There were nine drop-outs in the double-blind treatment: One in the placebo group (due to inefficacy); Five in the nebivolol 2.5 group (three for inefficacy, one for adverse events and one for treatment deviation); One in the nebivolol group (adverse events); Two in the nebivolol 10 group (adverse events, and, in addition, inefficacy or treatment deviation).

In the double-blind portion, the incidence of adverse events was inconsistently related to dose, being highest for nebivolol 5 and placebo, and lower for the lowest and highest doses, nebivolol 2.5 and nebivolol 10. There were no deaths. The incidence of adverse events was 42% for placebo, 26% for nebivolol 2.5, 47% for nebivolol 5, and 34% for nebivolol 10.

In the open-label portion, there was one death due to bronchial cancer. Another patient had a malignant breast neoplasm.

This reviewer found the individual adverse events difficult to count because the numbers did not always add up, and no explanation was given for the discrepancies.

The primary investigator concluded that nebivolol 5 mg is the optimal dose for the treatment of hypertension and that it is safe and well tolerated on long-term treatment. In the opinion of this reviewer, the data do not strongly support the 5 mg dose over the other two doses.

For further safety discussion, please see the safety review.

10 APPENDIX

10.1 N 101044/1 (NEB-BEL-3/6)

10.1.1 Name of Study

N 101044/1 (NEB-BEL-3/6) Double-blind, placebo-controlled multicenter study of nebivolol 2.5, 5 and 10 mg once daily in patients with essential hypertension, followed by an open-label period of nebivolol 5 mg treatment for up to 4 years. The study was performed by Janssen Research Products.

10.1.1.1 Investigator

B. Boxus, MD
Rue du Calvaire 72
6060 Gilly, Belgium

10.1.2 Basis of Review

The description of the study is based on the summary Clinical Research Report from Janssen Research Products dated November 1993. The protocol for the study was not included in the NDA submission.

10.1.3 Objectives

The purpose of the study was to establish the optimal dose of nebivolol in essential hypertension and assess its safety.

10.1.4 Population

Subject inclusion criteria:

- Male and female outpatients.
- Essential hypertension (either treated or untreated). At the end of the run-in period, diastolic blood pressure must be >/= 95 mmHg.

Exclusion criteria included:

- Age < 18 years. (This reviewer believes this is a typographical error in the summary and was meant to be "Age > 18 years.")
- Malignant hypertension.
- Known or suspected contraindications for beta-blockers.
- Recent myocardial infarction or stroke (within the last 3 months).
- Insulin-dependent diabetes.
- Severe hepatic or renal impairment.
- Pregnancy, pregnancy potential, lactation or inadequate contraception.
- Treatment with other antihypertensives (in the double-blind part of the trial), MAO-inhibitors, tricyclic antidepressants, anti-inflammatory drugs (used regularly), hormonal contraceptives.
- CARA. (This reviewer could not find a definition for this abbreviation.)
- Second or third degree AV-block, serious bradycardia (< 50 bpm).
- Any illness or medication which disturbs the normal function of the GI system, the liver or kidneys and can thereby affect the absorption, distribution or metabolism of nebivolol.
- Known inability to comply with the protocol or any factor that, in the investigator's opinion, could compromise compliance (e.g., alcohol or drug abuse, mental dysfunction, or severe disease necessitating a substantial quantity of medication.)

10.1.5 Procedures

During a 2-4 week run-in period, the patients were given 10 ml of an oral placebo solution, once daily, with breakfast, in a single-blind fashion. If antihypertensives were used, these were withdrawn gradually over 2 weeks. If at the end of this 2-week interval, the DBP was > 110 mmHg or the SBP > 200 mmHg, the double-blind treatment phase was started immediately. Otherwise it was started after 4 weeks. If after the first 2 weeks the DBP was < 95 mmHg, the patient was withdrawn.

10.2 Results

10.2.1 Enrollment

The study was initiated on October 17, 1987 and completed January 29, 1992.

There was one principal investigator and 33 co-investigators at 27 sites in Belgium.

Baseline characteristics: One hundred thirty-four patients (57 males/77 females) with essential hypertension entered the double-blind treatment phase of the study. Eighty-one (37 males/44 females) entered the open-label follow-up phase. Median age, therapeutic results and safety results are presented below in the two figures below (from pages 8 and 9 of the Clinical Research Report submitted by the sponsor).

Figure 112. Main Features of the Trial Sample and Summary of the Results. Summary of Therapeutic Results (BEL-3/6)

Baseline comparability - drop-outs	PLAC	NEB 2.5	NEB 5	NEB 10	Follow-up
Number of patients entered (M/F)	15/18	15/20	10/24	17/15	37/44
Age: median (min;max), yrs	56 (32; 77)	54 (24; 78)	56 (22; 76)	59 (32; 77)	56 (26; 78)
Withdrawal - reason :					
- Inefficacy	1	3			4
- Adverse events		1	1	2	9
- Treatment deviation		1			7
- Lost to follow-up					16
- Intercurrent treatment					1
- Illness of investigator					1
Total No. (%) of drop-outs	1 (3%)	5 (14%)	1 (3%)	2 (6%)	38 (47%)

Therapeutic results (n = number of patients with efficacy data)	PLAC (n = 33)	NEB 2.5 (n = 35)	NEB 5 (n = 34)	NEB 10 (n = 32)	Follow-up (n = 81)
Primary parameter:					
• DBP, trough, sitting (mmHg)					
- baseline double-blind	105.0	107.1	103.9	103.6	
- end point double-blind①	93.7	91.4	87.9	87.9	
- baseline follow-up					103.5 (n=79)
- 3 months					86.2 (n=63)
- 6 months					86.2 (n=73)
- 12 months					85.7 (n=68)
- 24 months					87.3 (n=48)
- 36 months					85.4② (n=41)
Secondary parameters:					
• SBP, trough, sitting (mmHg)					
- baseline double-blind	168.4	175.3	172.8	168.9	
- end point double-blind	153.9	150.7	150.3	146.4	
- baseline follow-up					169.6 (n=79)
- 3 months					145.6 (n=63)
- 6 months					145.1 (n=73)
- 12 months					145.3 (n=67)
- 24 months					144.2 (n=48)
- 36 months					141.4② (n=41)
• Response rate (DBP), n (%)	21 (64%)	27 (77%)	28 (82%)	28 (88%)	
- Normalized (DBP ≤ 90 mmHg at end)	17 (52%)	22 (63%)	25 (76%)	22 (69%)	
- Not-normalized (DBP ≥ 10 mmHg decreased)	4 (12%)	5 (14%)	3 (9%)	6 (19%)	
• Investigator global evaluation: % of patients with good or very good antihypertensive effect	48%	60%	56%	77%	84%

① Dose-response ranking: PLAC ≤ NEB 2.5 ≤ NEB 5 = NEB 10

(≤: statistical significance or non-significance at α = 10% level is uncertain

=: not statistically significantly different at α = 10% level)

② Intragroup changes throughout the follow-up period (Friedman test): $p < 0.001$

(Reproduced from Sponsor, BEL-3/6, page 8)

Figure 113. Summary of Safety Results (BEL-3/6)

Safety	PLAC	NEB 2.5	NEB 5	NEB 10	Follow-up
• Body weight, kg:					
- baseline double-blind	79.5	75.0	74.1	79.3	
- end point double-blind	79.4	73.9	73.7	79.1	
- baseline follow-up					79.1 (n=78)
- 3 months					78.1 (n=63)
- 6 months					77.3 (n=64)
- 12 months					77.1 (n=59)
- end point					78.4 (n=81)③
• Heart rate, sitting, bpm:					
- baseline double-blind	82.2	87.4	83.8	79.4	
- end point double-blind	77.2	74.6*	75.5	67.6*	
- baseline follow-up					81.9 (n=78)
- 3 months					71.1 (n=65)
- 6 months					69.4 (n=70)
- 12 months					72.9 (n=66)
- end point					73.9 (n=81)③
• Adverse events (AE):					
Most frequent AE headache (No. during run-in/during double-blind)	2/4	2/3	5/2	1/1	No AE prevailing
No. (%) of patients with one or more AE:					
- double-blind	14 (42%)	9 (26%)	16 (47%)	11 (34%)	
- follow-up:					
- up to 6 months					28 (35%)
- from > 6 months to 1 year					24 (32%)
- from > 1 to 1.5 year					16 (23%)
- from > 1.5 to 2 years					20 (31%)
- from > 2 to 2.5 years					15 (26%)
- from > 2.5 to 3 years					18 (32%)
- from > 3 to 4 years					7 (27%)
Laboratory parameters	No clinically important changes				
Important laboratory abnormalities: code 4 (normal laboratory value at start and pathological in at least 2 samples or in the last one)	6	3	5	5	33

③ Overall intragroup changes (Friedman test): p = 0.011
* Confidence intervals indicate a statistically significant difference *versus* placebo

(Reproduced from Sponsor, BEL-3/6, page 9)

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

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

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

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

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

There were nine drop-outs in the double-blind treatment: One in the placebo group (due to inefficacy); Five in the nebivolol 2.5 group (three for inefficacy, one for adverse events and one for treatment deviation); One in the nebivolol group (adverse events); Two in the nebivolol 10 group (adverse events, and, in addition, inefficacy or treatment deviation).

In the double-blind portion, the incidence of adverse events was inconsistently related to dose, being highest for nebivolol 5 and placebo, and lower for the lowest and highest doses, nebivolol 2.5 and nebivolol 10. There were no deaths. The incidence of adverse events was 42% for placebo, 26% for nebivolol 2.5, 47% for nebivolol 5, and 34% for nebivolol 10.

In the open-label portion, there was one death due to bronchial cancer. Another patient had a malignant breast neoplasm.

This reviewer found the individual adverse events difficult to count because the numbers did not always add up, and no explanation was given for the discrepancies.

10.2.2 Conduct

10.2.2.1 Interim analyses

There were no interim analyses.

10.2.2.2 Protocol violations

There was no treatment data for three placebo patients, five nebivolol 2.5, four nebivolol 5, and three nebivolol 10 patients. The sponsor reported no violations in the follow-up part of the trial.

10.2.2.3 Dosing

For the double-blind treatment portion, patients received 10 ml once daily of an oral solution of either placebo or nebivolol. For the open-label portion, patients received either nebivolol 0.5 mg/ml solution or 5 mg tablets. Based on the brief information given in the submission, this reviewer is unable to determine whether the solution is the same formulation as the tablet and whether the solution and tablet are equivalent in bioavailability.

10.2.3 Endpoints

10.2.3.1 Safety and Tolerability

The analysis was based on the intent-to-treat approach (using all patients randomized). The primary efficacy parameter was the shift from baseline for trough diastolic blood pressure (DBP) in sitting position vs. placebo and to investigate the dose-response relationship.

Response to treatment was defined as a decrease in sitting trough DBP to 90 mmHg or below or a decrease of at least 10 mmHg versus baseline, absolute DBP values still being above 90 mmHg. No individual results are given in the summary provided in the NDA. All results are presented as means.

Secondary efficacy parameters included change in systolic blood pressure, incidence of positive experiences and investigator's global evaluation.

10.2.3.2 Unplanned analysis

10.2.3.2.1 Concomitant diseases

Concomitant diseases were present in 29% of all patients. At the start of the run-in phase and of the follow-up phase, one patient had angina pectoris, two had heart failure and six were diabetics.

10.2.3.2.2 Concomitant and previous medications

During the double-blind treatment phase, 46% of patients took concomitant medications and 69% in the follow-up. The most frequent concomitant medications were the following: antianginals, taken by six patients in the double-blind phase and by eight in the follow-up phase, non-steroidal anti-inflammatory drugs by nine and 21, peripheral vasodilators by seven in both phases, and hypnosedative benzodiazepines by 20 and 16 patients. During the follow-up phase, one patient took another beta-blocker (sotalol) in combination with nebivolol, and ten patients took diuretics. According to the sponsor, possible interactions with other antihypertensives were not analyzed as too few patients were involved.

10.3 Summary and Conclusions.

10.3.1 Summary

1. This is an evaluation in which the antihypertensive effects of oral solution nebivolol at doses of 2.5, 5 and 10 mg once daily vs. placebo were studied in 134 adult patients with essential hypertension. No protocol was included in the NDA submission.
2. There were four parallel groups, 2-4 weeks placebo run-in followed by 4 weeks double-blind treatment. After the double-blind part of the trial, 81 patients continued on open-label nebivolol 5 mg for up to 4 years. There were two deaths during the open-label follow-up portion of the trial.
3. All results in the summary provided in the NDA are presented as means and percentages.
4. For the double-blind portion, patients received 10 ml once daily of an oral solution of either placebo or nebivolol. For the open-label portion, patients

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

5. For the primary endpoint, increasing effect with dose was not statistically significant, although dose dependent increments in blood pressure reduction were demonstrated with this dose range in this study.
6. During the open-label portion (up to 48 months), the blood pressure lowering effect of the nebivolol was maintained. No information was given in the summary as to who was on solution and who was on tablet during the open-label portion.
7. This reviewer found the individual adverse events difficult to count because the numbers did not always add up, and no explanation was given for the discrepancies. Doses appeared to be well tolerated.
8. The primary investigator concluded that nebivolol 5 mg is the optimal dose for the treatment of hypertension and that it is safe and well tolerated on long-term treatment. In the opinion of this reviewer, the data do not strongly support the 5 mg dose over the other two doses.

10.3.2 Conclusions

Based on the brief information given in the submission, this reviewer is unable to determine whether the solution given was the same formulation as the tablet, and whether the solution and tablet are equivalent in bioavailability. (This was discussed with chemist Dr. Ram Mittal.) Therefore, no conclusion can be made whether this study supports the safety and efficacy of the nebivolol formulation in the NDA submission.

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

The primary investigator concluded that nebivolol 5 mg is the optimal dose for the treatment of hypertension and that it is safe and well tolerated on long-term treatment. In the opinion of this reviewer, the data do not strongly support the 5 mg dose over the other two doses.

1.72 (Corresponds to #134 in Table 2). LMD NO. N/A. Study ID: NEBI-0126. ("Single-Dose, Dose-Proportionality Pharmacokinetic Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status") (Trial Period: August 11, 2001 – 22 September 22, 2001) (Study Report Dated October 31, 2001) (Reviewer: Karen A. Hicks, M.D.)

Objectives: To investigate the single-dose pharmacokinetics of nebivolol at four dose levels (2.5 mg, 5 mg, 10 mg, and 20 mg of free base nebivolol) in healthy, adult volunteers characterized according to their CYP2D6 metabolizing status.

Methods: This open-label single dose four period, randomized, crossover study in sixteen non-smoking males and females, ages 20 through 50, determined plasma concentration-time curves of *d*-nebivolol, *l*-nebivolol, and *d,l*-nebivolol. There were four study periods, conducted from 10-14 August 2001, from 24 -28 August 2001, from 7-11 September 2001, and from 21-25 September 2001. As per page 35 of the study, subjects were randomized to receive nebivolol 2.5, 5, 10, and 20 mg as single doses during each study period, as shown below.

Extensive Metabolizers [EM]
ABCD – Subject s 4 and 6
BDAC – Subject s 1 and 7*
CADB – Subject s 2 and 8
DCBA – Subject s 3 and 5

Poor Metabolizers [PM]
ABCD – Subject's 11 and 13
BDAC – Subject's 12 and 16
CADB – Subject's 10 and 14
DCBA – Subject's 9 and 15

*Subject #7 was discontinued prior to dosing Period 4 due to an adverse experience.

Investigators screened subjects within two weeks of first study drug administration. Subjects remained in clinic from the evening prior to dosing until 24 hours post study drug administration. Subjects fasted for at least 10 hours prior to dosing. Seated resting blood pressure and heart rate were measured within 30 minutes prior to study drug administration, hourly for the first 8 hours after dosing, and then at 12, 24, and 48 hours. Lead II ECGs were performed prior to dosing and then at 4, 8, 12, 24, and 48 hours following study drug administration. Serum chemistry, hematology, and urinalysis were performed at Screening, pre-dose, and at the end of study. Subjects were also tested for Hepatitis B, Hepatitis C, and HIV. Plasma samples for pk were obtained within 30 minutes prior to dosing and at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 10, 24, 36, 48, and 72 hours post dosing.

To estimate *d,l*-nebivolol plasma concentration, investigators added *d*-nebivolol and *l*-nebivolol together at each sampling point.

Exclusion criteria (page 34)

1. institutionalized subjects
2. subjects ingesting alcoholic, caffeine- or xanthine-containing food or beverage within the 48 hours prior to the initial study dose
3. subjects ingesting any vitamins or herbal products within the 48 hours prior to the initial study dose
4. subjects exhibiting any recent, significant change in dietary or exercise habits
5. subjects using any medication, including over the counter drugs, within the 14 days prior to the initial study dose, with the exception of hormonal contraceptives and hormone replacement therapy initiated at least 3 months prior to the start of the study
6. subjects using any medication known to alter hepatic enzyme activity within 28 days prior to the initial study dose
7. subjects with a history of using psychotropic agents
8. subjects testing positive for any drug included in the urine drug screen
9. subjects with a history of any significant cardiovascular, hepatic, renal, pulmonary, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, or neurologic disease
10. subjects with a history of drug and/or alcohol abuse within 1 year
11. subjects who had an acute illness at the time of either the pre-study medical evaluation or dosing
12. subjects with any clinically significant abnormalities
13. subjects with clinically significant ECGs
14. subjects who donated or lost a significant volume of blood or plasma (> 450 mL) within 28 day prior to the initial study dose
15. subjects who received an investigational drug within 30 days prior to study dose
16. subjects with an allergy or hypersensitivity to nebivolol hydrochloride or any ß-blocker, or to any tablet inactive ingredients (lactose monohydrate, starch, croscarmellose sodium, sodium lauryl sulfate, hydroxyl propylmethylcellulose, polysorbate 80, microcrystalline cellulose, silica, or magnesium stearate)
17. subjects with a history of difficulty swallowing or any gastrointestinal disease which could affect absorption
18. subjects with a resting heart rate less than 60 bpm after a 5 minute resting period in the
19. seated position
20. subjects who consumed grapefruit or grapefruit containing products within 7 days of study drug administration
21. subjects with a history of asthma or other pulmonary problems

Results: The demographic data for the study group is described in Table 140.

Table 140. Demographic Data (NEBI-0126)

Subject Number	Age	CYP2D6 Genotype	Sex	Race[¶]	Height (inches)	Frame Size[^]	Body Mass Index (kg/m^2)	Entry Weight (lbs)	Exit Weight (lbs)
1	20	EM (*1/*4)	M	W	67.5	M	23.0	149	148
2	37	EM (*1/*1)	M	W	74	L	22.9	178	181
3	23	EM (*1/*4)	M	W	71	L	27.3	190	185
4	42	EM (*1/*4)	M	W	72	L	28.4	209	210
5	41	EM (*1/*4)	M	W	69	L	26.8	181	181
6	20	EM (*1/*1)[§]	M	W	71	L	22.8	163	165
7	50	EM (*1/*5)	F	W	64.5	L	26.7	158	156
8	32	EM (*1/*1)	F	W	65	L	25.6	154	150
9	36	PM (*4/*5)	F	W	64.25	L	23.7	139	141
10	21	PM (*4/*6)	F	W	65.50	L	24.1	147	150
11	26	PM (*4/*4)	F	W	64	L	28.5	166	166
12	21	PM (*3/*4)	M	W	65	M	25.3	152	153
13	25	PM (*4/*4)	M	W	66	L	23.6	146	147
14	21	PM (*3/*4)	M	W	72	M	22.9	169	170
15	31	PM (*3/*4)	M	W	69.5	L	28.0	192	192

Source: Table T1, page 7 Clinical and Pharmacologic Research, Inc. Clinical Report in Section 14.11-Attachment 4 and Section 14.5-Attachment 2A, part 3.

§ Subject 6 demonstrated the presence of gene duplication.

¶ Race Key: W = Caucasian

^ Frame Key: M = Medium Frame; L = Large Frame

(Reproduced from Sponsor, NEBI-0126, Table 12.14, page 61)

Study Results for *d*-nebivolol, *l*-nebivolol, and *d,l*-nebivolol are shown in Tables 141 through 143.

Table 141. Mean (% CV) *d*-Nebivolol Pharmacokinetic Parameters in Healthy Male and Female Subjects Following a Single, Oral Dose of the Assigned Formulation of nebivolol Tablets Under Fasting Conditions

Treatment (Dose of nebivolol) [# of subjects]	Parameter – [EM Group; 6 males and 2 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr^{-1})	HALF (hr)	CL/F[§] (L/hr)	Vd/F[¶] (L)
A: (2.5mg) [n= 8]	0.765 (75.63)	0.970 (80.62)	0.208 (40.08)	1.125 (31.43)	0.240 (63.61)	5.068 (90.48)	1969 (56.62)	8833 (17.01)
B: (5mg) [n= 8]	1.988 (81.82)	2.349 (73.69)	0.437 (37.72)	1.500 (50.40)	0.105 (55.70)	8.925 (54.99)	1568 (58.19)	15858 (47.79)
C: (10mg) [n= 7]	5.164 (63.45)	5.765 (59.47)	0.988 (44.20)	1.429 (37.42)	0.063 (15.24)	11.17 (14.46)	1059 (40.92)	17012 (45.63)
D: (20mg) [n= 8]	13.67 (76.24)	14.25 (72.92)	1.605 (50.10)	1.750 (26.45)	0.060 (17.22)	11.82 (15.83)	1038 (55.67)	17387 (59.57)
Treatment (Dose of nebivolol) [# of subjects]	**Parameter – [PM Group; 4 males and 3 females]**							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr^{-1})	HALF (hr)	CL/F[§] (L/hr)	Vd/F[¶] (L)
A: (2.5mg) [n= 7]	26.43 (24.42)	31.86 (23.59)	0.898 (26.08)	3.857 (37.95)	0.031 (16.09)	23.02 (18.26)	41.38 (25.98)	1340 (18.89)
B: (5mg) [n= 7]	59.29 (26.03)	72.15 (19.68)	2.116 (16.78)	3.714 (43.17)	0.029 (17.41)	24.86 (18.16)	35.77 (18.87)	1279 (26.79)
C: (10mg) [n= 7]	112.8 (20.15)	127.4 (21.67)	3.801 (18.46)	4.286 (37.42)	0.031 (10.89)	22.73 (10.97)	40.79 (20.62)	1330 (21.56)
D: (20mg) [n= 7]	225.2 (20.86)	263.1 (19.27)	8.265 (22.63)	3.714 (29.96)	0.031 (27.76)	23.25 (22.27)	39.22 (18.72)	1305 (27.91)

§ CL/F refers to the apparent clearance and was calculated as CL/F = Dose/AUCI, where the Dose was equal to ½ of the administered nebivolol dose due to nebivolol being a racemic mixture of *d*-and *l*-nebivolol.

¶ Vd/F refers to the apparent volume of distribution and was calculated as Vd/F = (CL/F)/KEL.

Source: Section 14.1 Attachment 1A

(Reproduced from Sponsor, NEBI-0126, Table 4.1, page 16)

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Table 142. Mean (%CV) *l*-Nebivolol Pharmacokinetic Parameters in Healthy Male and Female Subjects Following a Single, Oral Dose of the Assigned Formulation of Nebivolol Tablets Under Fasting Conditions

Treatment (Dose of nebivolol) [# of subjects]	Parameter – [EM Group; 6 males and 2 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr^{-1})	HALF (hr)	CL/F§ (L/hr)	Vd/F¶ (L)
A: (2.5mg) [n= 8]	1.543 (35.48)	2.494 (25.69)	0.392 (30.25)	0.875 (26.45)	0.042 (97.40)	24.09 (43.09)	541.2 (34.82)	17201 (41.96)
B: (5mg) [n= 8]	4.222 (35.80)	4.998 (30.65)	0.876 (39.23)	1.500 (50.40)	0.035 (15.76)	20.17 (15.28)	542.5 (30.21)	16230 (42.04)
C: (10mg) [n= 7]	9.726 (31.91)	10.60 (28.83)	1.959 (41.91)	1.357 (46.18)	0.045 (21.46)	16.11 (21.87)	506.6 (29.09)	12124 (48.05)
D: (20mg) [n= 8]	22.79 (42.60)	23.77 (41.17)	3.043 (39.04)	1.625 (31.85)	0.045 (16.58)	15.85 (17.55)	477.8 (35.19)	11039 (46.56)
Treatment (Dose of nebivolol) [# of subjects]	**Parameter – [PM Group; 4 males and 3 females]**							
	AUCL (ng x hr/mL)	**AUCI (ng x hr/mL)**	**CPEAK (ng/mL)**	**TPEAK (hr)**	**KEL (hr^{-1})**	**HALF (hr)**	**CL/F§ (L/hr)**	**Vd/F¶ (L)**
A: (2.5mg) [n= 7]	53.96 (32.61)	126.8 (34.51)	1.022 (23.80)	8.286 (88.34)	0.010 (19.54)	73.21 (18.30)	10.86 (33.12)	1100 (21.79)
B: (5mg) [n= 7]	132.1 (22.10)	275.0 (17.47)	2.623 (19.11)	8.286 (88.34)	0.011 (35.56)	72.61 (42.81)	9.362 (19.61)	932.1 (30.14)
C: (10mg) [n= 7]	273.1 (19.11)	545.1 (27.68)	5.493 (18.93)	7.714 (93.99)	0.010 (20.86)	70.13 (19.40)	9.696 (23.32)	958.9 (21.79)
D: (20mg) [n= 7]	611.8 (26.42)	1319 (24.00)	12.98 (17.86)	6.714 (114.6)	0.011 (33.67)	75.83 (49.96)	7.901 (20.45)	811.2 (27.86)

§ Cl/F refers to the apparent clearance and was calculated as Cl/F = Dose/AUCI, where the Dose was equal to ½ of the administered nebivolol dose due to nebivolol being a racemic mixture of *d*- and *l*-nebivolol.
¶ Vd/F refers to the apparent volume of distribution and was calculated as Vd/F = (Cl/F)/KEL.
Source: Section 14.2 Attachment IB

(Reproduced from Sponsor, NEBI-0126, Table 4.2, page 17)

Table 143. Mean (%CV) *d,l*-Nebivolol Pharmacokinetic Parameters in Healthy Male and Female Subjects Following a Single, Oral Dose of the Assigned Formulation of Nebivolol Tablets Under Fasting Conditions

Treatment (Dose of nebivolol) [# of subjects]	Parameter – [EM Group; 6 males and 2 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr^{-1})	HALF (hr)	CL/F§ (L/hr)	Vd/F¶ (L)
A: (2.5mg) [n= 8]	2.402 (48.78)	3.501 (40.55)	0.595 (33.83)	0.875 (26.45)	0.099 (81.50)	9.640 (45.17)	834.0 (48.70)	9803 (34.18)
B: (5mg) [n= 8]	6.384 (46.57)	7.036 (46.09)	1.313 (37.54)	1.500 (50.40)	0.047 (15.19)	15.05 (14.59)	831.4 (39.28)	18316 (46.05)
C: (10mg) [n= 7]	15.15 (41.81)	15.81 (40.04)	2.923 (40.15)	1.429 (37.42)	0.059 (14.51)	12.07 (14.82)	709.0 (33.96)	12606 (46.19)
D: (20mg) [n= 8]	36.70 (54.28)	37.68 (53.80)	4.643 (42.07)	1.625 (31.85)	0.053 (17.02)	13.41 (15.81)	657.4 (44.07)	12549 (47.52)
Treatment (Dose of nebivolol) [# of subjects]	**Parameter – [PM Group; 4 males and 3 females]**							
	AUCL (ng x hr/mL)	**AUCI (ng x hr/mL)**	**CPEAK (ng/mL)**	**TPEAK (hr)**	**KEL (hr^{-1})**	**HALF (hr)**	**CL/F§ (L/hr)**	**Vd/F¶ (L)**
A: (2.5mg) [n= 7]	80.39 (28.80)	148.0 (29.13)	1.844 (23.50)	5.571 (57.56)	0.013 (21.84)	55.57 (27.12)	18.22 (30.09)	1390 (18.36)
B: (5mg) [n= 7]	192.79 (21.28)	299.9 (20.44)	4.676 (18.58)	5.143 (28.46)	0.018 (23.12)	41.00 (20.26)	17.26 (20.20)	993.3 (14.39)
C: (10mg) [n= 7]	385.9 (18.29)	613.5 (24.06)	9.213 (18.70)	4.429 (31.14)	0.014 (21.74)	50.15 (18.89)	17.05 (21.86)	1206 (19.16)
D: (20mg) [n= 7]	837.1 (23.19)	1428 (13.07)	20.94 (17.67)	4.429 (34.14)	0.014 (25.61)	54.17 (27.17)	14.23 (14.52)	1103 (25.60)

§ Cl/F refers to the apparent clearance and was calculated as Cl/F = Dose/AUCI, where the Dose was equal to the administered dose of nebivolol.
¶ Vd/F refers to the apparent volume of distribution and was calculated as Vd/F = (Cl/F)/KEL.
Source: Section 14.3 Attachment IC

(Reproduced from Sponsor, NEBI-0126, Table 4.3, page 18)

Table 144. Mean (%CV) nebivolol Glucuronides Pharmacokinetic Parameters in Healthy Male and Female Subjects Following a Single, Oral Dose of the Assigned Formulation of nebivolol Tablets Under Fasting Conditions (NEBI-0126)

Treatment (Dose of nebivolol) [# of subjects]	Parameter – [EM Group; 6 males and 2 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr^{-1})	HALF (hr)	CL/F§ (L/hr)	Vd/F§ (L)
A: (2.5mg) [n= 8*]	42.45 (38.07)	52.81 (32.44)	8.973 (33.57)	2.250 (20.57)	0.2349 (13.05)	2.998 (14.27)	52.02 (33.61)	223.3 (32.67)
B: (5mg) [n= 8]	106.8 (43.95)	119.4 (38.50)	20.01 (32.31)	2.250 (39.40)	0.2226 (17.19)	3.217 (21.68)	46.29 (29.28)	209.0 (26.24)
C: (10mg) [n= 7]	252.2 (40.50)	264.8 (37.95)	40.04 (29.02)	2.286 (21.35)	0.1940 (38.35)	4.045 (35.84)	42.38 (36.41)	226.6 (24.62)
D: (20mg) [n= 8]	643.7 (26.15)	653.7 (25.75)	91.30 (28.00)	2.500 (21.38)	0.1341 (21.11)	5.356 (18.93)	32.46 (25.87)	246.7 (28.10)
Treatment (Dose of nebivolol) [# of subjects]	**Parameter – [PM Group; 4 males and 3 females]**							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr^{-1})	HALF (hr)	CL/F§ (L/hr)	Vd/F§ (L)
A: (2.5mg) [n= 7]	569.4 (31.79)	678.2 (27.52)	34.89 (27.19)	4.000 (0.000)	0.0269 (41.44)	29.11 (34.03)	3.960 (30.16)	164.0 (37.57)
B: (5mg) [n= 7]	1217 (24.88)	1416 (19.16)	70.57 (30.18)	3.857 (9.799)	0.0250 (25.11)	29.50 (29.49)	3.649 (19.89)	158.8 (45.55)
C: (10mg) [n= 7]	2426 (23.38)	2725 (21.00)	157.6 (18.00)	3.714 (13.14)	0.0301 (39.51)	25.46 (29.61)	3.809 (20.48)	142.8 (40.44)
D: (20mg) [n= 7]	5133 (30.10)	6285 (27.56)	328.7 (20.64)	4.000 (0.000)	0.0269 (33.94)	32.16 (72.24)	3.389 (26.43)	145.5 (49.23)

§ Cl/F' refers to the apparent clearance and was calculated as Cl/F' = Dose/AUCI, where the Dose was equal to the administered nebivolol dose and F' refers to the fraction of the bioavailable dose of nebivolol systemically converted to nebivolol glucuronides.
Vd/F' refers to the apparent volume of distribution and was calculated as Vd/F' = (Cl/F')/KEL, where F' refers to the fraction of the bioavailable dose of nebivolol systemically converted to nebivolol glucuronides.
* n = 8 for CPEAK, TPEAK, and AUCL; n = 7 for all other PK parameters
Source: Section 14.4 Attachment 1D

(Reproduced from Sponsor, NEBI-0126, Table 4.11, page 26)

A summary of blood pressure, heart rate, and QTc results for EMs and PMs are shown in Table 145.

Table 145. Summary of DBP, SBP, HR, and QTC for EMs and PMs at Screening and Exit (NEBI-0126)

	Diastolic Blood Pressure		Systolic Blood Pressure		Heart Rate		QTc	
	EMs	PMs	EMs	PMs	EMs	PMs	EMs	PMs
Screen								
N	8	7	8	7	8	7	8	7
Mean (SD)	74.0 (5.95)	74.0 (6.32)	125.8 (6.88)	115.7 (10.23)	63.13 (6.27)	67.71 (9.03)	390.38 (15.64)	392.86 (22.46)
Median	72.0	74.0	129.0	116.0	64.0	65.0	389.0	395.0
Range	68.0-86.0	66.0-80.0	114.0-132.0	(98.0-130.0)	51.0-70.0	58.0-82.0	374.0-415.0	360.00-429.00
Exit								
N	8	7	8	7	8	7	8	7
Mean (SD)	74.3 (8.17)	75.4 (6.60)	120.3 (7.89)	122.6 (12.20)	60.13 (12.09)	63.0 (11.52)	399.5 (16.30)	397.29 (17.28)
Median	71.0	72.0	120.0	128.0	61.0	59.0	398.5	398.0
Range	64.0-88.0	70.0-88.0	110.0-130.0	100.0 - 134.0	42.0-78.0	54.0-87.0	381.0-433.0	376.0-421.0

(Adapted from Sponsor, Tables 1.24 and 1.4.4, pages 788, 790, 805, 806, 808, and 809)

There were no significant efficacy results.

Safety: 16 subjects entered the study, but only 15 subjects completed the study. Investigators discontinued one patient (Subject 7, EM) due to the adverse event of an elevated temperature. There were 16 adverse events reported in 7 subjects. Adverse events included headache, "flashes in peripheral vision", dizziness, URI symptoms, elevated temperature, and blood in urine.

Conclusions: There was a dose-dependent increase in mean *d*-, *l*-, and *d,l*-nebivolol CPEAK, AUCL, and AUCI. Mean TPEAK in EMs ranged from 1.1 to 1.8 hours for *d*-nebivolol, 0.9 to 1.6 hours for *l*-nebivolol, and 0.9-1.6 hours for *d,l*-nebivolol. Mean TPEAK in PMs ranged from 3.7-4.3 hours for *d*-nebivolol, 6.7-8.3 hours for *l*-nebivolol, and 4.4 to 5.6 hours for *d,l*-nebivolol. For EMs, mean t1/2 for *d*-nebivolol, *l*-nebivolol, and *d,l*-nebivolol were 9, 19, and 13 hours, respectively. For PMs, mean t1/2 for *d*-nebivolol, *l*-nebivolol, and *d,l*-nebivolol were 23, 73, and 50 hours, respectively.

Increases for mean CPEAK between PMs and EMs for *d*-nebivolol, *l*-nebivolol, and *d,l*-nebivolol, were 4 to 5 fold, 3 to 4 fold, and 3 to 5 fold, respectively. Increases in mean t1/2 between PMs and EMs for *d*-nebivolol, *l*-nebivolol, and *d,l*-nebivolol were 2 to 5 fold, 3 to 5 fold, and 3 to 6 fold, respectively. Increases for mean AUCL between PMs and EMS for *d*-nebivolol, *l*-nebivolol, and *d,l*-nebivolol were 16 to 35 fold, 27 to 35 fold, and 23 to 33,respectively.

For both EMs and PMs, *l*-nebivolol had higher AUCL, AUCI, and CPEAK than *d*-nebivolol and had a 2 to 4 fold lower clearance than *d*-nebivolol.

Cmax was 16 fold higher for nebivolol glucuronides compared with *d,l*-nebivolol in EMs and PMs.

According to Dr. Elena Mishina in her Biopharmaceutical review for NDA 21,742 for nebivolol, the sponsor did not accurately characterize the pharmacokinetics of nebivolol 2.5 mg. Additionally, Dr. Mishina believes the sponsor's estimation of *l*-nebivolol half-life as 24 hours in EMs is not accurate, given that nebivolol was still present in plasma samples up to 36 and 48 hours after the 2.5 and 5 mg doses, respectively. Because the sponsor also reported the t1/2 for glucuronides as shorter than *d,l*-nebivolol, Dr. Mishina believes the sponsor may not have accurately measured plasma concentrations of nebivolol glucuronides. For the doses tested, nebivolol PK was linear in PMs. In EMs, nebivolol PK was not linear since there was a 2 fold increase in AUCL when the 2.5 mg dose was compared to the 20 mg dose.

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Salma Lemtouni
Clinical Review
3/1/2005

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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
CABG	coronary artery bypass
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
LV	left ventricle
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
SVT	supraventricular tachycardia
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SP	secondary program
SVT	supraventricular tachycardia
TSH	thyroid stimulating hormone
Unk:	Unknown
UNL	upper normal limit
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 2464 patients who were exposed to doses ranging between 1.25 and 40 mg for an average of 12 weeks in three placebo-controlled and one active-controlled trial. 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 not significantly different from placebo.

Except for bradycardia as a cause of discontinuation that occurred predominantly on 20 mg, discontinuation for adverse events was not significantly different between the two treatment arms.

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

QT evaluation was less than accurate because both correction (Bazzet and Fridericia) methods overcorrected and consequently led to shortening of QT on NEB. Therefore, a conclusion cannot be drawn with certainty regarding the effect of this drug on QT. One reassuring factor is that no Torsade de Pointes was reported in the post marketing data.

There is a hint of an increased risk of angioedema on NEB, but other beta-blockers are also suspected with regard to angioedema. Therefore, the future label of NEB and that of the other beta-blockers concerned must be updated with regard to angioedema.

Bradycardia on NEB was shown to be of the same magnitude at peak and trough levels, but it was observed to a lesser extent than on carvedilol.

Chest pain, dyspnea, fatigue, dizziness, insomnia, visual abnormalities, LFTs abnormalities, and decrease in platelet count and an increase of triglycerides were observed on NEB and are described and/or mentioned in the labels of some other beta-blockers.

In this study population, there is a hint of an effect of NEB on the levels of HDL, BUN, creatinine, uric acid, phosphorus level, and C-reactive proteins.

The association of NEB with liver function abnormalities, the increase in triglycerides, the decrease in platelet count, and depression seems to be less strong than that of carvedilol with these events.

One case of pancreatitis secondary to multi-micro-cholecystolithiasis and one case of hepatic cirrhosis (attributed to alcohol) were observed in the secondary program.

One case of hepatic failure was reported post marketing. This 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.

Overall, 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 and found to be acceptable.

In conclusion adverse events known to be associated with beta-adrenergic antagonism were experienced by subjects exposed to NEB as expected. Abnormalities in liver function tests were observed on NEB as they were on carvedilol in hypertensive patients. Chest pain was experienced at a similar incidence as on metoprolol succinate in hypertensive patients. NEB may not be the only beta-blocker to be associated with potential angioedema because events of angioedema were reported in post marketing experience of many other beta-blockers. Therefore, the general experience of the NEB study population with regard to study drug adverse effects was not different from that of the carvedilol and metoprolol hypertension study populations.

4 RECOMMENDATION ON REGULATORY ACTION

The reviewer recommends including a warning in the label about potential angioedema.

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 were ample data to complete this comparison given the number of comparative studies included.

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 incidences. 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			
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		

[1] The total number exposed does not match the added total of subjects exposed in each study because all subjects

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					-tal 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 - 70.0	33.0 - 75.0	26.0 - 7.0	29.0 - 9.0	28.0 - 4.0	28.0 - 9.0	26.0 - 9.0	
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		Nebivolol mg			Total n (%)
		50 n (%)	100 n (%)	5 n (%)	10 n (%)	20 n (%)	
ITT	0	24	21	23	23	24	115

exposed in NEB-306 and NEB-323 were exposed in the randomized controlled trials.

Disposition	Non-ITT	Atenolol mg		Nebivolol mg			Total n (%)
		50 n (%)	100 n (%)	5 n (%)	10 n (%)	20 n (%)	
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
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
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	Nebivolol mg	All

	N=167 n (%)	5 N=168 n (%)	10 N=168 n (%)	20 N=166 n (%)	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 (%)	10 N=168 n (%)	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						
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)
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.

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	4[illegible]	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 cardio-circulatory 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, basic disease and other.

[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

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

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	Atenolol 45	NEB 70	P 372	NEB 2313	930	2464
SAEs	1	21	3	5	00	01	04	26	18	42

[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.

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	Atenolol 45	NEB 70	P 372	NEB 2313	930	2464
	(0.49)	(1.2)	(0.6)	(1.4)			(1.1%)	(1.1%)	(1.9%)	(1.7)
AE led to Discontinuation	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 PP

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), neoplasm (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 PP

Events	NEB n	Event	NEB n
Headache	09	Dyspnea NOS	04
Bradycardia	09	Nausea	05

Events	NEB n	Event	NEB n
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 abnormal	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
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.

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

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	
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

Angioedema

One confirmed angioedema that led to discontinuation in a patient who was not taking any concomitant medications, 2 face swellings one of which was taking ACE-Is and one tongue swelling were observed, with the latter cases having continued their study medication.

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 was determined to be of non-cardiac 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 was suspected.

-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 secondary program (SP)

5.3.1.3.2.1 Serious adverse events

Information regarding SAEs was 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 and duration. 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 observed events include one malignant breast neoplasm, two MIs that led to death, one aortic dissection, one angina and one atypical chest pain on 5 mg in for unknown durations.

5.3.1.3.2.2 Adverse Events that led to Discontinuation

Some of the adverse events that led to discontinuation include the following:

-Respiratory disorder in 2 subjects; dyspnea in 3, asthma in one; wheezing, bronchospasm and nocturnal dyspnea in one each;
- MI in 3; chest pain in 4; angina in 3; and cardiac failure in 2;
-Menstrual disorders in one;
Malignant breast cancer in 2; bladder papilloma in one; malignant lymphoma in 2; bronchial cancer leading to death in one; and malignant melanoma in one;
-AST and ALT increased (severity unknown) in one; and pruritus in one;

5.3.1.3.3 Conclusion on SAEs and events that led to discontinuation

Even if serious adverse events were observed on NEB at twice the incidence on placebo in the monotherapy trials of the primary program, the numbers are too small for a conclusive interpretation.

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. Dyspnea as a reason for discontinuation (in 6) was observed solely on NEB.

One case of hepatic cirrhosis believed to be secondary to alcoholism and one case of pancreatitis believed to be secondary to micro-lithiasis were reported in the secondary program.

5.3.1.4 Common Adverse Events

5.3.1.4.1 Common Adverse Events in the primary program

Table 22. Adverse events reported by ≥ 1% in the PC trials and in which the incidence on NEB is greater than on placebo (Table includes the same events in the extension trials 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%)
Dizziness	7 (1.9%)	65 (2.8%)	28 (3.0%)	87 (3.5%)
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%)
Insomnia	1 (0.3%)	25 (1.1%)	14 (1.5)	34 (1.4%)
C-reactive protein ↗	1 (0.3%)	22 (1.0%)	20 (2.0)	32 (1.3%)
Chest Pain	0.0	20 (0.9%)	8 (0.9%)	27 (1.1%)
Neoplasm B, M & unspecified	1 (0.3)	13 (0.6)	13 (1.4%)	20 (0.8)
Pharyngitis NOS	00	10 (0.4%)	9 (1.0%)	16 (0.6)

Table 23. 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)
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 on 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;

[7] Analysis and Table completed by sponsor

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;

Nausea occurred on NEB at a rate that is twice that on placebo;

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

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 24. 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)
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)
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)
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)
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	3 (0.8)	0.0	3 (2.3)	6 (1.0)	16 (2.5)	12 (1.9)	2 (0.9)	39 (1.7)
Dry mouth	0.0	0.0	2 (1.5)	3 (0.5)	4 (0.6)	1 (0.2)	0.0	10 (0.4)

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 (%)
Flatulence	0.0	0.0	0.0	2 (0.3)	1 (0.2)	5 (0.8)	1 (0.5)	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)
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)
Depression	0.0	0.0	0.0	0.0	1 (0.2)	3 (0.5)	2 (0.9)	6 (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)
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)
Neck pain	00	00	00	3 (0.5)	4 (0.6)	2 (0.2)	00	9 (0.4)
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)

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;

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

Headache with the RR on 5 mg statistically significantly different from 1;

Dizziness with the RR on 30/40 mg close to statistical significance;

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 primary program

Nervous system disorders

Somnolence in 9 (0.4%); postural dizziness in 8 (0.3%); hypoesthesia in 7 (0.3%);

blood bilirubin increased in 3; blood urea increased in 3; potassium decreased in 2; transaminase increase in 2; ECG ST segment abnormal in 1; ECG Q wave in 1; ECG ST segment depression in 1; neutrophil count decreased in 1; red blood cell count decreased in 1;

Respiratory disorders

allergic rhinitis in 3 (0.4%); pulmonary congestion in 5 (0.2%); wheezing in 4 (0.2%); seasonal rhinitis in 3 (0.1%); chronic obstructive airway disease exacerbated in 1; asthma aggravated in 1; emphysema in 1; lung infiltration in 1;

Skin and subcutaneous tissue disorders

contact dermatitis in 8 (0.3%); angioedema in 5 (face edema in 3 + angioneurotic edema in 1 + tongue edema in 1); urticaria NOS in 3 (0.1%);

Cardiac disorders

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

Psychiatric disorders

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

Metabolism and nutrition

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

Eye disorders

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

Renal and urinary disorders

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

Reproductive system and breast disorders

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

Vascular disorders

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

Ear and labyrinth disorders

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

Immune system disorders

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

Neoplasm

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

Blood and lymphatic system disorders

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

Endocrine disorders

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

Hepatobiliary disorders

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

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

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

Thirteen adverse events were observed in this trial with 6 on NEB and 7 on atenolol. The events that were associated with NEB are micturition urgency, urinary frequency, erectile dysfunction, pharyngeal pain, allergic rhinitis NOS, and acne NOS. And the events that were seen on atenolol

[8] Analysis completed by the sponsor

included disturbance in attention, dizziness, postural dizziness, 2 headaches, restlessness and one ovarian cyst.

5.3.1.4.4 Adverse Events in the Pharmacology Studies

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

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

5.3.1.4.5 Adverse Events Profile in Patients with Ischemic Heart Disease

One subject on NEB had an increase in liver enzymes.

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

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

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

5.3.1.4.6 Conclusion on adverse events

In the controlled trials, NEB was associated with an increase in the overall adverse rate compared to placebo. This increase is accounted for by adverse effects of beta-adrenergic antagonism symptoms, infections and headache.

The numbers for the other adverse events are too small to determine the nature of the association between NEB and these events.

5.3.1.5 Interaction with demographic characteristics

Table 25. Adverse events by demographics

AEs	Age				Race				Gender			
	< 65		≥ 65		Black		Other		Male		Female	
	NEB N=1466	P N=175	NEB N=30	P N=345	NEB N=466	P N=71	NEB N=1345	P N=134	NEB N=978	P N=108	NEB N=833	P N=97
Bradycardia	0.5	0.0	1.7	0.0	0.2	1.4	0.9	0.0	3.0	0.0	2.9	4.1
Dizziness	3.3	2.3	1.5	0.0	3.2	1.4	2.8	2.2	3.0	0.0	2.9	4.1
CRP ↗	1.4	0.0	0.6	3.3	0.4	0.0	1.5	0.8	1.1	0.9	1.3	0.0
Fatigue	3.4	1.1	4.9	3.3	2.3	0.0	3.9	2.2	3.6	0.9	3.6	2.1
Insomnia	1.3	0.6	0.3	0.0	0.6	0.0	1.3	0.8	1.0	0.0	1.3	1.0
Headache	7.5	4.6	5.2	13.3	9.7	4.2	6.2	6.7	5.8	3.7	8.5	8.3
Palpitations	0.6	0.0	0.0	0.0	1.5	0.0	0.8	0.0	0.3	0.0	0.7	0.0
Chest pain	1.0	0.0	0.9	0.0	1.5	0.0	0.8	0.0	0.6	0.0	1.4	0.0
Dyspnea	0.6	0.0	2.0	3.3	0.4	0.0	1.0	0.8	0.9	0.0	0.8	1.0

The numbers of individual adverse events which were too small to begin with have become even smaller when they were subdivided onto demographic sub-categories. Adverse events that show a hint of interaction with the above demographic characteristics are the elevation of CRPs and chest pain in females; bradycardia, dizziness, fatigue and headache in males; fatigue and headache in younger subjects; bradycardia and dizziness in older subjects; and headache in black subjects.

5.3.1.6 Interaction with concomitant substances

5.3.1.6.1 Interaction with Alcohol

The two cases below suggest a potential interaction with alcohol, there is no evidence and no data to support the possibility of an interaction.

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

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

5.3.1.6.2 Interaction with medication

Table 26. Interaction with medications in the placebo-controlled trials

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

CYP2D6

Headache, influenza and chest pain were observed in excess in subjects receiving the combination containing NEB compared to those receiving the combination containing placebo.

NSAID

Dizziness especially at the highest dose, headache, chest pain, arthralgia and influenza were observed in excess in subjects receiving the combination containing NEB compared to those receiving the combination containing placebo.,

Insulin

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

Calcium channel blockers

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

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

Table 27. Interaction with other medications in the long-term follow-up

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

5.3.1.6.3 Conclusion

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

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

In the long-term trial, the incidence of all adverse events, musculoskeletal, gastrointestinal, general disorder and respiratory events seem to be higher on the NEB/diuretic combination. The lack of a control group renders the interpretation of these findings difficult.

5.3.1.7 Timing of adverse events in all trials combined

Most infections started in the first seven days of treatment to peak between 7 and 30 days.

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

Bradycardia peaked before the end of 30 days.

Sinus bradycardia and hypertriglyceridemia peaked between 30 and 180 days.

ALT and AST elevation was observed between 30 and 180 days.

5.3.1.8 Common Adverse Events in the Secondary Program

Table 28. Type and incidence of adverse events in the SP[9]

Preferred Term	Dose Finding Data		Therapeutic-dose Data			
			Placebo-controlled		Active-controlled	
	Placebo N=222	NEB N = 858	Placebo N = 387	NEB N = 419	Other anti-HTN N = 493	NEB N = 521
Any AE	87 (39%)	326 (37.0)	33.6	35.3	54.8	41.8
Headache	33 (14.8)	59 (6.7)	11.1	6.0	14.0	10.6
Dizziness	5 (2.2)	31 (3.5)	2.3	4.8	--	18 (3.5)
Nausea	6 (2.7)	13 (1.5)	2.1	1.9	--	--
Fatigue	8 (3.6)	23 (2.6)	2.3	4.3	3.0	3.3
Rhinitis	9 (4.0)	17 (1.9)	1.0	2.6	--	--
Viral infection	--	--	--	--	3.0	2.9
Cough	6 (2.7)	11 (1.3)	2.1	1.2	4.3	1.5
Dyspnea	--	--	1.2	2.1	--	--
Bronchospasm	--	--		2 (0.5)	--	--
Palpitations	--	--	--	--	2.2	1.5
Common cold	--	--	--	--	2.6	1.7
Dependent edema	0.0	7 (0.8)	--	--	3.9	1.2
Edema	--	--	--	--	3.2	0.8
Parasthesia	0.0	12 (1.4)	0.3	2.6	2.2	3.3
Flushing	--	--	--	--	7.5	1.5
Vertigo	--	--	--	--	2.2	1.0
Rash	--	--	1 (0.3)	2 (0.5)	2.0	0.6
Bradycardia	0.0	10 (1.1)	--	--	--	--
Impaired vision	--	--	0.3	0.5	0.0	0.4
Depression	0.0	10 (1.1)	1 (0.3)	2 (0.5)	0.0	5 (1.0)
Nightmares	--	--	0.2	0.2	0.0	1.3
Impotence	--	--	00	1 (0.2)	0.0	3 (0.6)
Injury	2 (0.9)	11 (1.3)	--	--	--	--
Back pain	--	--	--	--	2.0	1.5
Diverticulitis	--	--	0.0	1	0.0	1
Diarrhea	2 (0.9)	11 (1.3)	0.8	1.2	0.0	1.3

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

Preferred Term	Dose Finding Data		Therapeutic-dose Data			
			Placebo-controlled		Active-controlled	
	Placebo N=222	NEB N = 858	Placebo N = 387	NEB N = 419	Other anti-HTN N = 493	NEB N = 521
Abdominal pain	--	--	3 (0.8)	3 (0.7)	0.0	7 (1.3)

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

Overall adverse events, headache and nausea were observed on NEB at a higher relative risk in the primary program.

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

Table 29. Comparison of NEB and carvedilol with regard to general adverse events

Preferred Term	Placebo N = 372 n (%)	NEB N = 2313 n (%)	RR	Placebo N= 462 n (%)	Carvedilol N = 1142 n (%)	RR
Insomnia	1 (0.3)	25 (1.1)	3.7	3 (0.6)	18 (1.6)	2.7
Dyspnea	1 (0.3)	19 (0.8)	2.6	4 (0.9)	16 (1.4)	1.6
Bradycardia	1 (0.3)	17 (0.7)	2.3	1 (0.2)	24 (2.1)	10.5
Nausea	3 (0.8)	39 (1.7)	2.1	8 (1.7)	16 (1.4)	0.8
Infection viral	1 (0.3)	13 (0.6)	2.0	6 (1.3)	20 (1.8)	1.4
Fatigue	7 (1.9)	83 (3.4)	1.8	18 (3.9)	49 (4.3)	1.1
Edema peripheral	2 (0.5)	21 (0.9)	1.8	2 (0.4)	16 (1.4)	3.5
Sinusitis	3 (0.8)	30 (1.3)	1.6	16 (3.5)	39 (3.4)	1.0
Headache	16 (4.3%)	153 (6.6)	1.5	81 (17.5)	123 (10.8)	0.6
Dizziness	7 (1.9)	65 (2.8)	1.5	25 (5.4)	71 (6.2)	1.1
Abdominal pain	1 (0.3)	10 (0.4)	1.3	6 (1.3)	16 (1.4)	1.1
Diarrhea	7 (1.9)	54 (2.3)	1.2	6 (1.3)	25 (2.2)	1.7
Somnolence	1 (0.3)	7 (0.3)	1.0	7 (1.5)	20 (1.8)	1.2
Hypertriglyceridemia	1 (0.3)	6 (0.3)	1.0	1 (0.2)	14 (1.2)	6.0
Upper respiratory tract infection	8 (2.2)	46 (2.0)	0.9	27 (5.8)	65 (5.7)	1.0
UTI	8 (2.2)	41 (1.8)	0.8	3 (0.6)	21 (1.8)	3.0
Dyspepsia	4 (1.1)	18 (0.8)	0.7	12 (2.6)	15 (1.3)	0.5
Injury	15 (4.0)	56 (2.4)	0.6	12 (2.6)	33 (2.9)	1.1
Chest Pain	00	20 (0.9)	NA	11 (2.4)	27 (2.4)	1.0
Pharyngitis NOS	00	10 (0.4)	NA	3 (0.6)	17 (1.5)	2.5
Rhinitis	00	8 (0.4)	NA	9 (1.9)	24 (2.1)	1.1
Pain	00	7 (0.3)	NA	5 (1.1)	13 (1.1)	1.0
Postural hypotension	00	4 (0.2)	NA	00	21 (1.8)	NA
Back pain	00	1 (0.04)	NA	7 (1.5)	26 (2.3)	1.5
Thrombocytopenia	00	00	NA	1 (0.2)	13 (1.1)	5.5

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

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

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

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

Bradycardia occurred on NEB at greater than twice the rate on placebo while it occurred on carvedilol at greater than 10 times the rate of its placebo;

Orthostatic hypotension appears to have more problematic on carvedilol than on NEB;

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

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

Diarrhea was observed less commonly on NEB compared to carvedilol;

5.3.1.10 Conclusion

Except for nausea, dyspnea, headache and chest pain, NEB was associated with fewer adverse events than carvedilol. The association of NEB with bradycardia, orthostatic hypotension, edema peripheral, hypertriglyceridemia, thrombocytopenia and urinary tract infection seems to be weaker than that observed with carvedilol.

Unspecified chest pain (20 vs. none on placebo) , few ECG abnormalities (6) including T-wave abnormalities, T-wave inversions and ST segment changes, and two MIs were observed on NEB. Given that some beta-adrenergic antagonists trigger myocardial vasoconstriction that might further compromise myocardial coronary blood flow in a population that is prone to atheromatous disease, the label should warn of the potential of this effect.

C-reactive protein level 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). It is not known whether this is causally related to NEB, but the increase in the rate of overall infections on NEB that was observed at a significant level on the highest dose, if infections were experienced concomitantly with the elevation of CRPs in the same subjects, could explain this association.

5.3.1.11 ECG Findings and QT intervals

5.3.1.11.1 Definition of ECG Abnormalities

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

5.3.1.11.2 ECG findings in the 2/3 phase trials

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

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

5.3.1.11.3 ECG findings in the placebo-controlled trials

Table 30. Mean changes in ECG parameters in all placebo-controlled trials

QT interval	Placebo	Nebivolol (mg)						
	N = 324	1.25 N = 75	2.5 N = 119	5 N = 550	10 N = 560	20 N = 574	30/40 N = 200	Any N = 2078
ΔHR ± SD	-0.01±0.5	-3.5±1.0	-4.4±0.8	-7.4±0.6	-8.4±0.4	-9.7±0.4	-10.8±0.6	-8.3±0.2
ΔQRS ± SD	1.1±0.6	1.5±0.7	-0.6±1.5	2.2±1.3	0.9±0.4	1.3±0.5	1.0±0.6	1.3±0.4
ΔRR ± SD	2.3±8.3	48.9±13.3	57.6±10.9	101.5±6.9	131.6±7.1	143.3±6.0	169.7±10.7	123.3±3.4
ΔQT ± SD	1.1±1.9	10.3±2.1	6.4±2.7	14.0±1.2	20.2±1.4	22.9±1.4	26.5±1.8	18.8±0.7
ΔQTc(F) ± SD	-1.2±3.0	3.5±1.7	-1.1±2.6	-5.3±3.3	-2.6±2.8	2.9±1.3	2.2±2.8	-1.0±1.3
ΔQTc(B) ±SD	-3.9±5.0	0.2±2.3	-5.2±3.0	-18.3±6.8	-17.3±5.4	-7.5±1.4	-11.3±4.6	-13.0±2.4

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

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

Table 31. Clinically significant QTc (F) findings in all placebo-controlled trials

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

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

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

Table 32. Significant ECG changes in subgroup analyses in the primary program

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

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

Subgroup category	Δ QTc			
	> 30		> 60	
	QTc (B)	QTc (F)	QTc (B)	QTc (F)
NEB N = 96	20 (20.8)	14 (14.6)	00	3 (3.1)
EM				
Placebo N = 180	30 (16.7)	17 (9.4)	7 (3.9)	00
NEB N = 1551	269 (17.3)	126 (8.1)	38 (2.5)	00
Blacks				
Placebo N = 65	17 (26.2)	14 (21.5)	7 (10.8)	4 (6.2)
NEB = 420	102 (24.3)	68 (16.2)	27 (6.4)	22 (5.2)
Non-Blacks				
Placebo N = 123	13 (10.6)	3 (2.4)	00	00
NEB N = 1227	187 (15.2)	72 (5.9)	14 (1.1)	4 (0.3)
Males				
Placebo N = 99	13 (13.1)	6 (6.1)	2 (2.0)	2 (2.0)
NEB N = 882	150 (17.0)	75 (8.5)	21 (2.4)	14 (1.6)
Females				
Placebo N = 89	17 (19.1)	11 (12.4)	5 (5.6)	2 (2.3)
NEB N = 765	139 (18.2)	65 (8.5)	20 (2.6)	12 (1.6)

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

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

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

5.3.1.11.5 Conclusion of ECG Findings

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

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

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

In placebo-controlled trials, only a small excess (9 vs. 0) in QTc (F) prolonged to > 500 msec was observed on NEB compared to placebo. Almost twice as many subjects on placebo had a change from baseline in QTc (F) > 60 msec.

The apparent excess (14 vs. 0) of QT prolongation in PM could be explained by the very small number of patients in the placebo group, for there were 12 subjects on NEB for every subject on placebo.

In conclusion, data from this program could not support a prolongation in QT.

5.3.1.12 Laboratory Findings

5.3.1.12.1 Definition of Laboratory abnormalities

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

5.3.1.12.1.1 Hematology Parameters

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

5.3.1.12.1.2 Chemistry Parameters

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

5.3.1.12.2 Laboratory Findings in the Primary Program

5.3.1.12.2.1 Clinically significant laboratory findings

Table 33. Clinically Significant Laboratory Findings

Parameter	Monotherapy placebo-controlled trials	All phase 2/3 studies

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

As can be seen from the table below, only few of the sponsor-defined clinically significant laboratory findings were observed. Of importance are the findings of the liver function tests, uric acid, BUN, creatinine and eosinophils, but the numbers observed in the placebo-controlled trials were to small to determine whether NEB is implicated or not.

5.3.1.12.2.2 Deviation from normal to out of normal range in laboratory parameters

Table 34. Laboratory parameters that changed in > 2% of all subjects or worth noting on NEB

Parameters	Below normal range N = 2464 %	Above normal range %
Hematology		
RDW	--	19.8
Lymphocytes (%)	2.4	6.2
Eosinophils (%)	--	4.6
Hematocrit	7.1	3.3
Hematocrit	--	3.3
Neutrophil segs (%)	3.4	3.2
Eosinophils absolute	--	2.8
MCH	--	2.6
MCH	--	2.6
MCV	--	2.4
WCC	2.5	2.4
Hemoglobin	7.3	--
Erythrocyte	5.4	--
HCMC	10	--
Monocytes absolute	10.6	--
Eosinophil absolute	5.8	--
Neutrophils absolute	3.7	--
Chemistry		
HDL cholesterol	5.6	--
Total cholesterol	--	28.1
Triglycerides	--	21.6
LDL Cholesterol	--	17.8
Glucose	--	11.3
Chloride	--	10.1
ALT (SGPT)	--	5.7
Phosphorus	--	5.6
Uric acid	--	5.3
Potassium	--	4.9
AST	--	3.7
Carbon dioxide	6.4	3.2
Magnesium		2.7
BUN		2.6
Sodium	--	2.4
Creatinine		2.4
Alkaline phosphatase	--	1.9
Total bilirubin	--	1.7
CRP↗	--	25.0 (73/286)

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

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

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

Table 35 Deviations from normal range in all placebo-controlled trials

Parameter	P	NEB
Hematology		
Eosinophils absolute > NR	00	19 (1.6)
MCV (FL) > NR	00	17 (1.1)
Platelets < NR	1 (0.5)	19 (1.1)
RDW > NR	11 (12.2)	112 (15.3)
Chemistry		
Calcium < NR	00	15 (0.9)
Uric Acid > NR	1 (0.5)	30 (1.8)
HDL < NR	2 (1.3)	54 (4.1)
Total bilirubin> NR	1 (0.5)	21 (1.3)
Phosphorus > NR	4 (2.1)	51 (3.1)
Potassium > NR	2 (1.0)	36 (2.1)
Total cholesterol > NR	13 (14.3)	149 (21.1)
Triglycerides > NR	16 (10.5)	206 (15.5)
Urine analysis		
Squamous epithelial cells abnormal	3 (9.7)	85 (26.2)
Specific gravity > NR	1 (0.5)	30 (1.8)

The denominator for incidence calculations depended on the test conducted.

Table 36. Deviation from normal to out of normal range in long-term exposure (only when a difference across time points was observed is reported here)[11]

	Day 91		Day 182		Day 273	
	NEB	NEB/Diuretics	NEB	NEB/D	NEB	NEB/D
Triglycerides	19 (12.4)	4 (17.4)	15 (11.1)	12 (22.2)	44 (16.6)	23 (18.5)
HDL	3 (2.3)	2 (9.1)	5 (4.0)	2 (4.1)	11 (4.8)	3 (2.9)
LDL	12 (9.9)	2 (9.5)	15 (13.0)	5 (10.9)	30 (13.2)	10 (10.4)
BUN	2 (1.3)	1 (4.3)	4 (3.0)	3 (5.5)	11 (4.2)	2 (1.6)

5.3.1.12.2.3 Change in means from baseline in laboratory parameters

Table 37. Mean change from Baseline in placebo-controlled trials of monotherapy

Parameters	P	Nebivolol mg						
	N=205 n(%)	1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 459 n(%)	10 N = 461 n(%)	20 N = 460 n(%)	30/40 N = 217 n(%)	Any N = 1811 n(%)
Hematology								
Δ Platelets x $10^3/mm^3$	-5.13	-9.88	-11.93*	-12.97**	-12.16*	-16.52***	-17.79***	-14.04***
Chemistry								
Potassium	0.00	0.07	0.05	0.07	0.07*	0.06	0.03	0.06*

Parameters	P	Nebivolol mg						
	N=205 n(%)	1.25 N = 83 n(%)	2.5 N = 131 n(%)	5 N = 459 n(%)	10 N = 461 n(%)	20 N = 460 n(%)	30/40 N = 217 n(%)	Any N = 1811 n(%)
mEq/L								
Chloride mEq/L	-0.3	0.0	0.2*	0.2	0.2*	0.2*	0.3*	0.2*
Carbon dioxide mEq/L	0.1	-0.1	-0.6	-0.0	-0.2	-0.2	-0.6*	-0.2
BUN mg/dL	0.1	0.5	0.5	0.2	0.8*	0.8**	0.1	0.6
Uric Acid	-0.03	-0.07	0.10	0.17**	0.18**	0.18**	0.16*	0.16***
HDL Cholesterol	1.6	-1.8**	-1.1*	-2.4***	-2.0***	-2.7***	-2.5***	-2.3***
Triglycerides Mg/Dl	1.6	7.9	17.7	5.4	23.3***	14.0	14.5	16.8**
Urinary pH	-0.00	0.0	-0.01	-0.12*	-0.11*	-0.10	-0.10	-0.10

The change in means from baseline was significant for platelets, HDL, triglycerides, chloride, and uric acid.

Table 38. Mean Change from baseline in laboratory values at 6 and 9-month follow-up[11]

	Day 91 Mean (SD)	Day 182 Mean (SD)	Day 273 Mean (SD)
Triglycerides	18.35* (7.03)	27.96* (8.11)	23.62* (6.50)
HDL	-2.02* (0.75)	-4.13* (0.80)	-5.37* (0.60)
Glucose	2.12 (1.1)	3.26* (1.27)	0.74 (1.16)
ALT	1.20 (0.91)	1.63 (2.05)	1.45* (0.57)
AST	0.87 (0.74)	2.52 (1.63)	1.26* (0.38)
LDH	4.78* (2.25)	12.41 (12.8)	-0.23 (1.13)
Sodium	0.17 (0.11)	0.05 (0.14)	0.63* (0.15)
BUN	0.01 (0.33)	1.28* (0.32)	0.65* (0.23)
Creatinine	0.17* (0.01)	0.17* (0.01)	0.16* (0.01)
Uric Acid	0.19* (0.07)	0.35* (0.80)	0.32* (0.05)
Potassium	0.11* (0.2)	0.10* (0.2)	0.10* (0.2)
Chloride	0.05 (0.11)	0.27* (0.13)	0.41* (0.15)
Phosphorous	0.11* (0.04)	0.02 (0.05)	0.07* (0.03)
CO_2	-1.12 (0.16)	-1.62* (0.2)	-1.43* (0.2)
Platelets	-13.03*	-19.62*	-26.89*
MCV (FL)	0.16 (0.23)	0.36 (0.32)	0.47* (0.14)

The change in means from baseline remained significant for as time went by fro triglycerides, HDL, uric acid, platelets and chlorides. It acquired significance for ALT, AST, potassium, phosphorus, CO_2, creatinine, BUN, sodium, glucose, and MCV.

As can be seen from the table above, the elevation in triglyceride, LDL and BUN levels, and the decrease in HDL level became more prominent as time went by.

5.3.1.12.2.4 Laboratory findings after withdrawal of therapy

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

5.3.1.12.2.5 Laboratory findings in the secondary program

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

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

In the therapeutic dose data

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

In the long-term data

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

ALT in 9, AST 5, chloride in 11, glucose in 42, potassium in 15, total bilirubin in 9, urea in 33, uric acid in 11, platelet count in 8, hematocrit in 9, hemoglobin in 7, WBC in 11 and RBC in 6;

5.3.1.12.2.6 Comparison to carvedilol

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

Liver function abnormalities and the effect on hematological parameters seem to be milder on NEB compared to carvedilol.

5.3.1.12.2.7 Conclusions

Very few laboratory parameters changed to a clinically significant level in the monotherapy controlled trials and the number of subjects who experienced a clinically significant change in a parameter on NEB was very small, less than 8, given that there were 8 NEB subjects for each placebo subject.

There were only 7 and 2 subjects whose AST exceeded 3 and 5 times the upper normal limit (ULN) respectively, only one subject whose ALT exceeded 3 times the ULN, and only 2 subjects whose AST or ALT exceeded 5 times the ULN. There were no subjects with clinically significant bilirubin or alkaline phosphatase abnormalities.

Given the small number of subjects with clinically significant abnormal LFTs, and since there were no clinically significant changes in bilirubin or alkaline phosphatase and the number of clinically significant abnormalities in ALT was only a fraction that of the AST abnormalities, we cannot draw a conclusion regarding whether the AST abnormalities observed here are drug related However, we can assume that they are related taking into account previous experience with other betablockers.

For the other parameters that were observed to be abnormal based on a change in the mean from baseline or a shift from the normal range, it cannot be concluded whether these observations are of any consequences given that a shift from normal range could be a borderline shift, and a change in the mean could result from a number of subjects shifting in one direction within their normal range. With that said, few parameters are worth noticing given the consistency of these potentially inconsequential changes and these include, a reduction in the platelet count which is known to be associated with beta-blocking therapies; a decrease in HDL level; and an elevation in triglyceride, uric acid, BUN, creatinine, phosphorus and C-reactive protein levels.

In conclusion, considering the available data, the association between NEB and the laboratory abnormalities discussed above cannot be considered as conclusive.

5.3.1.13 Clinically significant vital sign changes

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

5.3.1.13.1 Definition of Abnormal Vital Signs

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

5.3.1.13.2 Heart Rate

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

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

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

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

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

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

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

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

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

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

5.3.1.13.3 Orthostatic hypotension (definition 1)

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

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

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

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

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

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

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

5.3.1.13.4 Systolic and diastolic blood pressure

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

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

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

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

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

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

5.3.1.13.5 Conclusion

Nebivolol consistently caused clinically significant bradycardia that seems to be of the same intensity at both peak and trough, but with a dose response trend.

Orthostatic hypotension was observed with NEB at a moderate rate.

A drop in standing blood pressure was observed in very few subjects and it occurred in diastolic blood pressure.

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

5.3.1.14 Exposure during Pregnancy

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

One patient was lost to follow-up.

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

Patient 2111002270 (NEB-305 and NEB-306) was a 37 year-old Hispanic female patient in the US previously enrolled in NEB-302 on 19 Feb 2002 and in NEB-306 on 12 Jun 2002 and received Nebivolol 5 and 10 mg for hypertension for a total duration of 258 days. On [redacted] the patient informed the site that she was pregnant and her blood was collected for the serum pregnancy assay (qualitative human chorionic gonadotropin- HCG) and study drug was discontinued. The patient also took a urine pregnancy test at the investigator's office and it was negative. The test was repeated and again the result was negative. However, on [redacted] the HCG result was reported positive. The patient's last menstrual period was on [redacted]. The patient carried the pregnancy to full term and delivered a baby girl on [redacted] without complications. Sponsor reported having contacted the patient during this review and the baby is doing fine.

5.3.1.15 Experience with overdose

Two cases of overdose were reported with one from the post marketing pharmaco-vigilance database and the other from the literature.

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

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

Eight hours after the attempt, the patient had reduced vigilance, slow motor function, pale and sweaty skin, borderline hypotension (105/ 55 mmHg) and a sinus bradycardia of 55 beats/ min with normal cardiac function. Serum potassium and glucose were low and leucocytes were elevated. Capillary blood gas showed respiratory acidosis and ketone bodies and proteins were

detected in the urine. Other physical and laboratory findings were unremarkable. The patient was diagnosed with acute ß1- adrenergic antagonist poisoning, hypotension, sinus bradycardia with a normal cardiac function, respiratory global insufficiency and hypoglycemia.

The plasma level of nebivolol (by HPLC) was 480 ng/mL at the time of admission. About 8 hours after tablet ingestion (2 to 4 hours after treatment), the maximum plasma concentration was 88- 195 ng/ mL. The levels decreased to 240 ng/mL at 18 hours, 84 ng/ mL at 26 hours and around detection threshold of 25 ng/ mL at 48 hours. The level of acetylsalicylic acid was at nontoxic level of 8.8 mcg/ mL at 8 hours. Treatment consisted of warm- water gastric lavage with charcoal and sodium sulphate (every 6 hours for 24 hours). Also oxygen therapy was administered. A temporary pacemaker was applied and arterial blood pressure was monitored. Intravenous potassium, insulin and glucagon (for 14 hours) were given. The patient recovered and was discharged after 48 hours.

5.3.1.16 Worldwide Post-Marketing Pharmaco-vigilance

Table 39. Post marketing reports of adverse events

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

Preferred Term	Received up to 4/30/03	Received 5/01/03 to 6/30/03	Received up to 6/30/04
Asthenia	11	1	12
Chest pain	8	0	8
Chest pressure sensation	3	0	3
Chest tightness	2	0	2
Condition aggravated	3	1	4
Drug interaction NOS	8	0	8
Fatigue	47	2	49
Edema peripheral	9	1	10
Malaise	7	0	7
Hepatobiliary Disorders			
Hepatic failure	1	0	1
Jaundice NOS	1	0	1
Immune system disorders			
Allergy aggravated	1	0	5
Hypersensitivity NOS	5	0	1
Infections and infestations, Any	4	0	4
Injury, poisoning			
Any	8	0	8
Overdose	3	0	3
Investigations			
Any	16	7	23
ECG			
QRS complex prolonged	1	0	1
T wave inversion	1	0	1
ECG abnormal NOS	2	0	2
GGT ↗	0	1	1
Liver function tests NOS abnormal	4	2	6
Prothrombin time ratio ↘	0	1	1
Transaminases ↗	0	1	1
Metabolism and nutrition			
Any	9	1	10
Fluid retention	1	0	1
Hyperkalemia	1	0	1
Hypokalemia	1	0	1
Hypoglycemia	5	1	6
Lipid metabolism disorder NOS	1	0	1
Metabolic acidosis	1	0	1
Nervous system disorders			
Any	133	12	145
Cerebrovascular accident	3	0	3
Syncope	3	1	4
Headache	44	3	47
Dizziness	67	0	67
Dizziness postural	3	0	3
Dysgeusia	2	2	4
Hypoglycemic coma	0	2	2
Loss of consciousness	1	1	2
Parasthesia	11	1	12
Psychiatric Disorders			
Any	41	4	45
Anxiety	3	0	3
Nervousness	5	0	5
Confusional state	2	0	2
Hallucinations	1	1	2
Sleep disorders	4	0	4
Nightmares	7	1	8

Preferred Term	Received up to 4/30/03	Received 5/01/03 to 6/30/03	Received up to 6/30/04
Depression	8	0	8
Depression aggravated	1	0	1
Suicide ideation	0	1	1
Suicide attempt	2	0	2
Libido decreased	4	0	4
Reproductive system and breast disorders			
Any			
Amenorrhea/Metrorrhagia	1	1	2
Hot flushes	0	1	1
Erectile dysfunction NOS	25	2	27
Respiratory and thoracic disorders			
Apnea	1	0	1
Asthma	2	0	2
Asthma aggravated	1	1	2
Bronchospasm	6	1	7
Bronchospasm aggravated	15	0	15
Dyspnea NOS	35	1	36
Dyspnea exacerbated	1	0	1
Respiratory distress	6	0	6
Respiratory failure	1	0	1
Skin and subcutaneous tissue			
Any	49	10	59
Exanthema	5	1	6
Pruritus	11	0	11
Psoriasis aggravated	5	0	5
Rash	5	1	6
Sweating increased	9	3	12
Angioedema			
Any	7	0	7
Edema of the mouth	1	0	1
Edema of the tongue	1	0	1
Edema of the face	2	0	2
Angioneurotic edema	3	0	3
Vascular disorders			
Flushing	4	0	4
Peripheral coldness	9	0	9
Raynaud's phenomenon	1	2	3
Shock	1	0	1

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

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

QT prolongation

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

Liver function

LFTs: the report of 6 cases of LFTs abnormalities along with the known relation of other betablockers with this adverse event substantiates the hint of an association that was

observed between NEB and the effect of increasing ALT and AST in the Bertek primary program;

One case of liver failure was observed in a patient who was taking coumadin which is labeled for hepatitis, cholestatic hepatic injury, jaundice and elevated liver enzymes.

Blood and lymphatics

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

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

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

Respiratory disorders:

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

Skin and subcutaneous tissue

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

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

5.3.2 Adequacy of Patient Exposure and Safety Assessments

5.3.2.1 Description of Primary Clinical Data Sources

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

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

5.3.2.1.2 Study type and design/patient enumeration

Table 40. Pivotal studies conducted under the Primary Program

Placebo-controlled trials						
Protocol no	Design and type	Type of subjects	P	NEB	Days	Dose in mg
NEB-202 N = 300	R, DB, PC	Blacks with HT	49	251	84	2.5, 5, 10, 20 and 40

NEB-302 N = 901	R, DB, PC	95 ≤ SDBP ≤ 109	81	251	84	1.25, 2.5, 5, 10, 20 and 30/40
NEB-305 N = 807	R, DB, PC	95 ≤ SDBP ≤ 109	75	828	84	5, 10, 20
NEB-321 N = 669	R, DB, PC	95 ≤ SDBP ≤ 109	167	732	84	5, 10 and 20

Active-controlled trial						
Protocol N	**Design and type**	**Type of subjects**	**Atenolol N**	**NEB N**	**Days**	**Dose in mg**
NEB-203 N= 115	R, DB, AC	HT	45	70	28	5, 10 and 20

Extension trials							
Protocol N	**Design and type**	**Type of subjects**	**Treatment**				**Dose in mg Duration**
			NEB N	**NEB/ Diuretic N**	**NEB/ CCB N**	**NEB/Other N**	
NEB 306 N = 845	OL, LT	Completed NEB 202, 302, 305	607	206	21	06	5, 10, 20 mg up to 9 months
NEB 323	OL, LT	Completed NEB-306	85				5 → 10 → 20 mg up to 24 months

5.3.2.1.3 Demographics of patients in placebo-controlled trials

Table 41. Demographic and baseline medical characteristics

Patient Characteristics	Placebo N = 372	Nebivolol N = 2313
Demographic Characteristics		
Age		
Mean (SD)	53.4 (10.4)	53.7 (11.3)
(Min, Max)	(24, 80)	(19, 86)
Age Group – n (%)		
< 65	315 (84.7)	1892 (81.8)
≥ 65	057 (15.3)	0421 (18.2)
Gender – n (%)		
Male	199 (53.5)	1255 (54.3)
Female	173 (46.5)	1058 (45.7)
Race – n (%)		
Black	119 (32.0)	615 (26.6)
Other	253 (68.0)	1698 (73.4)
Genomic classification – n (%)		
PM	17 (4.6)	135 (5.9)
EM	350 (95.4)	2168 (94.1)
BMI		
Mean (SD)	29.51 (4.32)	29.38 (4.09)
(Min, Max)	(14.99, 46.23)	17.37, 43.00)
Cumulative exposure (days)		
Mean (SD)	77.6 (21.27)	78.6 (20.02)
(Min, Max)	(1, 99)	(1, 112)
Medical history		
Current smoking history	85 (22.8)	526 (22.8)

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

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

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

5.3.2.1.4 Extent of exposure (dose/duration)

Table 42. Drug exposure in placebo-controlled trials

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

Patients entering the long-term study were assigned to start NEB at 5, 10 or 20 mg daily based on the average sitting DBP, average HR and previous NEB dose. Titration was allowed for patients who did not respond to their original assigned dose level in the feeder study. Patients received NEB either as monotherapy or in combination with other anti-hypertension medications. By the end of the study, 607 (71.8%) patients were on NEB monotherapy, 206 (24.4%) were on NEB + diuretic, 21 (2.5%) were on NEB + CCB, and 11 (1.3%) were on NEB + other medication.

Table 43. Duration of exposure in the long-term trial (days)[12]

Duration	Nebivolol N = 607 n (%)	Nebivolol + Diuretic N = 206 n (%)	Nebivolol + CCB N = 21 n (%)	Nebivolol + Other N = 11 n (%)	Total N = 845 n (%)
Mean (SD)	178.1 (96.1)	231.0 (54.1)	199.3 (65.6)	231.2 (60.3)	192.2 (89.5)
Median	203.0	256.0	203.0	247.0	221.0

[12] Table completed by sponsor

Range	1.0 to 330.0	27.0 to 303.0	4.0 to 282.0	61.0 to 281.0	1.0 to 330.0
0 - 90 Days	146 (24.1)	4 (1.9)	1 (4.8)	1 (9.1)	152 (18.0)
91 - 180 Days	107 (17.6)	28 (13.6)	8 (38.1)	0 (0.0)	143 (16.9)
181 - 270 Days	171 (28.2)	83 (40.3)	7 (33.3)	7 (63.6)	268 (31.7)
271 - 360 Days	183 (30.1)	91 (44.2)	5 (23.8)	3 (27.3)	282 (33.4)
≥ 361 Days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

5.3.2.1.5 Patient Disposition

Table 44. Patient Disposition in the randomized placebo-controlled trials

Study Status	Placebo	Nebivolol
All Patients[13]		
N	372	2313
Completed – n (%)	315 (84.7)	2021 (87.4)
Discontinued – n (%)	57 (15.3)	292 (12.6)
AEs	8 (2.2)	64 (2.8)
Treatment Failure	14 (3.8)	34 (1.5)
Protocol Deviation	3 (0.8)	16 (0.7)
Loss to Follow-up	7 (1.9)	50 (2.2)
Withdrew Consent	20 (5.4)	88 (3.8)
Other	5 (1.3)	40 (1.7)
Disposition by Specific Subgroups [14]		
N	205	1811
Discontinued		
PM (P: 8; NEB: 108)	00	15 (13.9)
EM (P: 197; NEB: 1703)	36 (18.3)	227 (13.3)
Diabetics (P: 17, NEB: 151)	2 (11.8)	31 (20.5)
Non-Diabetics	34 (18.1)	211 (12.7)
< 65 years (P: 175; NEB: 1466)	34 (19.4)	193 (13.2)
≥ 65 years (P: 30; NEB: 345)	2.(6.7)	49 (14.2)
Discontinued for AEs		
Males	1 (0.9)	19 (1.9)
Females	3 (3.1)	28 (3.4)
Black	00	9 (1.9)
Non-black	4 (3.0)	38 (2.8)
Age > 65	00	14 (4.1)
Diabetic patients	2 (1.7)	23 (3.7)
Lost to follow-up		
Blacks	01 (1.4)	20 (4.3)
Other races	2 (1.5)	24 (1.8)
< 65 years (P: 175; NEB: 1466)	3 (1.7)	43 (2.9)
≥ 65 years (P: 30; NEB: 345)	00	01 (0.3)
Treatment failure		
Black	7 (9.9)	12 (2.6)
Non-black	4 (3.0)	20 (1.5)
Withdrew Consent		
Diabetics	00	9 (6.0)

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

Study Status	Placebo	Nebivolol
Non-Diabetics	10 (5.3)	58 (3.5)

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

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

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

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

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

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

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

Table 45. Patient disposition in the long-term trial[15]

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

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

[15] Table completed by sponsor

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

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

Most of the information in this review comes from a small proportion of these patients, especially information concerning death and SAEs. This is because no datasets were submitted for the non-IND studies, and those that were submitted for IND 33060 were done informally and the sponsor was unable to guarantee their accuracy.

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

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

Table 46. Hypertension Studies conducted under IND 33-060

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

5.3.2.2.2 Secondary Program, Dose-Finding Data

Table 47. Number of patients with dose-finding data

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

5.3.2.2.3 Secondary Program, Therapeutic-Dose Data

Table 48. Number of patients with therapeutic-dose data

Protocol no	Duration weeks	All NEB	PC	5 mg	AC
INT-1	4	86	84	86	--
BEL-12/18	4	42	41	42	--
BEL-3/6	4	34	33	34	--
USA-4	4	44	46	44	--
CAN-3	12	20	20	20	20
GBR-1	4	119	124	119	119
NED-12/8	8	74	40	74	--

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

Protocol no	Duration weeks	All NEB	PC	5 mg	AC
INT-5	12	211	--	--	211
INT-3	12	208	--	--	208
FRA-5	6	12	--	--	12
Total		932	388	419	652

5.3.2.2.4 Secondary Program, Long-term Treatment Data

Table 49. Long-treatment data in the secondary program

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

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

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

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

Table 50. Enumeration of Trials in which Death and SAE information are Unknown

Protocol no	Duration	Number of patients		Exposure Treatment	SAEs	Deaths
		AC or P	NEB			
INT-1	PC: 4 W	84	425	NEB 0.5 to 10 mg:	Unk	Unk
GBR-1 UK	AC: 4 W OL: 3 years	124+121	119	Neb 5 mg Atenolol 50 mg	Unk	Unk
ITA-3	CP: 6 months	24	24	Neb mg	Unk	Unk
TCH-1/2	CP: 3 M OL phase: 3 years	73	82	NEB 5 mg OL: 97	Unk	Unk

Protocol no	Duration	Number of patients		Exposure Treatment	SAEs	Deaths
		AC or P	NEB			
INT-3	CP: 3M	211	208	NEB 5 mg	2	Unk
INT-4	AC, CO: 4 W OL: 36 M	35	35	NEB 5 mg d-NEB 2.5 mg l-NEB 2.5 mg	Unk	Unk
INT-7	CP: 7 M	81	82	NEB 5 mg	2	Unk
GER-12	CP: 8 W	27	41	NEB 5 mg	0	Unk
INT-5	CP: 3 M	209	211	NEB 5 mg	Unk	Unk
CAN-9	CP: 4 W	30	30	NEB 5 mg d-NEB 2.5 mg	Unk	Unk
RSA-6	CP: 14 D	21	21	NEB 5 mg	1	Unk
NED-12/8	PC: 4 W NEB solution: 2 M OL: 12-36 M	114	114	NEB 5 mg NEB solutions	Unk	Unk
NED-13/10	PC: 2 W OL: 14 W	19	19	NEB 5 mg	Unk	Unk
CAN-10	OL: 12 W		37	NEB 5 mg	0	Unk
GER-5	PC: 4 W	15	30	NEB 2.5 or 5 mg	Unk	Unk
CAN-3	AC + PC: 12 W	60	180	NEB 1, 5 or 10 mg NEB/HCT	1	Unk
CAN-6	AC: 8 W	4	30	NEB 2.5 to 10 mg	1	Unk
POR-1/5	OL: 4 W OL: 12 to 24 M	--	133	NEB 2 – 5 mg: 81	Unk	Unk
MEX-1	SB: 1 year	--	42	NEB 5, 7.5 or 10 mg	Unk	Unk
BEL-23	OL: 1 W	--	22	NEB 10, 15, 20 mg	Unk	0
NED-4	OL: 1 W	--	12	NEB 2.5 or 7.5 mg	Unk	Unk
NED-9	OL/DI: 4 W	--	10	NEB 10, 15, 20 mg	Unk	Unk
NED-1	SB/DI: 1-2 W	--	10	NEB 2.5, 5 mg	Unk	Unk
AUS-3	DB, AC, CO 4 W	5	13	NEB 5 mg,	2	Unk
AUS-5	DB, AC & PC, CO 1 W	20	20	NEB 5 mg NEB 10 mg	0	Unk
MEX-2	DB, AC, CO 4 W	14	14	NEB 5 mg	Unk	Unk
GER-9	DB, PC	8	23	NEB 5 mg, l-NEB 2.5 mg d-NEB 2.5 mg	Unk	Unk
ARG-1	DB 8 W	15	15	MEB 5 mg	Unk	Unk
FRA-5	DB, AC, CO 4 W	12	12	NEB 5 mg	Unk	Unk
BEL-11	OL 2 years	--	37	5 mg	Unk	Unk
GER-2	OL	--	22	NEB 5 mg	Unk	Unk

Protocol no	Duration	Number of patients		Exposure Treatment	SAEs	Deaths
		AC or P	NEB			
	1 W					
BEL-10	DB, PC, CO 4 W	23	23	5 mg solution	Unk	Unk
HKG-2	DB, PC 4 W	14	18	5 mg	Unk	Unk

5.3.2.3 Other studies

Table 51. Non-IND Studies in non-hypertensive patient

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

5.3.3 Listing of Deaths

Table 52. Listing of deaths in the Primary Program

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

Table 53. Listing of deaths in hypertension trials under IND-33-060

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

Table 54. Listing of deaths in hypertension Non-IND trials

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

Table 55. Listing of deaths in non-hypertension, non-IND studies

Study	Subject	Age	Gender	Treatment	Trial period; Days	Adverse event
TCH-4	57	55	M	2.5 mg	DB; 34 days	Sudden death
RSA-8	19	56	M	5 mg	DB; 26 days	Sudden death
TCH-4[21]	Unk	64	M	5 mg	After TCH-4	Sudden death
TCH-4[21]	Unk	51	M	2.5 mg	After TCH-4	Sudden death
RSA-8	Unk	24	F	P	DB; Unk	Sudden death
TCH-4	Unk	43	M	P	PRI; Unk	MI

Table 56. Listing of post marketing deaths

Subject	Age	Gender	Dose / Duration	Indication / Condition	Cause of death
—— 613	70	M	5 mg / 7 months	HTN	Sudden death
MENIT43883	71	M	2.5 mg / 3 days	HTN	Sudden death

[18] Redefined by reviewer as such because autopsy report does not support reported cause of death of alcohol intoxication and asphyxiation by vomit aspiration; See 5.3.6.2.1; page 67
[19] Information about death is not complete because Death data was missing in many studies (studies where death and SAEs events were reported as unknown are listed in Table 50, page 57)
[20] Patient received NEB in previous phase
[21] Patients received NEB under compassionate use

7072	81	F	2.5 mg / 25 days	CHF	MI
6744	75	F	5 mg / 6 days	HTN	MI
1191	85	M	1 mg / Unk	CHF	Basic disease
1193	54	F	Neb / Unk	Unk	MVA
1194	68	M	Neb / 416 days	CHF	??
1195	70	M	5 mg / Unk	HTN	Bronchial carcinoma
42428	73	M	5 mg/10 months	CHF + HTN	Sudden death
42429	74	F	5 mg/Unk	CHF + HTN	Severe bradycardia Cerebral embolism
42431	79	F	Unk/28 days	CHF	Stroke + pneumonia

5.3.4 Listing of Serious Adverse Events

Table 57. Listing of all serious adverse events in the Primary Program

Study	Subject	Age	Sex	Dose	Days	Adverse event
NEB_302	2571000714	54	M	30/40	85	ECG, ST segment abnormal
NEB_202	2203000950	52	M	30/40	17	Bladder cancer
NEB_202	2053000150	64	F	30/ 40	89	Chest pain
NEB_321	7393210001	54	M	20	55	Chest pain & angioplasty + bleeding gastric ulcer
NEB_305	7332000886	79	F	20	31	Withdrawal arrhythmia
NEB_306	7272001051	42	M	20	90	Erectile dysfunction
NEB_305	7272000566	61	M	20	85	Leucopenia
NEB_321	7193210004	62	F	20	48	Ischemic colitis
NEB_305	7102001373	51	M	20	42	Headache
NEB_305	7092000576	46	F	20	31	DVT
NEB_306	7052001753	45	M	20	323	Viral infection NOS
NEB_321	6243210022	55	F	20	84	Congestive cardiac failure
NEB_321	6213210003	60	F	20	41	Small cell lung cancer
NEB_306	2691002033	35	M	20	134	Ureteric stenosis
NEB_306	2632001686	71	M	20	108	Bradycardia
NEB_306	2571003527	74	F	20	113	Instable Angina
NEB_302	2571000326	49	F	20	85	ECG, T wave abnormal
NEB_302	1981005683	52	F	20	83	Appendicitis, perforated
NEB_302	1981005683	52	F	20	85	Staphylococcal infection NOS
NEB_305	1652004187	46	F	20	31	Orthostatic hypotension
NEB_302	1571000166	67	f	20	33	Intermittent claudication
NEB_306	1542002986	73	F	20	182	Vertigo, positional
NEB_305	1432000330	65	F	20	43	Bradycardia
NEB_302	1411008463	59	F	20	3	AMI
NEB_305	1132000282	54	F	20	8	Chest pain + NOS ECG changes
NEB_306	7052001462	82	M	10	185	Lung squamous cell carcinoma
NEB-203	3315001384	46	M	10	19	AMI[22]
NEB_306	2741000101	59	F	10	210	Breast cancer
NEB_306	2063001141	46	M	10	126	Influenza + blood pressure increased

[22] Reviewer reclassified this event from pericarditis to AMI; for more information see 5.3.6.1 Deaths in the Primary Program; page 66

Study	Subject	Age	Sex	Dose	Days	Adverse event
NEB_305	1812000449	66	M	10	44	Severe bradycardia and CHF
NEB_305	1662004984	50	M	10	45	Dysphagia
NEB_305	1642003972	65	M	10	61	Rash
NEB_306	1621001629	62	M	10	242	Throat cancer
NEB_306	1621000756	71	F	10	103	Bladder diverticulum
NEB_306	1551001288	64	F	10	318	Amnesia
NEB_302	1411001285	64	M	10	8	Hepatitis A
NEB_306	1301001539	40	F	10	194	Abdominal pain, upper
NEB_305	1182001648	62	F	10	23	Shortness of Breath
NEB_306	2632000231	50	F	10	213	Colon Cancer
NEB_305	7242001376	41	M	5?	54	MI
NEB_305	7242000988	66	M	5	81	Aortic aneurysm ruptured
NEB_321	6813210015	75	F	5	3	MI and Cardiac death
NEB_321	6603210016	73	F	5	24	Bursitis infective NOS
NEB_321	6413210046	70	M	5	45	Dyspnea NOS, Wheezing
NEB_321	6323210016	57	M	5	39	SVT
NEB_306	2571002557	59	M	5	252	Gastroenteritis
NEB_202	2203001920	46	F	5	55	Cerebral hemorrhage
NEB_202	2203001726	60	F	5	5	Road traffic accident
NEB_302	1451005249	69	M	5	65	Colon cancer
NEB_305	1232005342	55	F	5	28	ECG Q wave + ST segment elevation
NEB_202	2613000841	39	M	5	1[23]	Chest Pain
NEB_302	1981003452	46	F	2.5	86	Cholecystitis NOS
NEB_302	1971000424	36	M	2.5	34	Appendicitis
NEB_302	1611000153	52	F	2.5	48	Road traffic accident
NEB_302	1371003335	42	M	1.25	58	Unstable angina
NEB_321	7233210011	49	M	P	94	Atrial fibrillation
NEB_302	6973210017	49	F	P	70	AMI + cardiorespiratory arrest
NEB_321	6243210017	51	M	P	68	Schizo-affective disorder
NEB_305	2942001367	61	F	P		Headache
NEB_305	1662004596	52	F	P		Fatigue
NEB_305	1662003432	57	F	P		DM aggravated
NEB_302	1471000344	44	M	P	15	Back pain
NEB_305	1232002917	59	M	P		AF
NEB_202	2563000542	49	M	Run-in	-21	Prostate cancer
NEB_305	7192000786	59	M	Run-in	-10	Diverticulitis

5.3.5 Listing of adverse events that led to discontinuation

Table 58. Listing of Serious Adverse events in the Secondary Program[24]

Study	Subject	Dose	Days	Adverse event
Bel-12/18	Unk	5	Unk	MI, cardiac failure
Bel-12/18	Unk	5	Unk	Angina pectoris Coronary artery occlusion

[23] This patient had chest pain and convulsion during the two-hour surveillance after the first dose. The sponsor reported that it occurred 2 days pre-first dose; see 5.3.7 Narrative of Serious Adverse Events in the Primary Program; page 69

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

Study	Subject	Dose	Days	Adverse event
Bel-12/18	Unk	5	Unk	Arteriosclerosis
Bel-12/18	18	Unk	574	Depression
CAN-3	Unk	5	Unk	atypical chest pain Generalized edema, pruritus,
	Unk	5	Unk	Subarachnoid hemorrhage / action unknown
AUS – 3	ID Unk	Unk		Hemorrhagic stroke / action Unk
Bel-12/18	220	Unk	275	Diabetic coma
Bel-12/18	68	5	749	Femoral artery thrombosis
RSA – 6	5	Unk		Broken bone after traffic accident / discontinued
Bel-12/18	186	5	7	Fracture after fall
Bel-12/18	116	Unk	369	Hysteria
AUS-3	Unk	5	Unk	Hiatal hernia with esophageal erosion
Bel-12/18	Unk	5	Unk	Hemorrhage complication of melanoma
BEL-3/6	Unk	5	Unk	Breast neoplasm
Bel-12/18	Unk	5	Unk	Hysterectomy
INT-8	3057	5	168	Injury / continued
INT-3	Unk	5	Unk	Subarachnoid hemorrhage
FRA – 6	11	20	63	Depression / discontinued
INT-3	7-710	P[25]	3	Anxiety, palpitation, paranoid reaction
INT-8	2061	P[25]	229	Cerebrovascular disorder

Table 59. Listing of adverse events associated with discontinuation in the PP

Study	Subject	Age	Sex	Dose	Days	History
NEB_302	1371002559	43	F	30/40	24	Angioneurotic edema
NEB_202	2203000950	52	M	30/40	17	Bladder cancer
NEB_202	2463000138	45	F	30/40	33	Bronchitis NOS
NEB_302	2171003754	75	M	30/40	5	Tachycardia NOS
NEB_302	1311000202	42	F	30	66	Dizziness
NEB_202	1643000453	51	F	20	1	Age indeterminate MI
NEB_302	1411008463	59	F	20	3	AMI
NEB_302	1981005683	52	F	20	83	Appendicitis, perforated, W
NEB_306	2451000171	44	m	20		Blood triglycerides increased
NEB_306	2632001686	71	M	20	108	Bradycardia + edema peripheral
NEB_306	2632000425	70	M	20	145	Bradycardia NOS
NEB_306	2632001686	71	M	20	108	Bradycardia NOS
NEB_306	2331003217	58	M	20	109	Bradycardia NOS
NEB_306	2331002344	63	M	20	117	Bradycardia NOS
NEB_305	1432000330	65	F	20	6	Bradycardia NOS
NEB_321	6763210005	72	M	20	13	Bradycardia NOS
NEB_305	1132000282	54	F	20	8	Chest pain + NOSE ECG changes

[25] Received NEB in previous phase

Study	Subject	Age	Sex	Dose	Days	History
NEB_321	6243210022	55	F	20	84	Congestive cardiac failure, W
NEB_305	2942000203	68	F	20	58	Diarrhea
NEB_302	2681000557	68	M	20	29	Dizziness
NEB_306	1682003377	60	M	20	1	Dizziness
NEB_302	1371000910	53	M	20	45	Dyspnea NOS
NEB_321	6023210002	64	M	20	26	Edema peripheral
NEB_306	7272001051	42	M	20	90	Erectile dysfunction
NEB_321	6623210002	69	F	20	1	fatigue
NEB_306	3081000330	37	M	20	55	Fatigue
NEB_	7123210002	56	M	20	1	Fatigue + headache
NEB_305	7102001373	51	M	20	42	Headache
NEB_306	1411005165	62	M	20	112	Headache
NEB_306	1981001415	76	F	20	1	Heart rate decreased
NEB-306	1232002529	59	M	20	165	Hyperkalemia
NEB_302	2151000123	75	M	20	15	Hypoventilation
NEB_302	2181002126		F	20	2	Hypoventilation
NEB_306	2571003527	74	F	20	113	Instable Angina, W
NEB_306	1451004376	48	M	20	182	Malaise
NEB_305	2662001167	74	M	20	16	Muscle weakness
NEB_302	1281000527	64	M	20	48	Nausea
NEB_305	1652004187	46	F	20	31	Orthostatic hypotension
NEB_321	6673210009	47	M	20	15	Platelet count decreased
NEB_306	2181006782	49	M	20	176	Sinus bradycardia
NEB_321	6213210003	60	F	20	41	Small cell lung cancer
NEB_305	2882000950	41	F	20	22	Somnolence
NEB_306	1542002986	73	F	20	182	Vertigo, positional
NEB_306	7292000123	65	F	20	48	Vision blurred, W
NEB_302	1411008269	40	M	10/20	113	Headache
NEB_305	7332000886	79	F	20	1	Withdrawal arrhythmia
NEB_305	1682001534	66	F	10	22	Abdominal pain
NEB_302	2691001548	38	m	10	31	Aggravated headache
NEB-203	3315001384	46	M	10	19	AMI[26]
NEB_306	2711000911	47	M	10	267	Bradycardia NOS
NEB_306	1642000868	42	M	10	94	Bundle branch block
NEB_302	2801000324	56	F	10	14	Chest pain
NEB_302	1411006135	55	F	10	14	Chest pain
NEB_306	2632000231	50	F	10	213	Colon Cancer

[26] Reviewer reclassified this event from pericarditis to AMI; for more information see 5.3.6.1 Deaths in the Primary Program; page 66

Study	Subject	Age	Sex	Dose	Days	History
NEB_	7222000558	10	F	10	36	cough
NEB_305	1662000813	40	M	10	60	Depression + somnolence
NEB_306	1991000757	34	M	10	?	Depression aggravated
NEB_305	1662004984	50	M	10	45	Dysphagia
NEB_306	2331002441	49	M	10	91	Dyspnea NOS
NEB_305	1182001648	62	F	10	23	Dyspnea NOS
NEB_306	3021006024	48	F	10	79	Edema aggravated
NEB_302	2781000864	55	F	10	15	Eye irritation, W
NEB_306	1642003293	41	F	10	64	Fatigue aggravated
NEB_321	6553210003	39	M	10	?	Headache
NEB_302	1411001285	64	M	10	8	Hepatitis A
NEB_306	1053003094	56	M	10		Hepatitis B
NEB_306	7052001462	82	M	10	185	Lung squamous cell carcinoma
NEB_	7052002238	65	M	10	?	Nausea + diarrhea
NEB_305	1682004056	57	F	10	2	Nausea and headache
NEB_	6763210012	64	F	10	78	Meniscus lesion
NEB_302	1961000597	64	F	10	18	Orthostatic hypotension
NEB_	2711002560	54	F	10	57	Phlebitis NOS
NEB_306	2571003236	56	F	10	DB	Proteinuria
NEB_305	1642003972	65	M	10	34	Rash NOS
NEB_305	1812000449	66	M	10	44	Severe bradycardia and CHF, w
NEB_	7143210005	41	M	10	29	Severe disorientation
NEB_302	2391000530	54	M	10	37	Skin irritation
NEB_321	7413210008	68	M	10	50	Vertigo, W
NEB_321	6603210050	63	F	10	1	Weakness
NEB_305	7242000988	66	M	5	81	Aortic aneurysm ruptured
NEB_321	6413210024	73	F	5	24	Bursitis infective NOS
NEB_202	2203001920	46	F	5	55	Cerebral hemorrhage
NEB_202	2613000841	39	M	5	1[27]	Chest Pain, w
NEB_321	7013210005	53	F	5	38	Conjunctival hemorrhage, W
NEB_321	6523210003	71	m	5	?	Dizziness + nausea
NEB_321	6413210046	70	M	5	76	Dyspnea NOS, wheezing
NEB_305	1232005342	55	F	5	1	ECG, Q wave, ST segment elevation
NEB_306	2892000389	63	F	5	20	Fatigue
NEB_321	6073210002	76	M	5	5	Flatulence
NEB_321	7253210005	59	F	5	52	Increased BP
NEB_321	6813210015	75	F	5	3	MI and Cardiac death, W
NEB_305	7242001376	41	M	5	54	MI, W

[27] Patient had chest pain and convulsion during the two-hour surveillance after the first dose. The sponsor reported that it occurred 2 days pre-first dose; see 5.3.7; page 69