program. They occurred at slightly higher rate (3.5%) on 20 mg compared to placebo (2.2%) and the other doses.

Adverse events that led to discontinuation were more common on the 10 and 20 mg dose levels. All bradycardia cases that led to discontinuation but one occurred on 20 mg. The "other cardiac" events that led to discontinuation occurred on NEB at twice (0.6%) the rate on placebo (0.3%). Dyspnea as a reason for discontinuation (in 6) was observed solely on NEB.

One case pancreatitis in the secondary program (SP) was reported to be secondary to microlithiasis.

One case of hepatic cirrhosis was reported to be secondary to alcoholism. The association of this case with alcoholism was surprising to the reviewer because per the baseline CRF, and the patient's history and illnesses, "No" is checked for "Alcohol Use", "No" is checked for "Other Concomitant

Afflictions and/or Complaints", and "No" was always checked for Item 10 "Concomitant condition (chronic and/or undercurrent illnesses)" of the "Long-Term Treatment Visit" on the CRF. Not until October 22, 1990 when "Yes" was checked for item 10 with "Alcohol > 1/2 bottle of wine + beers, NSAIDS –> coxarthrosis", was noted along with the mention that the patient was taking Naprosyn twice a day. On the same date, it was entered that the patient discontinued permanently and death was entered as reason.

Two breast cancers were observed in the SP which brings the total number of breast cancers observed with NEB in clinical trials to 5.

Six malignant neoplasms, including 2 lymphomas were observed in the SP, which brings the number of all malignant neoplasms observed on NEB to 13;

The cases of observed bronchospasm, wheezing and asthma in the SP confirm a respiratory beta-adrenergic effect that was suspected in the primary program.

Cases of dyspnea (2), and respiratory disorder (2) (although unspecified and the duration of exposure is unknown for one of them) observed after long-term exposure are likely to be non-beta-adrenergic related. In the light of the pre-clinical findings (of possible phospholipidosis), one cannot help thinking about the possibility of a similar mechanism;

5.3.1.4 Common Adverse Events

5.3.1.4.1 Common Adverse Events in the PP

Table 22. Adverse events reported by ≥ 1% or adverse on NEB in PC, extension and all trials combined

Preferred Term	PC Trials		Extension Trials N = 920 n (%)	All Trials N = 2468 n (%)
	Placebo N = 372 n (%)	NEB N = 2313 n (%)		
Any Adverse Event	144 (38.7)	1008 (43.6)	510 (55.4%)	1193 (48.3%)
Headache	16 (4.3%)	(7.6%)	50 (5.4%)	193 (7.8%)
Fatigue	7 (1.9%)	(3.4%)	40 (4.3%)	112 (4.5%)
Nasopharyngitis	11 (3.0%)	68 (2.9)	36 (3.9%)	94 (3.8%)
Dizziness	7 (1.9%)	65 (2.8%)	28 (3.0%)	87 (3.5%)
Upper Respiratory Tract Infection	8 (2.0%)	46 (2.0%)	36 (4.0%)	73 (3.0%)
Arthralgia	6 (1.6)	31 (1.3)	37 (4.0)	60 (2.4%)
Diarrhea	7 (1.9%)	(2.3%)	10 (1.1)	59 (2.4%)
Urinary tract infection	8 (2.2)	41 (1.8)	22 (2.4%)	56 (2.3)
Sinusitis	3 (0.8%)	30 (1.3%)	23 (2.5%)	50 (2.0%)
Nausea	3 (0.8%)	39 (1.7%)	16 (1.5)	51 (2.1)
Bradycardia	1 (0.3%)	30 (1.2)	14 (1.5%)	42 (1.7)
Bronchitis NOS	2 (0.5%)	23 (1.0%)	14 (1.5%)	38 (1.5%)
Cough	5 (1.3%)	24 (1.0%)	17 (1.8)	37 (1.5%)

Preferred Term	PC Trials		Extension Trials N = 920 n (%)	All Trials N = 2468 n (%)
	Placebo N = 372 n (%)	NEB N = 2313 n (%)		
Insomnia	1 (0.3%)	25 (1.1%)	14 (1.5)	34 (1.4%)
Blood triglycerides ↗	(1.3%)	20 (0.9%)	20 (2.2%)	33 (1.3%)
C-reactive protein ↗	1 (0.3%)	22 (1.0%)	20 (2.0)	32 (1.3%)
Back pain	3 (0.8)	20 (0.9)	12 (1.3%)	31 (1.3%)
Edema peripheral	2 (0.5)	21 (0.9)	15 (1.6)	28 (1.1%)
Dyspepsia	4 (1.1%)	18 (0.8)??	13 (1.4)	29 (1.2)
Chest Pain	0.0	20 (0.9%)	8 (0.9%)	27 (1.1%)
Blood cholesterol ↗	4 (1.1)	15 (0.7)	11 (1.2)	25 (1.0%)
Rash NOS	3 (0.8)	18 (0.8)	9 (1.0)	24 (1.0%)
Pain in limb	01	16 (0.7)	9 (1.0)	23 (0.9)
Constipation	8 (2.2)	14 (0.6)	9 (1.0)	22 (0.9)
Sinus congestion	1 (0.3)	14 (0.6)	11 (1.2)	20 (0.8)
Neoplasm B, M & unspecified	1 (0.3)	13 (0.6)	13 (1.4%)	20 (0.8)
Blood glucose ↗	2 (0.5)	10 (0.4)	13 (1.4)	19 (0.8)
Pharyngitis NOS	00	10 (0.4%)	9 (1.0%)	16 (0.6)
Hyperlipidemia NOS	1	8 (0.4)	9 (1.0)	16 (0.6)
Hypercholesterolemia	1 (0.3)	7 (0.3)	9 (1.0)	13 (0.5)
Hypercholesterolemia aggravated	00	3 (0.1)	11 (1.2)	11 (0.4)

The events that were observed at a greater rate after a longer-term exposure include hypercholesterolemia, hyperlipidemia NOS; increases in blood triglycerides, blood cholesterol, blood glucose and C-reactive protein; sinus congestion, sinusitis, upper respiratory tract infections, bronchitis, cough, dyspepsia, constipation, edema, arthralgia, pharyngitis, and neoplasms.

The events that were observed at a lower rate after long-term exposure are fewer and these include headache, diarrhea and influenza.

The events that did not change were chest pain, dizziness, nausea, bradycardia and rash NOS.

Table 23. Other Events believed to be of clinical importance

Preferred Term	PC Trials		Extension Trials	All Trials
	Placebo N = 372 n (%)	NEB N = 2313 n (%)	N = 920 n (%)	N = 2468 n (%)
Blood uric acid↗	0	11 (0.4)	7 (0.8)	17 (0.7)
ALT↗	0	10	8 (0.9)	13 (0.5)
AST↗	0	9	8	12 (0.5)
LDL ↗	4	9	7	15 (0.6)
Weight↗	0	9	8	16 (0.7)
Hematocrit↘	0	8	0	8 (0.3)
Hypercholesterolemia	1	7	9	13
hypertriglyceridemia	1	6	8	9 (0.4)
Platelets count↘	0	6	2 (0.2)	7 (0.3)
Protein present in urine	0	6	2	6 (0.2)
Cardiac murmur NOS	0	5	4 (0.5)	5 (0.2)
Hemoglobin↘	0	5	1 (0.1)	6
Alkaline phosphatase↗	0	4	1	5
QT prolonged	0	4	1	4 (0.2)
T wave abnormal	0	4	3 (0.3)	6 (0.2)
Blood urea↗	0	3	0	3 (0.1)
HDL↘	0	3	0	3
Heart rate↘	0	3	1	4
Hypercholesterolemia aggravated	0	3	11 (1.3)	11 (0.5)
LFTs NOS abnormal	0	3	2	4
T wave inversion	0	3	1	3
Bilirubin ↗	0	2	3	3
Blood creatinine↗	0	2	4	6
DM aggravated	1	2	8	9
Eosinophil count↗	1	2	1	3
Gout	0	2	4	5
Gout aggravated	0	2	3	5
Hyperuricemia	0	2	0	2 (0.08)
Potassium↗	0	2	2	3
ST-T change NOS	0	2	1	2
Non-insulin-dependent DM	0	1	2	2
DM NOS	3	1	3	3
P wave abnormal	0	1	2	2
ST segment depressed	0	0	1	1

Preferred Term	PC Trials		Extension Trials	All Trials
	Placebo N = 372 n (%)	NEB N = 2313 n (%)	N = 920 n (%)	N = 2468 n (%)
Transaminase	0	0	2	2

Table 24. Adverse events reported by > 1% of patients on nebivolol in combined dosage groups in the placebo-controlled trials[7]

Preferred Term	Randomized placebo-controlled trials		
	Placebo N=372 n(%)	2.5-10 mg N=1387 n(%)	20-40 mg N=843 n(%)
Any Adverse Event	144 (38.7)	580 (41.8)	399 (47.3)
Headache	16 (4.3)	96 (6.9)	51 (6.0)
Fatigue	7 (1.9)	39 (2.8)	43 (5.1)
Nasopharyngitis	11 (3.0)	38 (2.7)	28 (3.3)
Dizziness	7 (1.9)	31 (2.2)	33 (3.9)
Diarrhea	7 (1.9)	26 (1.9)	27 (3.2)
Nausea	3 (0.8)	25 (1.8)	14 (1.7)
Upper Respiratory Tract Infection	8 (2.2)	24 (1.7)	22 (2.6)
Sinusitis	3 (0.8)	17 (1.2)	12 (1.4)
Insomnia	1 (0.3)	13 (0.9)	12 (1.4)
Bronchitis	2 (0.5)	11 (0.8)	10 (1.2)
Chest Pain	0	10 (0.7)	10 (1.2)
Back Pain	3 (0.8)	10 (0.7)	10 (1.2)
Influenza	1 (0.3)	9 (0.6)	9 (1.1)
Dyspnea	1 (0.3)	8 (0.6)	11 (1.3)
Bradycardia	1 (0.3)	5 (0.4)	12 (1.4)

The adverse events that were observed in excess on NEB compared to placebo and in which a trend of a dose response was observed include the following:

Dyspnea occurred on NEB 2.5 to 10 mg and NEB 20 to 40 mg at twice and 4 times the rate observed on placebo;

Bradycardia occurred on NEB 20 to 40 mg at almost 5 times the rate observed on placebo;

Chest pain was not experienced by subject on placebo and it was experienced on NEB in a dose response fashion;

Insomnia occurred on NEB 2.5 to 10 mg and on NEB 20 to 40 mg at 3 times and almost 5 times the rate observed on placebo;

[7] Analysis and Table completed by sponsor

Fatigue, dizziness and nausea occurred on NEB at a rate of at least twice that on placebo and in a dose response fashion;

Bronchitis and **influenza** occurred on NEB in a dose response fashion and at twice the rate on placebo;

Headache and Diarrhea were observed on NEB at about 1.5 times their incidence on placebo;

Table 25. Common adverse events by dose in the placebo-controlled trials

Adverse Events	0 N = 372 n(%)	Nebivolol 1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 627 n(%)	10 N = 629 n(%)	20 N = 626 n(%)	30/40 N = 217 n(%)	Any N = 2313 n(%)
Any Adverse Events	144 (38.7)	29 (34.9)	46 (42.8)	258 (41.1)	266 (42.3)	292 (46.7*)	107 (49.3*)	1008 (43.6)
Infections and infestations								
Any	47 (11.3)	7 (8.4)	13 (9.9)	86 (13.7)	61 (9.7)	90 (14.4)	43 (19.8*)	300 (13.0)
Upper Respiratory	8 (2.2)	0.0	2 (1.5)	13 (2.1)	9 (1.4)	15 (2.4)	7 (3.2)	46 (2.0)
Sinusitis	3 (0.8)	1 (1.2)	0.0	8 (1.3)	9 (1.4)	7 (1.1)	5 (2.3)	30 (1.3)
Bronchitis	2 (0.5)	2 (2.4)	0.0	6 (1.0)	5 (0.8)	8 (1.3)	2 (0.9)	23 (1.0)
Influenza	1 (0.3)	0.0	0.0	6 (1.0)	3 (0.5)	7 (1.1)	2 (0.9)	18 (0.8)
Viral Infections	1 (0.3)	1 (1.2)	1 (0.8)	2 (0.3)	3 (0.5)	3 (0.5)	3 (1.4)	13 (0.6)
Pharyngitis	0.0	1 (1.2)	1 (0.8)	2 (0.3)	1 (0.2)	4 (0.6)	1 (0.5)	10 (0.4)
Gastroenteritis	0.3	0.0	0.0	0.0	1 (0.2)	3 (0.5)	4 (1.8)	8 (0.4)
Nervous System disorders								
Any	33 (8.9)	7 (8.4)	17 (13.0)	69 (11.0)	62 (9.9)	71 (11.3)	31 (14.3*)	257 (11.1)
Headache	16 (4.3%)	6 (7.2%)	8 (6.1%)	49 (7.8%)*	39 (6.2%)	34 (5.4%)	17 (7.8%)	7.6
Dizziness	7 (1.9)	1 (1.2)	4 (3.1)	12 (1.9)	15 (2.4)	23 (3.7)	10 (4.6)	65 (2.8)
parasthesia	1 (0.3)	00	1 (0.8)	1 (0.2)	4 (0.6)	4 (0.6)	2 (0.9)	12 (0.5)
General disorders								
Any	4.8	3.6	8.4	5.7	7.0	10.1*	7.8	7.5
Fatigue	7 (1.9)	1 (1.2)	6 (4.6)	17 (2.7)	16 (2.5)	33 (5.3*)	10 (4.6)	83 (3.4)
Edema peripheral	2 (0.5)	2 (2.4)	1 (0.8)	5 (0.8)	6 (1.0)	5 (0.8)	2 (0.9)	21 (0.9)
Peripheral swelling	0.0	0.0	0.0	2 (0.3)	2 (0.3)	2 (0.3)	0.0	6 (0.3)
Chest pain	0.0	0.0	2 (1.5)	3 (0.5)	5 (0.8)	9 (1.4)	1 (0.5)	20 (0.9)
Vertigo	0.0	0.0	0.0	0.0	3 (0.5)	3 (0.5)	0.0	6 (0.3)
Respiratory disorders								
Any	14 (3.8)	6 (7.2)	8 (6.1)	29 (4.6)	28 (4.5)	31 (5.0)	5 (2.3)	107 (4.6)
Dyspnea NOS	1 (0.3)	0.0	0.0	2 (0.3)	6 (1.0)	8 (1.3)	3 (1.4)	19 (0.8)

Adverse Events	0 N = 372 n(%)	Nebivolol						
		1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 627 n(%)	10 N = 629 n(%)	20 N = 626 n(%)	30/40 N = 217 n(%)	Any N = 2313 n(%)
Dyspnea exertional	00	00	00	2 (0.3)	2 (0.3)	00	00	4 (0.2)
Sinus congestion	1 (0.3)	00	3 (2.3)	6 (1.0)	4 (0.6)	1 (0.2)	00	14 (0.6)
Nasal congestion	1 (0.3)	2 (2.4)	00	3 (0.5)	2 (0.3)	4 (0.6)	1 (0.5)	14 0.6)
Pharyngolaryngeal pain	1 (0.3)	1 (1.2)	1 (0.8)	1 (0.2)	3 (0.5)	5 (0.8)	1 (0.5)	12 (0.5)
Gastrointestinal disorders								
Any	27 (7.3)	4 (4.8)	11 (8.4)	42 (6.7)	52 (8.3)	59 (9.4)	20 (9.2)	188 (8.1)
Diarrhea	7 (1.9)	1 (1.2)	2 (1.5)	14 (2.2)	10 (1.6)	19 (3.0)	8 (3.7)	54 (2.3)
Nausea Vomiting	3 (0.8) 1 (0.3)	0.0 0.0	3 (2.3) 0.0	6 (1.0) 1 (0.2)	16 (2.5) 1 (0.2)	12 (1.9) 4 (0.6)	2 (0.9) 1 (0.5)	39 (1.7) 7 (0.3)
Abdominal pain	1 (0.3)	0.0	1 (0.8)	2 (0.3)	3 (0.5)	2 (0.3)	2 (0.9)	10 (0.4)
Dry mouth	0.0	0.0	2 (1.5)	3 (0.5)	4 (0.6)	1 (0.2)	0.0	10 (0.4)
Flatulence	0.0	0.0	0.0	2 (0.3)	1 (0.2)	5 (0.8)	1 (0.5)	9 (0.4)
Pain								
Pain in Limb	1 (0.3)	1 (1.2)	1 (0.8)	5 (0.8)	3 (0.5)	3 (0.5)	3 (1.4)	16 (0.7)
Neck Pain	0.0	0.0	0.0	3 (0.5)	4 (0.6)	2 (0.3)	0.0	9 (0.4)
Ear Pain	0.0	0.0	0.0	2 (0.3)	3 (0.5)	4 (0.6)	0.0	9 (0.4)
Cardiovascular disorders								
Any	8 (2.2)	2 (2.4)	2 (1.5)	15 (2.4)	11 (1.8)	24 (3.8)	6 (2.8)	60 (2.6)
Bradycardia NOS	1 (0.3)	00	00	2 (0.3)	3 (0.5)	11 (1.8)	1 (0.5)	17 (0.7)
Sinus Bradycardia	00	1 (1.2)	00	3 (0.5)	2 (0.3)	4 (0.6)	3 (1.4)	13 (0.6)
Palpitations	1 (0.3)	0.0	2 (1.5)	3 (0.5)	4 (0.6)	2 (0.3)	00	11 (0.5)
Orthostatic hypotension	00	00	00	00	1 (0.2)	3 (0.5)	00	4 (0.2)
Psychiatric disorders								
Any	3 (0.8)	2 (2.4)	4 (3.1)	12 (1.9)	14 (2.2)	23 (3.7)*	3 (1.4)	58 (2.5)
Insomnia	1 (0.3)	0.0	3 (2.3)	4 (0.6)	6 (1.0)	11 (1.8)*	0.5	25 (1.1)
Somnolence	1 (0.3)	00	00	00	2 (0.3)	2 (0.3)	3 (1.4)	7 (0.3)
Depression	0.0	0.0	0.0	0.0	1 (0.2)	3 (0.5)	2 (0.9)	6 (0.3)
Anxiety	0.0	0.0	0.0	3 (0.5)	2 (0.3)	2 (0.3)	0.0	7 (0.3)
Libido ↘	00	1 (1.2)	1 (0.8)	00	1 (0.2)	1 (0.2)	00	4 (0.2)
Eye disorders								
Any	0.0	1 (1.2)	3 (2.3*)	8 (1.3*)	10 (1.6*)	8 (1.3*)	0.0	1.3*
Vision blurred	00	00	2 (1.5)	3 (0.5)	4 (0.6)	3 (0.5)	00	12 (0.5)

Adverse Events	0 N = 372 n(%)	Nebivolol						
		1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 627 n(%)	10 N = 629 n(%)	20 N = 626 n(%)	30/40 N = 217 n(%)	Any N = 2313 n(%)
Musculoskeletal + connective tissue disorders								
Any	18 (4.8)	3 (3.6)	7 (5.3)	34 (5.4)	35 (5.6)	30 (4.8)	14 (6.5)	123 5.3)
Pain in Limb	1 (0.3)	1 (1.2)	1 (0.8)	5 (0.8)	3 (0.5)	3 (0.5)	3 (1.4)	16 (0.7)
Neck pain	00	00	00	3 (0.5)	4 (0.6)	2 (0.2)	00	9 (0.4)
Arthralgia								
Investigations								
CRP ↗	1 (0.3)	1 (1.2)	5 (3.8)	4 (0.5)	4 (0.6)	5 (0.8)	4 (1.8)	22 (1.0)
Blood uric acid ↗	00	00	1 (0.80)	4 (0.6)	3 (0.5)	2 (0.3)	1 (0.5)	11 (0.5)
ALT↗	00	1 (1.2)	00	3 (0.5)	3 (0.5)	3 (0.5)	00	10 (0.4)
AST↗	00	1 (1.2)	00	2 (0.3)	2 (0.3)	3 (0.5)	1 (0.5)	9 (0.4)
Weight ↗	00	00	00	1 (0.2)	3 (0.5)	5 (0.8)	00	9 (0.4)
Hematocrit ↘	00	00	1 (0.80)	2 (0.3)	2 (0.3)	3 (0.5)	00	8 (0.4)
Platelet count ↘	00	00	00	2 (0.3)	2 (0.3)	2 (0.3)	00	6 (0.3)
Reproductive and hormonal disorders								
Erectile Dysfunction	1 (0.3)	0.0	0.0	0.0	3 (0.5)	1 (0.2)	1 (0.5)	5 (0.2)
Dysmenorrhea	0.0	0.0	0.0	1 (0.2)	1 (0.2)	2 (0.3)	1 (0.5)	5 (0.2)
Neoplasm, benign & malignant								
Any	1 (0.3)	0.0	1 (0.8)	3 (0.5)	2 (0.3)	6 (1.0)	1 (0.5)	13 (0.6)

Table 26. Adverse events that were observed solely on NEB

Adverse events	NEB N = 2468 n	Adverse events	NEB n
Eye disorders	30	Hemoglobin ↘	4
Chest pain	20	Libido ↘	4
Sinus bradycardia	13	Flushing	4
Blurred vision	12	Orthostatic hypotension	4
Uric acid ↗	11	First degree artio-ventricular block	4
pharyngitis	10	T wave abnormal	4
rhinitis	10	QT prolonged	4
Dry mouth	10	Deafness/impaired hearing	4
Ear pain	9	T wave inversion	3
Neck pain	9	Urea↗	3
Flatulence	9	Heart rate ↘	3

Adverse events	NEB N = 2468 n	Adverse events	NEB n
ALT ↗	9	HDL ↘	3
AST↗	9	Sweating ↗	3
Weight↗	9	LFTs abnormal	3
Hematocrit↘	8	Angioedema	3
Somnolence	7	Breast lump NOS	3
Anxiety	7	Solar keratosis	3
Depression	6	CHF	2
Peripheral swelling	6	Potassium ↘	2
Vertigo	6	ST-T segment change	2
Platelet ↘	6	Eosinophil count↗	2
Postural dizziness	5	Bilirubin↗	2
Contact dermatitis	5	Creatinine↗	2
Dysmenorrhea	5	RBC in urine	2
Cardiac murmur	5	Urinary occult blood test positive	2
Hemoglobin↘	5	Ventricular extrasystoles	2
Conjunctival hemorrhage	4	Lipoma NOS	2
Alkaline phosphatase ↗	4	Chest pressure/tightness	2

There were 6.2 subjects on NEB per one placebo. Most of the events that are listed above including the ones that were observed in less than 6 patients are known to be effects of beta-adrenergic blockade.

Adverse events of concern:

Myocardial ischemia: Chest pain, T-wave abnormalities, T-wave inversions and ST segment changes do raise the question of a potential myocardial ischemic effect of NEB. The diversity of the findings in addition to the known mechanism of cardiac vasoconstriction that is observed with some beta-blockers cast doubts on the concept of a chance finding;

Angioedema in 3 + the other 2 that were observed in the extension trial;

Reproductive/hormonal: Dysmenorrhea in 5 and breast lumps in 3 in the placebo-controlled trial + 2 other breast lumps in the extension trial + 2 breast cancers observed in the extension trials + 6 female reproductive and breast disorders;

Adverse events with an incidence at least 1.5 times that of placebo:

C-reactive protein: was increased on NEB in 3.5 times as many subject on placebo and on the 30/40 mg dose level in 7 times as many subjects as placebo (p-value=0.06). More subject experience an increase in the extension trial.

Infections: sinusitis, bronchitis, influenza, viral infections and pharyngitis;

Nervous system: headache dizziness and parasthesia,

General disorders: fatigue and peripheral edema;

Cardiovascular disorders: bradycardia and sinus bradycardia and palpitations;

Respiratory disorders: dyspnea and dyspnea exertional, sinus congestion, nasal congestion and pharyngolaryngeal pain;

Gastrointestinal disorders: nausea, dry mouth, flatulence and abdominal pain;

Musculoskeletal disorders: pain in limb and neck pain,

Psychiatric disorders: any psychiatric disorder, insomnia, anxiety and depression;

Adverse events with a dose relation or a statistically significant finding:

All adverse events combined with the RR associated with the two highest doses (20 and 30/40 mg) statistically different from 1;

All infections combined with the RR associated with the highest dose statistically different from 1;

Upper respiratory tract infection with a RR on the highest dose being 1.5;

Sinusitis with a RR on the different doses of NEB ranging from 0 on the 2.5 mg dose level to 2.86 on the highest dose;

Gastroenteritis viral NOS: with 7 of the 8 cases on NEB occurring on the 20 and 30/40 mg dose levels;

All nervous system disorders combined with the RR associated with the highest dose being statistically significantly different from 1;

Headache with the RR on NEB dose levels 1.25, 5 and 30/40 mg exceeding 1.5 and the RR on 5 mg statistically significantly different from 1;

Dizziness with the RR on NEB dose levels 2.5, 20 and 30/40 mg exceeding 1.5 and the RR on 30/40 mg close to statistical significance;

Paresthesia with an increase in the RR as the dose increases starting at the 10 mg dose level;

Diarrhea with the RR associated with the two highest dose levels > 1.5;

All general disorders combined with the RR on NEB 20 mg being double and statistically significantly different from 1;

Fatigue with the RR on NEB 2.5, 20 and 30/40 mg > 2 and that associated with 20 mg statistically different from 1;

All psychiatric disorders combined with a RR on NEB of 3, and that associated with the 20 mg dose level statistically different from 1;

Insomnia with the RR on NEB 20 mg being statistically significantly different from 1;

Depression with all 6 cases occurring on the 3 highest dose levels;

Somnolence with all 7 cases on NEB occurring on the 3 highest doses;

Dyspnea with the RR increasing starting at the 5 mg dose level, and in a dose response fashion;

Bradycardia with 11 out of 17 events occurring on the 20 mg dose level, a statistically significant RR on this dose level, and a hint of a dose response starting at 5 mg, peaking at 20 mg and tapering down at the highest dose;

Eye disorders with an increase in the risk that is statistically significant at all dose levels except the lowest with one case and the highest with none;

5.3.1.4.2 Less common adverse events in the phase 2/3 trials of the PP