U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-742
Drug Name:	Bystolic (nebivolol)
Indication(s):	Treatment of elderly patients with chronic heart failure
Applicant:	Forest Research Institute
Date(s):	May 1, 2009
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD-710)
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

There is one study with a marginally significant p-value for the primary endpoint. For a single study, the FDA normally needs a small p-value, say less than 0.01, and internal consistency to support the claim. Changes to the study design while the trial was ongoing, neither component of the primary endpoint significant alone, and the lack of enrollment from the United States tend to weaken the results.

1.2 Brief Overview of Clinical Studies

There is one study of subjects 70 years old or older with chronic heart failure. The primary endpoint was the time to first event in the composite of cardiovascular hospitalization or death.

1.3 Statistical Issues and Findings

The primary endpoint was statistically significant (p=0.03). The study was extended late in the study with no adjustment for this late change. The primary analysis was also changed from an unadjusted Cox regression model to include adjustments for several covariates. It is hard to know how to make an adjustment for either of these changes. Neither component was significant and therefore it is hard to know how the label should be written even if we were sure that the drug had an effect on either time to hospitalization or on death without knowing which component the effect is on.

2. INTRODUCTION

2.1 Overview

SENIORS was a randomized double-blind placebo-controlled Phase III study. The demographic and other baseline information is shown in Table 1. Most patients were white, the majority were male, most were taking an ACE inhibitor and a diuretic and did not have prior revascularization.

Table 1 Summary of demographics and other baseline data.

	Nebivolol (N = 1067)		Placebo (N = 1061)		Overall (N = 2128)	
Age (years)						
Median	75.2		75.3		75.2	
Mean (SD)	76.1 (4.8)		76.1 (4.6)		76.1 (4.7)	
Min, Max	69.7, 92.7		69.4, 94.7		69.4, 94.7	
Sex , n (%)						
Male	657	(61.6%)	686	(64.7%)	1343	(63.1%)
Female	410	(38.4%)	375	(35.3%)	785	(36.9%)
Race , n (%)						
Caucasian	1031	(99.3%)	1028	(99.8%)	2059	(99.6%)
Black	3	(0.3%)	-	-	3	(0.1%)
Asian	2	(0.2%)	-	-	2	(0.1%)
Other	2	(0.2%)	2	(0.2%)	4	(0.2%)
Medication for CHF, n (%)						
Any medication	1058	(99.2%)	1052	(99.2%)	2110	(99.2%)
ACE inhibitor	872	(81.7%)	876	(82.6%)	1748	(82.1%)
Diuretic	915	(85.8%)	907	(85.5%)	1822	(85.6%)
Cardiac glycoside	415	(38.9%)	422	(39.8%)	837	(39.3%)
Aldosterone antagonist	307	(28.8%)	280	(26.4%)	587	(27.6%)
Antiarrhythmic	122	(11.4%)	145	(13.7%)	267	(12.5%)
Angiotensin receptor blocker	66	(6.2%)	75	(7.1%)	141	(6.6%)
Other	353	(33.1%)	396	(37.3%)	749	(35.2%)
Prior revascularisation, n (%)						
Coronary artery bypass graft	87	(8.2%)	87	(8.2%)	174	(8.2%)
Coronary artery bypass graft + percutaneous transluminal coronary angioplasty – stent	13	(1.2%)	7	(0.7%)	20	(0.9%)
Coronary artery bypass graft + other	1	(0.1%)	-	-	1	(0.0%)
Percutaneous transluminal coronary angioplasty – stent	34	(3.2%)	27	(2.5%)	61	(2.9%)
Other	6	(0.6%)	4	(0.4%)	10	(0.5%)

Source: p 116 and 119 of Study Report.

Patients were randomized in blocks of size 8 stratified by center. All centers were in Europe. The first dose of nebivolol was 1.25 mg/day and was titrated up to a target dose of 10 mg/day within about 6 weeks. Patients were followed a minimum of 12 months and a maximum of 40 months. The plan was to enroll 2000 patients during a 28 month recruitment period.

The primary endpoint is the time to first cardiovascular (CV) hospitalization or death for any cause. The sample size was based on assumptions of an event rate of 25% per year in the placebo group, with a 25% risk reduction in the nebivolol group, 90% power and

two-sided α=0.05. The primary analysis used a proportional hazards model and adjusted for baseline left ventricular ejection fraction as a continuous variable, sex, and age. The analysis used the ITT population. After the study was completed, phone calls were made in some instances to determine vital status, but otherwise subjects were censored at the last known date alive without a CV hospitalization. There were 3 planned and one unplanned interim analyses at approximately equally spaced information times and a conservative alpha-spending rule was used for stopping for efficacy (0.001).

There were no formal secondary endpoint analyses although many secondary endpoints were listed and there was no adjustment for the multiple secondary analyses. According to p. 159 of the Study Report "The primary analysis of the primary efficacy variable was considered as confirmatory analysis, all other analyses as sensitivity or exploratory analyses. Thus, there were no multiple comparisons in the final confirmatory analysis."

2.2 Data Sources

Electronic study reports and data sets (\\Cdsesub1\evsprod\NDA021742\0000) and sponsor-provided tables.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Before describing the efficacy results of the SENIORS trial, I would like to recommend to the reader to look up and read Richard Feynman's 1974 commencement address at Caltech (Cargo Cult Science *Engineering and Science*, Volume 37:7, June 1974). If the reader doesn't have time to read the entire article, I have excerpted two paragraphs below.

> We have learned a lot from experience about how to handle some of the ways we fool ourselves. One example: Millikan measured the charge on an electron by an experiment with falling oil drops and got an answer which we now know not to be quite right. It's a little bit off, because he had the incorrect value for the viscosity of air. It's interesting to look at the history of measurements of the charge of the electron, after Millikan. If you plot them as a function of time, you find that one is a little bigger than Millikan's, and the next one's a little bit bigger than that, and the next one's a little bit bigger than that, until finally they settle down to a number which is higher.
>
> Why didn't they discover that the new number was higher right away? It's a thing that scientists are ashamed of—this history—because it's apparent that people did things like this: When they got a number that was too high above Millikan's, they thought something must be wrong—and they would look for and find a reason why something might be wrong. When they got a number closer to Millikan's value they didn't look so hard. And so they eliminated the numbers that were too far off, and did other things like that. We've learned those tricks nowadays, and now we don't have that kind of a disease.

The first subject was enrolled on September 12, 2000 and the last date of followup was March 12, 2004. Things happened this study in between these dates and soon after March 12, 2004 that were like what Richard Feynman was talking about.

The original protocol stated that subjects would be followed for a minimum of 6 months so that the study would end 6 months after the last subject was randomized. On September 3, 2002 the Steering Committee met and discussed increasing the duration of followup. Their own calculations done after that meeting noted that a total of 578 events would be needed to achieve 90% power.

During the meeting Prof. Van Veldhuisen asked for the number of events to be observed in the SENIORS study to reach a power of 90%
Post meeting note: 578 events would be required to reach 90% power (α 0.05, risk reduction 25%, log rank test, 20% non-compliance to treatment). This number is not given in the protocol. Currently there have been 339 events reported and about 50% of the patient years observed.

At that time, it was after the second interim analysis and they knew that about 50% of the original total planned number of patient years, there were 339 events observed, which is slightly more than would be needed (578/2 = 289). In other words, there was no need to increase the duration of followup in order to get more events. Moreover, the study could have been planned to achieve a fixed number of events, such as 578, but it was not. Rather, it was planned to enroll a fixed number of subjects and follow them for a fixed amount of time. With this design, there is no way to increase the number of subjects or the duration of followup based on observed event rates and know how to correctly adjust for that change.

The original analysis of the primary endpoint according to the protocol dated May 5, 2000 was not to include any covariate adjustments:

"The primary outcome ‘all cause mortality and cardiovascular hospital admissions‘ will be analysed in a confirmatory manner. The principal analysis of the trial will be the Cox Proportional Hazards Regression Model with a single treatment group covariate."

However, this was changed in the Statistical Analysis Plan dated July 9, 2004:

"The primary outcome ‘all cause mortality or cardiovascular hospital admission’ will be analysed in a confirmatory manner. The principal analysis of the trial will be the Cox proportional hazards regression model with treatment as major covariate adjusted by age, sex and LVEF in compliance with CPMP/EWP/2863/99. Age and LVEF covariates will be inserted in the model as continuous variables."

In January 2004, the Steering committee decided to change the way that deaths were captured: "The investigator will contact by phone all patients who prematurely terminate the study or patients who were lost to follow up. During the phone call the investigator will obtain information on the vital status of the patients and fill in this information in a questionnaire (enclosure 2)." This was based on the recommendation of the DSMB after the second interim analysis. I cannot think of any justification for the DSMB to request this in order to protect the safety of the subjects in the ongoing study. The ethics committee in the United Kingdom did not allow these phone calls for patients in the UK. Subsequently, the procedure was modified in the UK, "The investigator will contact the General Register Office (PO Box 2, Southport, Merseyside PR8 2JD England) and ask

for death certificates for all patients who prematurely terminate the study or patients who were lost to follow up. The date of the death will be used for the vital status analysis (see enclosure 3). If no certificate can be provided for a patient by the General Register Office the vital status of these patients will be documented as “alive “."

Almost all patients were followed for mortality until the end of the study, which could be 12 months for subjects randomized late. Figures 1 shows the censoring distribution for the primary endpoint (censored at time of censoring for mortality if later than censoring time for hospitalization). Figure 2 shows the censoring distribution for hospitalization. Close to 10% of subjects in both groups were censored for CV hospitalization within 12 months.

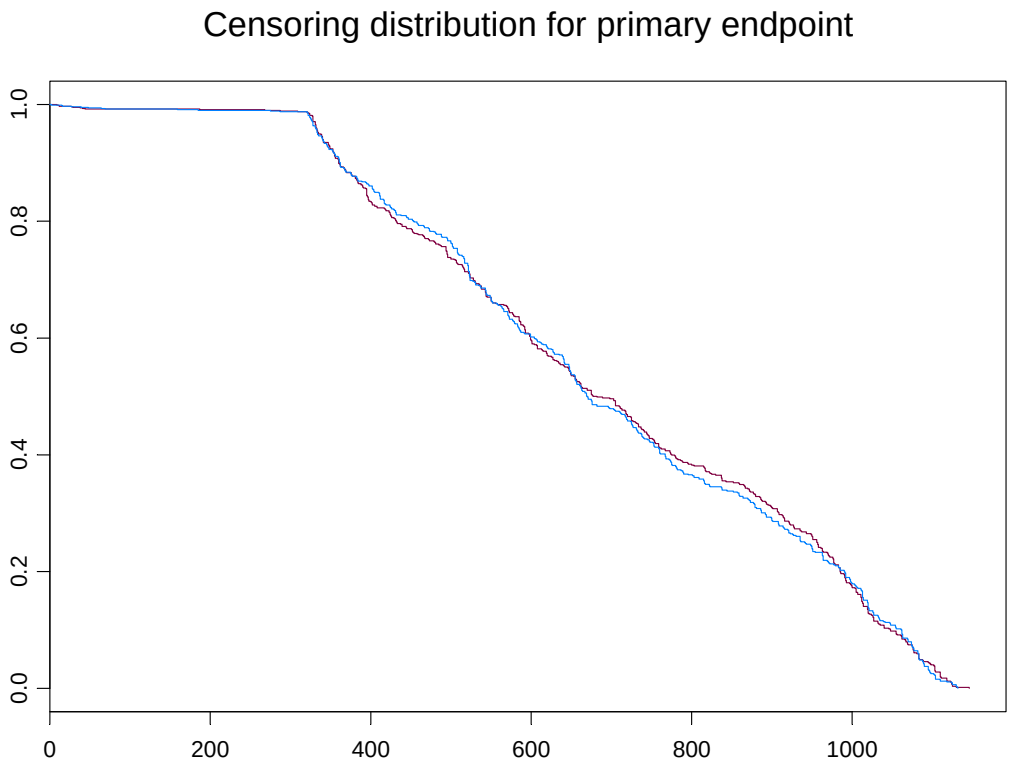

Figure 1. Censoring distribution for primary endpoint in two groups (x-axis in days) [FDA analysis].

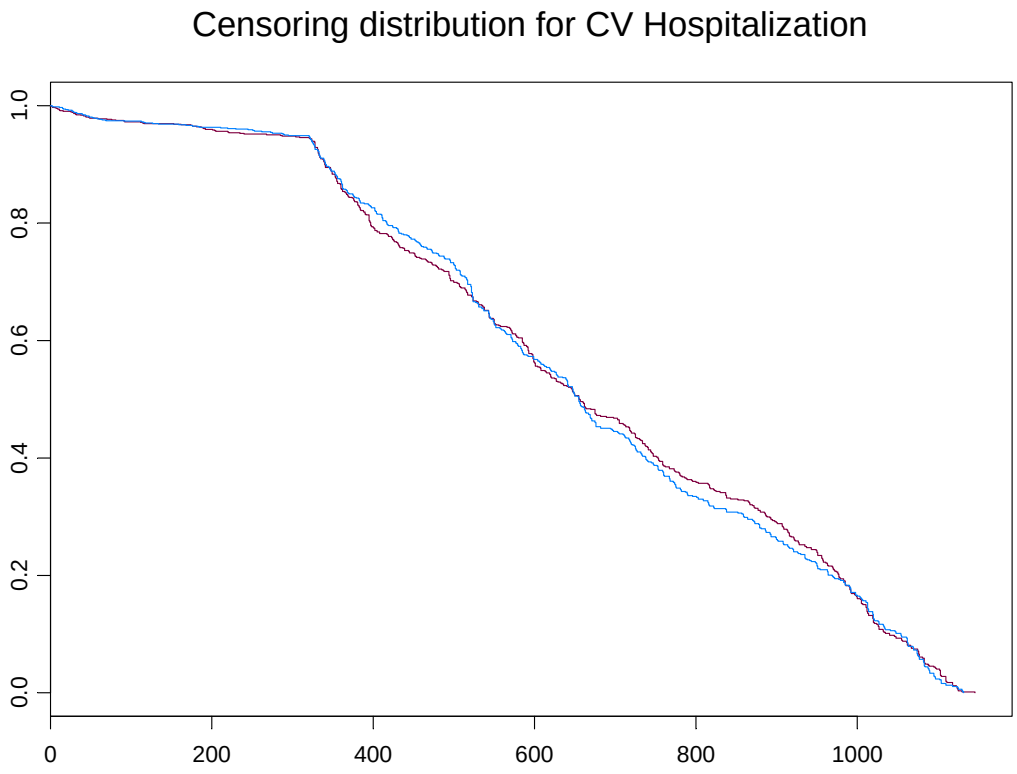

Figure 2. Censoring distribution for CV hospitalization in two groups (x-axis in days) [FDA analysis].

In the ITT population, 332 patients in the nebivolol group (31.1%) and 375 patients in the placebo group (35.3%) experienced an event of death or of cardiovascular hospital admission during the course of the study (see Table 2). There was not a convincing effect on either component alone. Mean time to the event was 796.0 days in the nebivolol group and 774.1 days in the placebo group; in other words, a difference of about 3 weeks. The Kaplan-Meier curves for the primary endpoint are in Figure 3. These curves appear to separate after about 3 months (Note: the y-axis goes from 50% to 100% and the difference between the curves may look magnified because of that).

Table 2. Primary endpoint and components using the extended followup (minimum 12 months) [Source: FDA analysis]

Endpoint	Nebivolol N=1067	Placebo N=1061	HR	P-value
Primary	332	375	0.85	0.034
All cause mortality (as first event)	76	99		
All cause mortality (at any time)	169	192	0.87	0.17
CV Hospitalization	256	276	0.89	0.20

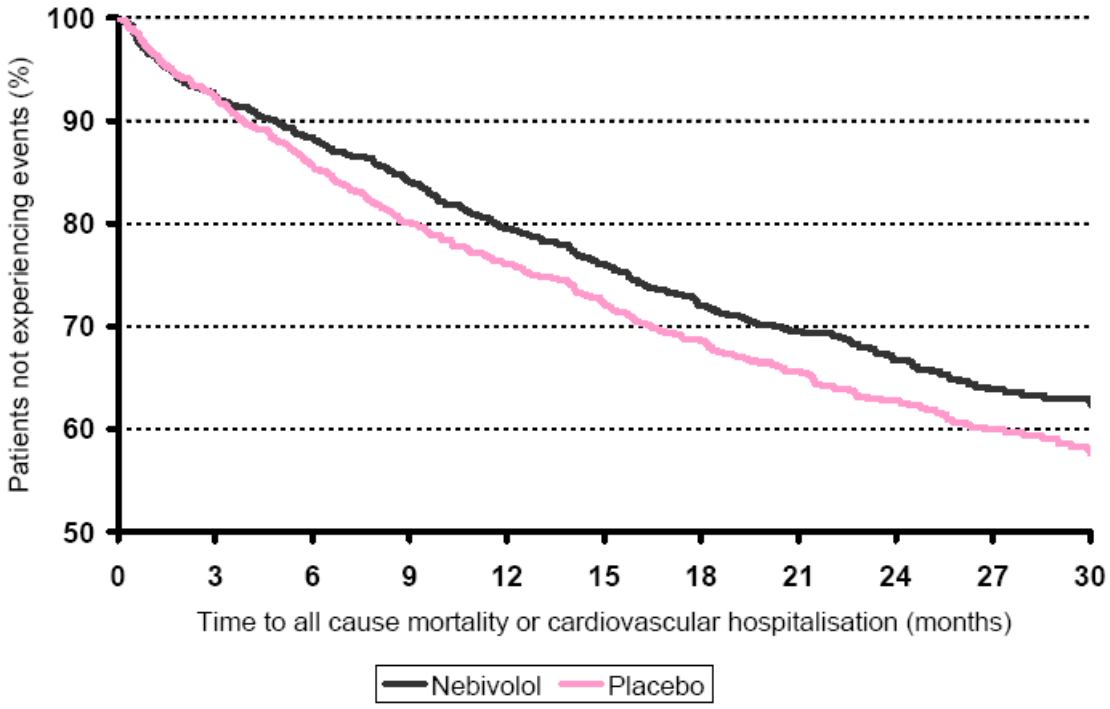

Figure 3. Kaplan-Meier curves for primary endpoint (ITT population) [Source: Figure 3 of Study Report]

A Bayesian distribution for the adjusted log-hazard ratio using all the data and a noninformative prior is normal with mean -0.855 and standard deviation 0.0758. The posterior probability that the hazard ratio is less than 0.855 is 50%. The posterior probability that the hazard ratio is less than 0.75 (the original postulated effect size on which the study was designed) is about 4%; that is, there is only a 4% chance that the risk reduction (1-hazard ratio) is 25% or more.

For the primary analysis, using the modified analysis plan, 17 subjects (8 from placebo and 9 from nebivolol) had to be excluded from the analysis because they had no baseline LVEF measured. These subjects included 3 (out of 8) in the placebo group that had an event and 4 (out of 9) in treatment group had an event.

In Western European centers, there were 121 events out of 382 subjects in the nebivolol group and 134 events out of 376 subjects in the placebo group. In Central European centers, there were 90 events out of 274 subjects in the nebivolol group and 94 events out of 269 subjects in the placebo group. In Eastern European centers, there were 121 events out of 411 subjects in the nebivolol group and 147 events out of 416 subjects in the placebo group. [Source: Table 3.1.1.1.4 of the study report]. This shows that the difference between the groups was slightly in favor of nebivolol in both Western and Central European centers (a difference between groups of 13 and 4 events respectively), but was much greater in Eastern European centers (a difference of 26 events). We don't have any US data in this study, so we have no idea what the effect would be in the US.

Figure 4 shows the p-value for the primary endpoint (using the original analysis plan that does not adjust for LVEF, sex, or age and does not include deaths that were found as a result of phone calls or checking for death certificates) as a function of calendar time of the study. I am also using the final adjudicated endpoints, which is different than the data that would have been known to the DSMB at the unblinded interim analyses. The dates on the x-axis correspond to the cutoff dates of the data used in the four interim analyses (which was in general a few weeks before the actual date of the meeting); these dates were 2/4/02, 8/23/02, 1/10/03, and 8/8/03. The last of these was an unplanned interim analyses added after the Steering committee decided to extend the minimum duration of followup from 6 months to 12 months. 12/30/02 was the date the last patient was randomized. 6/30/03 was the date 6 months after the last patient was randomized, which would have been the last date of data collection according to the original plan. 12/30/08 is 12 months after the last patient was randomized, which is the last date of data collection according to the modified plan. The blue background shows the cumulative number of events. Several things are noteworthy in this graph. First, the p-value varies alot and hovers around 0.05 after about March 2003. This suggests that the p-value is not very robust and if the data had stopped being collected one or two days earlier or later, the p-value could have easily been greater than 0.05. If we do the analysis as originally planned using data up to 6/30/03, the p-value is 0.058. If we do the analysis as originally planned using the data up to 12/30/03, the unadjusted p-value is 0.048. While this is less than 0.05, it is not adjusted for anything, including the 3 planned and one unplanned interim analyses that used α=0.001 each time (at least the first three did, I couldn't find any documentation of the purpose of the unplanned interim analysis in August 2003 or what the stopping boundary would be, but the DSMB did look at unblinded data analyses then). Finally, there is a straight line from the middle of November 2003 to the end of December 2003. The reason for this is that no data were collected after the middle of November, no events and nobody was censored during that time. So, the actual extended followup was not 12 months after the last subject was randomized, it was really about 10.5 months.

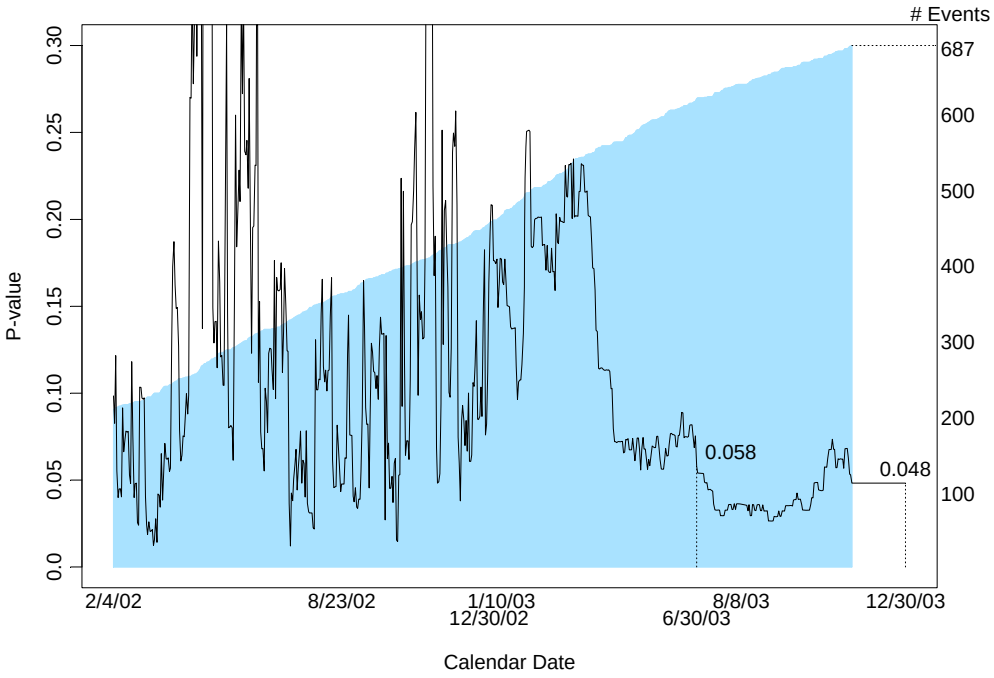

Figure 4. P-values for primary endpoint by calendar time. [FDA analysis]

Figure 5 shows the estimated hazard functions for both groups. The circles are the estimated annual event rate using the data from intervals of 90 days. For example, in the first 90 days, there were 80 events in the placebo group and there were 89,977 patient days of follow-up (the patients that didn't have an event contribute 90 days each to this total, the ones with an event contribute however many days there were until the event). The annual event rate based on the data in this interval is then 365*80/89,977 ≈ 0.325 and there is a red circle with x-coordinate in the middle of the interval (45 days, or 45/365 years) and y-coordinate 0.0325. I did that for each interval [0, 90], [90, 180], etc. in each group. The smooth curves are more complicated. For each group, I calculated the number of subjects at risk every day and the number of events every day. I then fit a weighted local regression model with weight proportional to the inverse of the estimated variance. These curves come close to the circles. The same information can be seen either by the circles or the curves. The event rate in both groups is higher for about the first 6 months after randomization, then decreases and stays relatively constant after that. For the first 90 days and, there is little difference between the groups in event rates. For the next 180 days, there appears to be a difference favoring nebivolol. After that, there is no difference. Similar information can be seen from the Kaplan-Meier curves in Figure 3. The survival curves seem to be equal for the first 3 months, then go apart for about 6 months, after which the distance between them stays relatively constant.

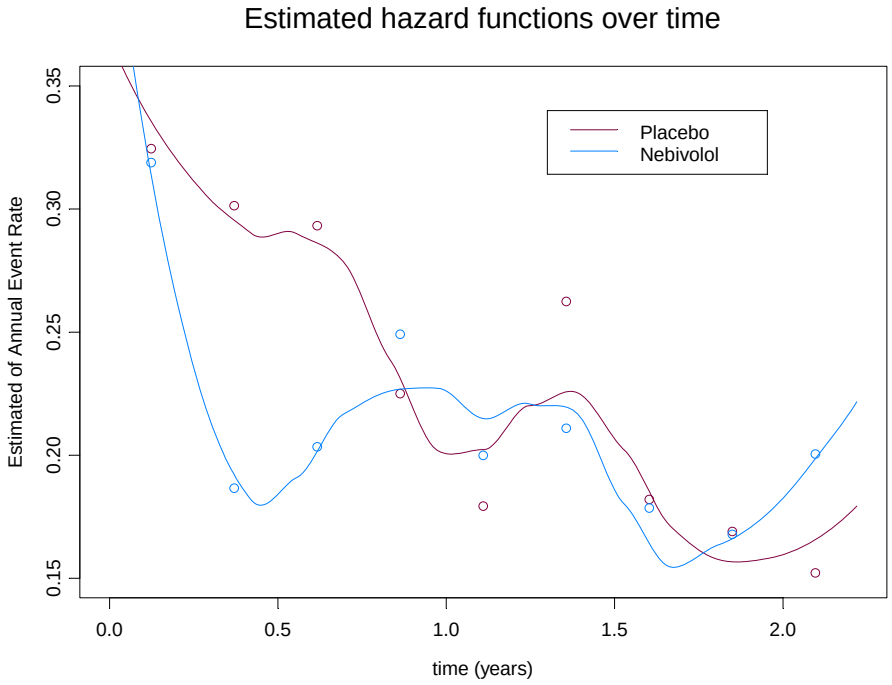

Figure 5. Estimated hazard functions by time in study. [FDA analysis]

3.2 Evaluation of Safety

See Clinical Review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

All the analyses in this section are from Appendix 16.2.1 of the study report.

In males, there were 224 events out of 657 subjects in the nebivolol group and 241 events out of 686 subjects in the placebo group. The estimated odds ratio was 0.96. In females, there were 100 events out of 410 subjects in the nebivolol group and 121 events out of 375 subjects in the placebo group. The estimated odds ratio was 0.68.

Only 9 subjects were of non-Caucasian race in the entire study and it is not possible to show any subgroup analyses by race.

In subjects at or younger than the median age in the study, there were 145 events out of 539 subjects in the nebivolol group and 170 events out of 525 subjects in the placebo group. The estimated odds ratio was 0.77. In subjects older than the median age in the study, there were 179 events out of 528 subjects in the nebivolol group and 192 events out of 536 subjects in the placebo group. The estimated odds ratio was 0.92.

4.2 Other Special/Subgroup Populations

The point estimate of the odds ratio was 0.84 in subjects with low (<=35%) baseline LVEF and was 0.83 in subjects with high (>35%) baseline LVEF (Appendix 16.2.1 of the study report).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary endpoint was statistically significant (p=0.03). The study was extended late in the study with no adjustment for this late change. The primary analysis was also changed from an unadjusted Cox regression model to include adjustments for several covariates. It is hard to know how to make an adjustment for either of these changes. Neither component was significant and therefore it is hard to know how the label should be written even if we were sure that the drug had an effect on either time to hospitalization or on death without knowing which component the effect is on.

5.2 Conclusions and Recommendations

There is one study with a marginally significant p-value for the primary endpoint. For a single study, the FDA normally needs a small p-value, say less than 0.01, and internal consistency to support the claim. Changes to the study design while the trial was ongoing, neither component of the primary endpoint significant alone, and the lack of enrollment from the United States tend to weaken the results.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21742	SUPPL-7	FOREST LABORATORIES INC	NEBIVOLOL TABLETS 1.25/2.5/5/10/20MG

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/s/

JOHN P LAWRENCE
11/23/2009

HSIEN MING J J HUNG
11/25/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-742
Priority or Standard	Standard
Submit Date(s)	May 1, 2009
Received Date(s)	May 1, 2009
PDUFA Goal Date	March 1, 2010
Division / Office	DCRP/OND
Reviewer Name(s)	Shona Pendse, MD, MMSc
Review Completion Date	December 11, 2009
Established Name	Nebivolol
(Proposed) Trade Name	Bystolic
Therapeutic Class	Beta-Blocker
Applicant	Forest Research Institute
Formulation(s)	Oral tablets
Dosing Regimen	Once Daily
Indication(s)	Treatment of heart failure
Intended Population(s)	Adult subjects with heart failure

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is not recommended for nebivolol for the treatment of heart failure.

1.2 Risk Benefit Assessment

1.2.1 Efficacy

Nebivolol's development program in heart failure consisted of the SENIORS trial [Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure], a single, randomized, double-blind, placebo-controlled, parallel-group, titrated-dose trial designed to evaluate the effects of nebivolol on the combined endpoint of all-cause mortality or cardiovascular hospitalization in clinically stable elderly subjects (70 years of age or older) with chronic congestive heart failure (CHF) with or without impairment of left ventricular (LV) systolic function. The first subject in this trial was enrolled in September 2000 and the Last Patient, Last Visit (LPLV) was in March 2004.

During the course of these nearly four years, however, several critical changes were made that affect the interpretation of the data. The first of these is that the Steering Committee (SC) amended the protocol to extend the duration of follow-up for efficacy events from 6 months to 12 months. This change was made after the 3rd interim analysis. The SC stated that the purpose of this change was to "increase the power of the study;" however, this argument did not seem to make sense since, based on the accrued number of events, the trial was well on its way to achieving 90% power without any change in follow-up. Furthermore, it was noted by the SC that this decision was "based on the recommendation of the Data Safety and Monitoring Committee [DSMC] given after the review of the data of the 3rd Interim Analysis." This communication between the DSMC and the SC is concerning. Second in this series of changes is the fact that the original statistical analysis plan (SAP) did not adjust for covariates in the primary analysis, while in the final SAP, dated July 9, 2004 (after the completion of the trial), the primary analysis was changed to include adjustment for the covariates of age, sex, and left ventricular ejection fraction [LVEF]. The final change is that the primary endpoint was changed to include 'vital status' information for subjects who discontinued the trial (i.e. whether the subjects were dead or alive) but this information pertained only to the mortality component of the primary endpoint, not to hospitalizations. Furthermore, this change was also made late in the study, on June 14, 2004, after the trial had ended. If the data is analyzed per the original protocol, without adjustment for covariates and without the 'vital status' deaths, the p-value would be 0.058 if the minimum duration of follow-up was maintained at 6 months as was originally planned, and 0.048 if the minimum follow-up duration was extended to 12 months. Thus, these changes, which were instituted late in the trial, did impact the ultimate significance of the results. Finally, even if one keeps the analysis as it was performed by the sponsor (with all of the aforementioned changes), the results were still not very robust,

hovering around a p-value of 0.05 after March 2003, sometime above and sometimes below this value. This means that, depending on the date that the study was stopped, the results could either be significant or non-significant. Furthermore, exclusion of only 2-3 subjects in each arm would be sufficient to change the results from significant to non-significant. In a study where the majority of the events contributing to the primary endpoint were cause-specific (CV) hospitalizations - a not-so-hard endpoint where there is room for subjective adjudication - this lack of robustness becomes extremely relevant.

Thus, in summary, the results from the SENIORS trial lack robustness. In addition, several critical changes were made late in the study that raise concerns as to the interpretability of the findings. Given these results and late changes to the trial, the totality of the evidence is not convincing to support a claim for treatment of heart failure.

1.2.2 Safety

With regard to the safety database for nebivolol during the development program for heart failure, the population analyzed was adequate, consisting of 1067 subjects receiving nebivolol and 1061 subjects receiving placebo. Of these treated subjects, approximately 11% in each arm discontinued the trial for reasons other than death, the most common of which was subject's desire to withdraw. With regard to dose of exposure, 67.9% of the nebivolol-treated subjects reached the maximum maintenance dose of 10 mg/day, while 80.4% reached a dose of ≥5 mg/day. The estimated exposure in total for the trial was 606,376 days, amounting to approximately 1660 patient-years.

There were 1539 subjects with treatment-emergent serious adverse events [SAEs] in the trial, of which the most common, in both the nebivolol and placebo arms, was worsening of heart failure, with 143 events in the nebivolol group (13.4%) and 153 events in the placebo group (14.4%). The next most common SAEs (listed in descending order by frequency in the nebivolol arm) were those related to cerebrovascular disorder (36 events or 3.4% and 21 events or 2.9% in the nebivolol and placebo arms, respectively), myocardial infarction (34 events or 3.2 % and 26 events or 2.5% in the nebivolol and placebo arms, respectively), and then sudden death, pneumonia, and unstable angina. The SAEs found at a higher incidence in the nebivolol compared with the placebo group were anemia (13[1.2%] and 4[0.4%] in the nebivolol and placebo arms, respectively), renal dysfunction (12[1.1%] and 6[0.6%], in the nebivolol and placebo groups, respectively), and edema (5[0.5%] vs. 1 [0.1%] in the two groups, respectively). Overall, however, the numbers of these SAEs in the two groups were two small to make any significant conclusions.

Treatment-emergent adverse events that were seen in the trial that were expected based on the drug-class of beta adrenergic blockers were bradycardia (which was the most commonly seen of these in the nebivolol group – noted in 14.3% of the nebivolol-treated subjects compared with 3.6% of the placebo subjects), hypotension, orthostasis, dizziness, syncope, and fatigue and weakness.

Finally, with regard to all adverse events [AEs], the most commonly seen treatment-emergent AE seen at a greater frequency in the nebivolol group compared with placebo were renal dysfunction (present in108 subjects, or 10.1%, in the nebivolol group compared with 78, or

7.4%, in the placebo group), edema (present in 103 subjects, or 9.7%, in the nebivolol-treated subjects compared with 61, or 5.7%, in the placebo-treated subjects), and hyperuricemia (present in 79 subjects, or 7.4% of the nebivolol group compared with 41 subjects, or 3.9%, in the placebo group).

Thus, analysis of the safety profile of nebivolol does not reveal any specific causes for concern.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Approval is not recommended. Therefore, there are no recommendations for post-market risk evaluation and mitigation strategies [REMS].

1.4 Recommendations for Postmarket Requirements and Commitments

Approval is not recommended. Therefore, there are no recommendations for post-market requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Nebivolol is a cardio-selective, $\beta_1 > \beta_2$ adrenergic blocker which is currently approved in the United States [US] for the treatment of hypertension and is approved in multiple ex-US territories for treatment of hypertension and congestive heart failure.

Chemical Name:	(1RS,1'RS)-1,1'-[(2RS,2'SR)-bis(6-fluoro-3,4-dihydro-2H-1-benzopyran- 2-yl)]-2,2'-iminodiethanol hydrochloride
Properties:	Nebivolol is a racemic mixture of two enantiomers, d-nebivolol [or SRRR-nebivolol] and l-nebivolol [or RSSS-nebivolol]
Molecular Formula:	$C_{22}H_{25}F_2NO_4$•HCl (Nebivolol Hydrochloride)
Molecular Weight:	441.90 (Nebivolol Hydrochloride)
Dosing Form:	tablets

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently approved therapies for the treatment of chronic CHF include ß-adrenergic receptor antagonists, angiotensin converting enzyme inhibitors [ACE inhibitors], angiotensin receptor blockers [ARB], diuretics, and digoxin. Please see Table 1 below for a listing of currently available therapies for heart failure, adapted from the 2009 ACC/AHA guidelines.

Note, however, that this table lists all available therapies, of which not all are approved specifically for the indication of CHF. Relevant to this discussion is the fact that only two beta-blockers, carvedilol and metoprolol, are approved for the specific indication of CHF. Outcome trials for both of these beta-blockers were terminated early because of large, statistically significant reductions in mortality.

COPERNICUS [Carvedilol Prospective Randomized Cumulative Survival Study Group] trial was a randomized, double-blind, placebo-controlled trial of carvedilol in addition to standard therapy in heart failure therapy in 2289 subjects with moderate to severe heart failure who were clinically euvolemic and had an ejection fraction [EF] of less than 25%. Mean duration of follow-up was 10.4 months. The trial was terminated early for a statistically significant reduction in all-cause mortality (34% decrease in all-cause mortality; 95% confidence interval [CI] 18, 47; p=0.00013, unadjusted; p=0.0014, adjusted for interim analyses) and a 24% decrease in the combined endpoint of all-cause mortality + all-cause hospitalization (95% CI 13, 33; p<0.001). The size of the reduction in risk was quantitatively smaller for those greater than 65 years of age.

MERIT-HF [Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure] was a double-blind, placebo-controlled trial of metoprolol CR/XL randomizing 3991 subjects (1990 to metoprolol CR/XL) with ejection fraction ≤ 40% and New York Heart Association [NYHA] Class II-IV heart failure attributable to ischemia, hypertension, or cardiomyopathy. The protocol excluded those with recent (within 28 days) history of myocardial infarction or unstable angina. The primary endpoints of the trial were (1) all-cause mortality plus all-cause hospitalization (time to first event) and (2) all-cause mortality. The mean EF of enrolled subjects was 28% and mean duration of follow-up was one year. At the trial's conclusion, the mean dosage achieved of TOPROL-XL was 159 mg. The trial was terminated early for a statistically significant reduction in all-cause mortality (34%, nominal p= 0.00009). The risk of all-cause mortality plus all-cause hospitalization was reduced by 19% (p= 0.00012). The trial also showed significant improvements in heart failure-related mortality and heart failure-related hospitalizations (mortality due to heart failure – 30 vs. 58 deaths, RR 0.51 (p=0.0023); heart failure related hospitalizations – 317 vs. 451, p<0.00001).

Table 1: Cardiovascular Medications Used for the Treatment of Heart Failure (adapted from the 2009 ACCF/AHA Guidelines)[i]

Drug	Stage A	Stage B	Stage C
ACE Inhibitors			
Benazepril	H	—	—
Captopril	H, DN	Post MI	HF
Enalapril	H, DN	HF	HF
Fosinopril	H	—	HF
Lisinopril	H, DN	Post MI	HF
Moexipril	H	—	—
Perindopril	H, CV Risk	—	—
Quinapril	H	—	HF
Ramipril	H, CV Risk	Post MI	Post MI
Trandolapril	H	Post MI	Post MI
Angiotensin Receptor Blockers			
Candesartan	H	—	HF
Eprosartan	H	—	—
Irbesartan	H, DN	—	—
Losartan	H, DN	CV Risk	—
Olmesartan	H	—	—
Telmisartan	H	—	—
Valsartan	H, DN	Post MI	Post MI, HF
Aldosterone Blockers			
Eplerenone	H	Post MI	Post MI
Spironolactone	H	—	HF
Beta Blockers			
Acebutolol	H	—	—
Atenolol	H	Post MI	—
Betaxolol	H	—	—
Bisoprolol	H	—	HF
Carteolol	H	—	—
Carvedilol	H	Post MI	HF, Post MI
Labetalol	H	—	—
Metoprolol succinate	H	—	HF
Metoprolol tartrate	H	Post MI	—
Nadolol	H	—	—
Penbutolol	H	—	—
Pindolol	H	—	—
Propranolol	H	Post MI	—
Timolol	H	Post MI	—
Digoxin	—	—	HF

*See Figure 1 for explanation of stages of heart failure.
Asymptomatic CV Risk indicates reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; LVSD, asymptomatic left ventricular systolic dysfunction; and Post MI, reduction in heart failure or other cardiac events following myocardial infarction.

Reviewer's Comments: *Both beta blockers currently approved in the United States for the indication of CHF, carvedilol and metoprolol, won on all-cause mortality, and, in fact, both the carvedilol trial, COPERNICUS, and the metoprolol trial, MERIT-HF, were terminated early due to large reductions in mortality [Carvedilol won with a 35% reduction (95% CI 19-48%, p = 0.0014 adjusted for interim analyses) and metoprolol with a 34% reduction (p = 0.00009) in mortality]*

i Hunt et al. 2009 Focused Update Incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. Journal of the American Society of Cardiology. Vol. 53: No x, 2009.

2.3 Availability of Proposed Active Ingredient in the United States

Nebivolol is currently marketed in the United States for the treatment of hypertension (NDA 21-742, approved December 17, 2007 for the indication of hypertension).

2.4 Important Safety Issues with Consideration to Related Drugs

Numerous class-associated side effects have been found with use of ß adrenergic receptor antagonists. ß adrenergic blockers depress the sinus node and the atrioventricular node, and thus can result in bradycardia and atrioventricular block. They can cause hypotension and lightheadedness, fatigue, sexual dysfunction, diarrhea and other gastrointestinal [GI] symptoms, cold extremities, and depression or confusion (particularly in older adults). ß adrenergic blockers can induce bronchoconstriction and bronchospasm with acute dosing, which is concerning for subjects with asthma and chronic obstructive lung disease. ß blockers have been implicated in altering glucose homeostasis through suppression of pancreatic insulin secretion and development of insulin resistance, thereby resulting in worsening of glycemic control. In subjects with diabetes and history of hypoglycemic events, ß adrenergic blockers can mask the tachycardia associated with these events, rendering diagnosis more difficult. ß blockade is also thought to contribute to the metabolic syndrome via its role in promoting weight gain and dyslipidemia. In subjects with peripheral vascular disease, ß blockers can precipitate or exacerbate arterial insufficiency. When administered in the absence of α blockade to subjects with known or suspected pheochromocytoma, ß blockers can cause a severe increase in blood pressure.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original IND for nebivolol hydrochloride (IND 33,060) was filed on April 13, 1989 by Janssen Research Foundation (Piscataway, NJ). This IND was then placed on inactive status on August 4, 1994 at the request of the sponsor. The IND was then transferred to Mylan Bertek on May 1, 1998, after which Mylan then submitted a request to reactivate the IND on June 5, 2000. Mylan then continued the clinical development of nebivolol hydrochloride and filed NDA 21-742 on April 29, 2004, receiving approval for Bystolic (nebivolol) for the treatment of hypertension on December 17, 2007. Forest Laboratories then assumed ownership of NDA 21-742 on December 21, 2007 and IND 33,060 on July 2, 2008.
With regard to the heart failure indication, the SENIORS trial was conducted solely in Europe from 2000 to 2004. Nebivolol was subsequently approved in Europe for the treatment of heart failure in September 2005. FDA was not involved in any of the discussions regarding the design, endpoints, or conduct of the SENIORS trial. In February 2007 Mylan with Forest Laboratories submitted a pre-IND (PIND 101,565) meeting request to discuss the SENIORS trial as the basis for a heart failure indication. The initial meeting with FDA for this supplemental indication then occurred, in May of 2008, (four years after the completion of the SENIORS trial), and focused primarily on the format of the NDA submission.

2.6 Other Relevant Background Information

No other relevant background information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Menarini Ricerche SpA and its current and former licensing partners, Forest Laboratories, Inc. and Mylen Bertek Pharmaceuticals, respectively, have conducted quality assurance activities for the trial both during the course of the trial and during the post-trial period.

During the audits done by Menarini, site number 429 in the United Kingdom, led by Dr. Shah as the primary investigator, was found to have major protocol deviations and unreliable data and this site was therefore excluded from the analyses.

Prior to the filing of this New Drug Application (NDA), Forest Laboratories, Inc. sponsored a Source Data Verification exercise for 21 of the highest enrolling sites. Given the large time lag between the date of the trial conduct (2000) versus the date of the NDA application (2009), this exercise, performed by the contract research organizations [CROs] Parexel and Verum, was done, according to the sponsor's statement, "*to ensure that all relevant source documentation, including patient medical files and original case report forms (CRFs), data queries, and general study documents would be available for potential FDA foreign inspections.*" **[From pg 78, Volume 1 of the Forest SENIORS Study Report]** Subsequently, they conducted 4 additional site audits.

The sponsor states that, in general, the study files, CRFs, and data change documentation were found to be readily available. They did find that a number of sites had undergone significant changes in personnel since the trial ended, with many of the primary investigators no longer at the original institutions, particularly in the Czech Republic. They found study electrocardiograms, which had been captured on thermal paper, degraded since their generation, making the reading of the results difficult. They also state that some of the subjects' original x-rays were found to have been destroyed at some institutions after 5 years as a result of hospital retention policies. They also attempted to locate and confirm subject medical records, which according to the sponsor appears to have been generally available, with the exception of 4 sites listed in Table 2.

Table 2: Findings from the Forest site audits

Site	*Investigator*	*Country*	*Enrollment*	*Issue*
203	Alexandru	Romania	24	Portions of the records were damaged/destroyed during a flood.
214	Dumitrascu	Romania	24	Missing hospitalization records for approximately 33% of the patients
315	Gregor	Czech Republic	32	No hardcopy ECHO images. Video available for approximately 60% of the patients
603	Hermans	Netherlands	33	Hospital medical charts for all patients undergoing digitization. Only approximately 33% patient records are available at this time. Expected by end of 2Q2009

ECHO = echocardiogram.

At the time of study conduct, there was no evidence of the records outlined above as having been missing.

[Source: pg 79, Volume 1 of the Forest SENIORS Study Report]

3.2 Compliance with Good Clinical Practices

The sponsor states that 'the study was carried out in compliance with ICH-E6 Good Clinical Practice'. They also state that 'this study was designed and monitored in accordance with the sponsor's or CRO's standard operating procedures (SOPs), which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki as amended by the 48th General Assembly, Somerset West, Republic of South Africa, 1996 and all subsequent amendments'.

3.3 Financial Disclosures

During the Pre-IND Meeting between Forest Laboratories, Inc and FDA dated September 19, 2008, the sponsor requested a waiver for the requirement to include financial disclosure information in Module 1 of the sNDA, which was accepted by FDA. The sponsor's reasoning towards this request for waiver was that 'the SENIORS study was conducted solely in Europe and, as such, financial disclosure information was not collected at the 198 sites that participated in the study'.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The CMC review team approved the sponsor's biowaiver request of the 1.25 mg tablet based on the similarity of this tablet to the approved 2.5 mg tablet high potency drug substance, where the amount of the active drug substance in the dosage form is relatively low. The Biopharmaceutics Review Staff – ONDQA recommended that the sponsor adopt a dissolution specification of > 80% in 30 minutes for *in vitro* dissolution testing of the 1.25 mg tablet. During the course of the CMC review the issue of "processing losses" during the manufacture of the 1.25 mg strength came up. The sponsor stated that these processing losses are due to the fluid bed granulation process. Nebivolol HCl is present in microionized form in the pre-blend, and a small portion of the drug is lost in the filter bag and other areas during the initial fluidization. The sponsor stated that these losses were not significant for the higher strengths, and a 3% manufacturing overage was chosen for the 1.25 mg strength based on assay results with the quantity of Lactose Monohydrate, NF adjusted to compensate for the overage. This overage was approved by the FDA CMC reviewer.

4.2 Clinical Microbiology

Not applicable given that nebivolol is an oral formulation

4.3 Preclinical Pharmacology/Toxicology

No new preclinical Pharm/Tox data

4.4 Clinical Pharmacology

No new Clinical Pharmacology Data

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Only one trial has been submitted in support of this supplemental NDA for the indication of heart failure, the SENIORS trial.

5.2 Review Strategy

A detailed review of the efficacy analysis and safety data of the SENIORS trial was performed. For this review, the reviewer utilized both the study reports, including the details of the

proceedings of the SC, Clinical Event Review Committee [CERC] and DSMC in the appendices, as well as the data sets provided to us by the sponsor. We also reviewed the narratives as well as the clinical event [CE] forms for all clinical events.

5.3 Discussion of Individual Studies/Clinical Trials

Since there is only one trial in support of this indication, the SENIORS trial, this trial will be discussed in detail in Sections 6 (Review of Efficacy) and 7 (Review of Safety).

6 Review of Efficacy

Efficacy Summary

Nebivolol's development program in heart failure consisted of the SENIORS trial, a single, randomized, double blind, placebo-controlled, parallel-group, titrated-dose trial designed to evaluate the effects of nebivolol as add-on therapy to already optimized CHF treatment on the combined endpoint of all-cause mortality or cardiovascular hospitalization in clinically stable elderly subjects (70 years of age or older) with chronic CHF with or without impairment of LV systolic function. The first subject in this trial was enrolled in September 2000 and the LPLV was in March 2004.

During the course of these nearly four years, however, several critical changes were made very late during the course of the trial that affect the interpretation of the data. These changes were 1) the increase in duration of follow-up from 6 months to 12 months; 2) modification of the primary analysis to include adjustment for covariates of age, sex, and LVEF, and 3) inclusion of data on mortality in the primary endpoint from discontinued subjects – "vital status' information. The first of these, the increase in duration of follow-up, was done by the SC after the 3rd interim analysis. The SC stated that the purpose of this change was to "increase the power of the study" but this argument did not seem to make sense based on the number of events that had occurred by that point in time. Furthermore, it was noted by the SC that this decision was "based on the recommendation of the [DSMC] given after the review of the data of the 3rd Interim Analysis". Of note, the latter two modifications (adjustment for covariates and inclusion of vital status data) were made in June - July of 2004, after the trial had been completed. Moreover, the inclusion of data on discontinued subjects pertained only to the mortality component of the primary endpoint, and not to the hospitalization component.

If the data are analyzed per the original protocol, without adjustment for covariates and without the 'vital status' deaths, the p-value would be 0.058 if the minimum duration of follow-up was maintained at 6 months as was originally planned, and 0.048 if the minimum follow-up duration was extended to 12 months. Thus, these changes, all of which were instituted late in the trial, impacted the ultimate outcome.

Finally, even if one keeps the analysis as it was performed by the sponsor (with all of these late-occurring changes), the results were still not very robust, hovering around a p-value of 0.05 after March 2003. This means that, depending on the date that the trial was stopped, the results could either be significant or non-significant. Furthermore, exclusion of only 2-3 subjects in each arm would be sufficient to change the results from significant to non-significant. In a study where the majority of the events contributing to the primary endpoint

were cause-specific (CV) hospitalizations - a not-so-hard endpoint where there is plenty of room for subjective adjudication - this lack of robustness becomes extremely relevant.

Thus, in summary, the results from the SENIORS trial are not very robust. In addition, several critical changes were made late in the study that raise concerns about interpretability of the results. Given these results and late changes to the trial, the evidence is not convincing to support a claim for treatment of heart failure.

6.1 Indication

6.1.1 Methods

6.1.1.1 Overall Trial Design

Randomized, double blind, placebo-controlled, parallel-group, titrated-dose trial designed to evaluate the effects of nebivolol as add-on therapy to already optimized CHF treatment (e.g. ACE Inhibitors, diuretics, cardiac glycosides), on the combined endpoint of all-cause mortality or cardiovascular hospitalization in clinically stable elderly subjects (70 years of age or older) with chronic congestive heart failure with or without impairment of LV systolic function.

Reviewer's Comments: *This was not an event-driven trial, but was instead designed to target a specific number of subjects who were to be followed for a minimum length of time.*

6.1.1.2 Trial Duration (including Dates), Trial Sites and Trial Population:

Trial Duration: The total recruitment period was 28 months. The first subject was enrolled on September 12, 2000, and the last subject completed the trial on March 12, 2004.

Trial Sites: 198 centers in 11 European countries

Trial Population: Elderly subjects (70 years of age or older) with chronic CHF. The trial was aimed at recruiting 2000 subjects from approximately 200 European centers and ultimately recruited 2135 subjects.

6.1.1.3 Inclusion/Exclusion Criteria:

Subjects with documented clinical heart failure who had attended the hospital outpatient clinic within the year prior to the trial start, or had been under the care of local primary care physicians, were screened for trial eligibility. Any recognized objective assessment of LV function, including transthoracic echocardiogram (ECHO), radio-isotope methods including radionuclide angiography, multiple gated acquisition, or magnetic resonance imaging, was acceptable.

Inclusion Criteria

- Age greater than or equal to 70 years
- Clinical history of CHF with at least one of the following:
  - Documented hospital admission within the previous 12 months with discharge diagnosis of CHF

  or

  - Documented LVEF ≤ 35% within previous 6 months
- Written informed consent prior to trial enrollment

Clinical history of HF was characterized by at least one symptom and one sign as specified below:

Symptoms

- Excessive breathlessness on exertion or at rest
- Fatigue
- Orthopnea
- Paroxysmal nocturnal dyspnea

Signs

- Raised jugular venous pressure
- Peripheral edema
- Pulmonary edema
- Cardiomegaly
- Raised respiratory rate at rest
- Elevated heart rate (HR) at rest
- Third heart sound or "gallop" rhythm on auscultation

The diagnosis of HF based on clinical assessment was left to the judgment of the treating physician or investigator.

Exclusion Criteria

- Introduction of new drug therapy for HF in the 6 weeks prior to randomization
- Any change in cardiovascular drug therapy in the 2 weeks prior to randomization
- HF due primarily to valvular heart disease
- Any important contra-indication to beta-blockers including, but not limited to:
  - Regular medication with inhaled bronchodilators
  - History of bronchospasm and/or asthma
  - Second or third degree heart block without permanent pacemaker *in situ*

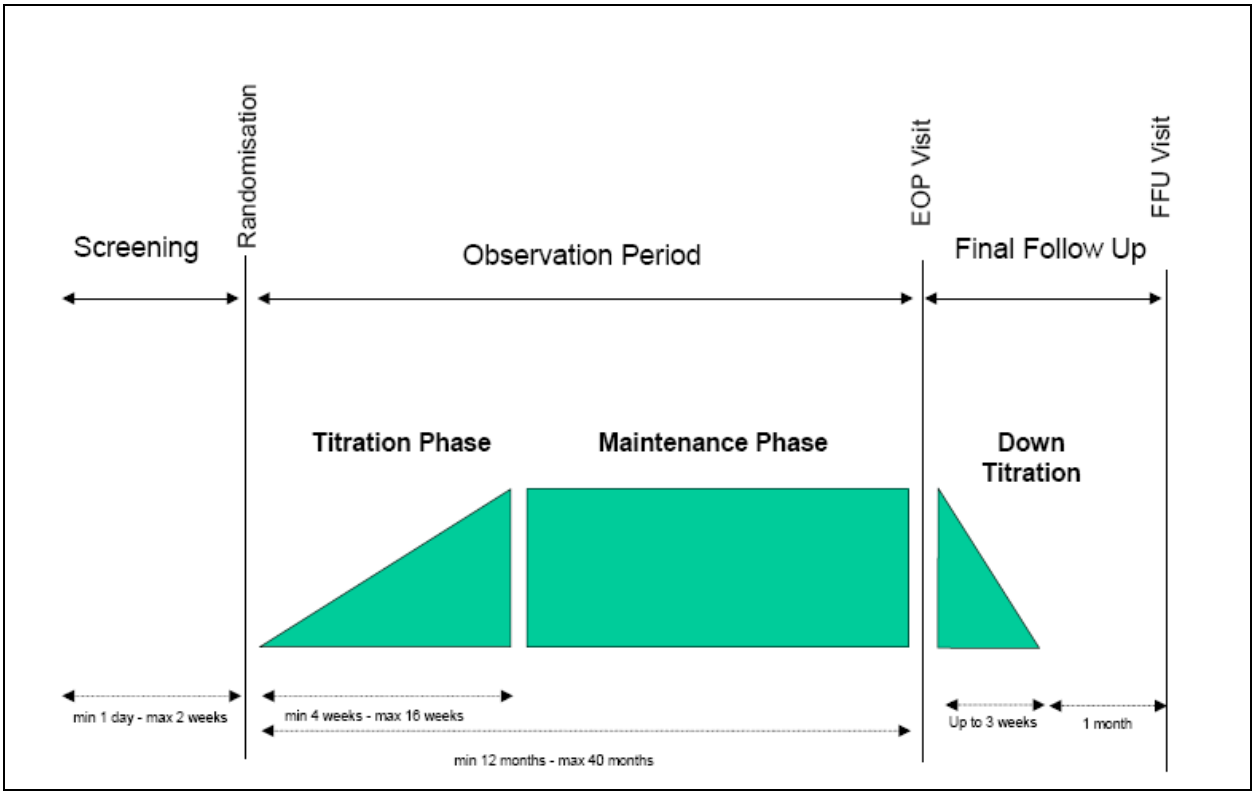
- Sick sinus syndrome
- HR < 60 beats per minute [bpm]
- Systolic blood pressure (SBP) < 90 mmHg
- Previous intolerance to beta-blocker therapy

- Current use of beta-blockers
- Known hepatic failure defined as elevation of aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), or bilirubin levels to three times the upper limit of the normal reference range
- Known renal dysfunction defined as serum creatinine ≥ 250 μmol/L
- Being on the waiting list for percutaneous coronary intervention or cardiac surgery
- Cerebrovascular accident [CVA] within 3 months of the planned randomization date
- Presence of any other major medical condition potentially reducing survival during the trial
- Subject unlikely to comply with protocol
- Subjects participating in another investigative clinical research trial
  - If the subject was eligible and willing to participate in this trial, a minimum wash out period of one month following the completion of the prior medication trial was suggested prior to enrollment in the SENIORS trial

6.1.1.4 Trial Procedures:

An individual's trial participation time consisted of a screening period (which was to occur no more than two weeks prior to randomization), an observation period consisting of a titration phase and a maintenance phase, and a final follow up period which consisted of a down titration phase and a follow up phase which was completed one month after the last dose of trial medication. Please see Figure 1 for details of the trial design and Table 3 for details of the assessments obtained during each of the trial visits.

Figure 1: Trial Design



[Source: Sponsor's Table, pg 50, Volume 1 of the Forest SENIORS Study Report]

Screening Period

Prior to randomization, all subjects were required to have blood tests as well as an assessment of LV function. Although an assessment of LV function was not mandatory for inclusion into the trial, it was required once subjects were entered into the trial, to characterize the subject population and for subgroup analysis. It was recommended that subjects be randomized on the same day of screening, but a maximum of 2 weeks was allotted between screening and randomization.

At Visit T0 the following were obtained (Also seen in Table 3):

- Demographics
- Physical examination
- Previous / concomitant illnesses and medication
- NYHA classification
- Electrocardiogram [ECG]
- Chest X ray (unless a previous test has been performed within 3 months)
- 2 dimensional echocardiogram
- 6-minute walk test
- Blood and Urine sample for laboratory tests

Titration and Maintenances Phases: The Observation Period

At the first visit of the titration phase, occurring immediately after randomization, (T0, or the baseline visit), the subjects received their first dose of nebivolol at 1.25 mg/day, or placebo. At this visit, subjects were asked to remain at the trial center for at least 2 hours after trial drug administration for observation for AEs. During this period blood pressure [BP] and heart rate [HR] were followed to ensure acute tolerance of dose. The subjects then attended at least 4 additional titration phase visits (T1 to T4), occurring at 1 to 2 week intervals, during which their doses were titrated up to 2.5 mg, 5 mg, and 10 mg. At each visit where a higher dose of trial drug was administered, the subjects were observed for a minimum of 2 hours to ensure acute tolerance of drug. If the administered dose was not tolerated, investigators were asked to attempt to up-titrate the dose to the next level for a maximum of 2 times during the titration period before fixing the maintenance dose level.

The following findings suggested that the subject might not be tolerating the current dose (though the final decision as to tolerance was left up to the clinical judgment of the investigator):

- Resting heart rate ≤ 50 bpm
- SBP ≤ 90 mmHg
- Drop in SBP > 30 mmHg upon standing
- Symptoms of postural hypotension
- New symptoms of dizziness which interfered with activities of daily living

At each visit a supply of trial medication was given to the subject to take home and use, at 1 tablet per day, until the following trial visit.

At the investigator's discretion, up to 4 additional titration phase visits (TA1 to TA4) were allowed to be scheduled based upon individual subject need. The maximum period of dose titration in the trial was 16 weeks, while the minimum titration period to reach the highest dose of 10 mg was 4 weeks.

Figure 2: Schedule of dose titration

Visit	Time after randomisation	Study Medication
T0	Baseline	After randomisation first dose of nebivolol 1.25 mg or placebo
T1	1-2 weeks	Increase to 2.5 mg nebivolol or placebo*
T2	2-4 weeks	Increase to 5 mg nebivolol or placebo*
T3	3-6 weeks	Increase to 10 mg nebivolol or placebo*
T4	4-8 weeks	10 mg nebivolol or placebo* is fixed for the maintenance phase

* Assuming that patient tolerates current dose

[Source: Sponsor's Table, pg 57, Volume 1 of the Forest SENIORS Study Report]

The maintenance phase began immediately after the last titration phase visit, either when the subject reached their maximum tolerated dose or at 16 weeks post-randomization (in which case the subject would remain at whichever dose level they had reached by this maximum

titration period end date). The first 2 maintenance visits, M1 and M2, were scheduled 4 and 6 months following randomization, after which the additional maintenance visits (to a maximum of 11 additional maintenance visits) occurred at 3 month intervals.

The titration and maintenance phases together comprised the observation period, which was the period in which subjects were followed for efficacy events.

If symptoms or signs of intolerance to medication developed, the trial medication was to be titrated downwards, temporarily stopped, or permanently discontinued. If the trial medication was temporarily titrated downwards by the investigator, subsequent up-titration to the earlier dose was advised at the investigator's discretion.

If the trial medication was temporarily discontinued for more than 72 hours, the investigator had to contact the CRO (responsible monitor) immediately. The subject was to enter a new titration phase with the same treatment allocation and undergo a similar medication titration procedure to that when first up-titrated.

Permanent discontinuation was only to be done if:

- The subject remained intolerant to the lowest dose of 1.25 mg nebivolol/placebo.
- A clear contraindication to beta-blockers developed during the course of the trial.
- A mandatory indication to beta-blockers developed during the course of the trial.
- Subjects' request.

Subjects permanently discontinuing study medication were to be observed until the end of the trial.

This observation period was to take place for a minimum duration of 1 year, as per protocol amendment 4. This amendment was instituted in May of 2003 by the SC, in efforts to increase the power of the trial by prolonging this minimum observation time from 6 months to 12 months, thereby allowing for additional time for accrual of efficacy events. It was estimated that this amendment would result in an increase in the average duration of observation from 18 months to 26 months.

The trial had been designed to have the observation time for efficacy events end on one particular date which would be common for all subjects in the trial who had not died prior to that point. Subjects who had died prior to this trial-wide end of observation date, which was termed the End of Efficacy Evaluation or EEE, or, used synonymously, the End of Observation Period or EOP, would be considered discontinued from the trial after appropriate reporting of the terminal events. Although this trial-wide end date (EEE or EOP) was set up by design prior to the start of the trial, the precise date had not been decided upon and was instead left up to the decision of the SC. On September 30, 2003, the SC decided that this trial-wide end date for efficacy observations would be November 15, 2003, which is documented in a post-meeting note of the SC meeting minutes of August 31, 2003. Any death or hospitalization that occurred after the EEE/EOP date of November15, 2003 was not considered to be an efficacy event but rather an AE and was analyzed as a safety event. In contrast, any death or hospitalization occurring before this date was to be adjudicated by the CERC and could potentially be counted as an efficacy event. For subjects that prematurely discontinued the trial prior to EEE/EOP or who did not attend an EOP visit, the vital status information (whether alive or dead, and, if dead, the date of death) was collected by investigators prior to the end of the trial. This vital

status information was not adjudicated by the CERC but could potentially contribute to efficacy endpoints involving all-cause mortality. Vital status was determined by direct inquiry of subjects, their relatives, national death registers, or by review of practice reports. This vital status information was collected in a blinded fashion and was done prior to database lock.

Within 1 month following the EOP, all subjects were required to attend an EOP visit. Thus, this EOP visit was to be scheduled a maximum of 1 month after November 15, 2003. However, due to difficulties with scheduling of this EOP visit, there were numerous instances which had greater than 1 month intervals between the EOP of November 15 and the EOP visit. At this visit, trial medication was dispensed for the final tapering of the medication. In addition, if a subject's second echocardiography examination had not been done at the 12 month maintenance phase visit, this was done at the EOP visit.

Final Follow-up Period

After this EOP visit, the down-titration period was then initiated, which could continue to a maximum of 3 weeks, during which time the trial medication was gradually reduced and then stopped. Any other medications could be started during this phase at the investigator's discretion, including any beta-adrenergic blockers approved for treatment of heart failure.

One month after the last intake of trial medication, the Final Follow-up Visit [FFU] was to be performed to check for any AE's and to return all unused trial medication. However, again, due to scheduling difficulties, this visit was often done greater than one month after the last intake of trial drug. During this visit a final blood and urine sample was also taken. The last subject's Final Follow-up Visit (LPLV) in the trial occurred on March 12, 2004.

Please see Table 3 for the trial assessments obtained during each visit.

Reviewer's Comments: *Although the trial-wide end date (EEE, End of Efficacy Evaluation or EOP, End of Observation Period) was set up by design prior to the start of the trial, the precise date was not decided upon and was instead left up to the decision of the SC.*

6.1.1.5 Randomization

Randomization was done centrally by an independent CRO in Gauting, Germany using the program RANCODE. One to One [1:1] randomization with a center block design was used, with a block size of eight (this block size was not disclosed to the investigators). A copy of the randomization list was given to the sponsor's Galenical department, the randomization center/call center CDC (Lund, Sweden), the DSMC, and one copy was kept at the CRO in Germany. Two sets of emergency envelopes containing trial treatment information were produced by CRO, with one set kept by the randomization center and one set given to the respective investigators.

The treatment allocation code for a specific subject was to be unblinded only if it was deemed absolutely necessary to know whether the subject received nebivolol or placebo (i.e. it was not to be unblinded following the death of a subject). Unblinding was to be done via the randomization center. Only if the randomization center was not able to be contacted was the

unblinding then done by opening the emergency envelope. If this occurred, the randomization center had to be informed as soon as possible about the opening of the emergency envelope.

If a randomization code was broken, the investigator had to complete a serious adverse event (SAE) form. In case the emergency envelope was opened the date and the reason for breaking the code had to be stated on the emergency envelope and signed. The safety surveillance group of the CRO was to be informed via telephone or fax as soon as possible (and in any case within 24 hours). At the end of the trial, all emergency envelopes were collected.

6.1.1.6 Study Medication

All study medications had to be secured in a locked cupboard and kept at a temperature between 15°C and 30°C under protection from humidity. The study medications were exchanged several times during the study due to limited shelf life.

The study medication was to be taken in the morning with tap water, preferably at the same time each day.

6.1.1.7 Blinding

To maintain blinding, all the strengths of nebivolol and the corresponding placebo tablet were matched in size, shape, color, and weight.

All interim analyses on unblinded data were done by an independent statistician (T Brady) without involvement of the sponsor, the CRO, or the SC. Results of the interim analyses were discussed by the DSMC in closed meetings and recommendations based on these results were given to the SC without breaking of the SC's blind conditions. T Brady confirmed to Forest that, to his knowledge, the data remained blinded pre-database lock to everyone except for himself and the DSMC.

6.1.1.8 Prior and Concomitant Therapy

All relevant concomitant medications taken at baseline and throughout the study were documented in the case report forms (CRF). Medications that were excluded from the study were any non-study beta blockers including those in eye drops. Intravenous verapamil was also not to be administered during the course of the trial.

6.1.1.9 Treatment Compliance

Subjects were required to return all study medication materials, including all blister packs, both used and unused, at each follow-up visit. Compliance was checked by counting any returned tablets.

6.1.1.10 Endpoints:

6.1.1.10.1 Primary Endpoint

The primary endpoint was the composite of all-cause mortality or cardiovascular hospitalization (time to first event).

6.1.1.10.2 Secondary Endpoints

The following secondary efficacy variables were evaluated:

- Time to all-cause mortality
- Time to all-cause mortality or all-cause hospital admission
- Time to cardiovascular mortality
- Time to cardiovascular hospital admission
- Functional capacity by NYHA class (4-grade scale)
- Functional capacity by 6-minute walk test (distance walked in the time frame)

In addition to the variables stated in the trial protocol, the following secondary variables, which were pre-specified in the SAP, dated July 9, 2004, were evaluated:

- Time to cardiovascular mortality or cardiovascular hospital admission
- Time to all-cause hospital admission
- Hospital admission or death due to:
    - Worsening of heart failure [HF]
    - Occurrence of stroke
    - Occurrence of myocardial infarction [MI]
- Cause of death
- Cause of hospitalization

6.1.1.10.3 Mortality

The CERC adjudicated deaths occurring during the observation period into pre-defined categories. However, if minimum information, such as the date of a death, was not available, the death was not classifiable.

- Cardiovascular deaths were defined as those occurring as a result of:
    - Cardiac causes including MI, cardiac arrhythmia, unstable angina and worsening of CHF
    - Cerebrovascular accidents
    - Other vascular causes including bleeding and thrombo-embolic events
- Non-cardiovascular were defined as deaths occurring as a result of:
    - Malignant disease
    - Accident, suicide, violence
    - Death from other known causes.
- Unknown

On decision of the CERC, sudden death was adjudicated as a cardiovascular death provided that other causes of death could be excluded with reasonable certainty.

For subjects who prematurely discontinued the trial, vital status was obtained during the final follow-up study period from subjects, subjects' relatives, national death registers, and subject

files in order to record whether the subject was still alive and, in case of death, the date of death. In these cases of death, the cause of death was not adjudicated by the CERC. The vital status information was used for the calculation of the primary outcome and of the secondary endpoints which included an analysis of "all-cause mortality".

6.1.1.10.4 Hospital Admissions

A hospital admission was defined as admission to hospital involving a stay of at least 24 hours. A visit to the hospital of less than 24 hours was regarded as an emergency room visit and not documented as a CE. All hospital admissions were recorded and classified by the CERC as either:

- Cardiovascular admissions, which included admissions for
    - worsening HF
    - acute coronary syndromes
    - stroke
    - thrombo-embolic events
- All other causes of hospital admissions

If, during a hospital admission for a non-cardiovascular event, there was documented evidence of a new cardiovascular event which lead to a prolongation in the hospitalization, this was considered to be a separate CE, i.e. a prolongation of a hospital admission for a cardiovascular reason.

Hospitalizations planned prior to randomization were not considered to be SAEs or CEs.

Furthermore, routine elective hospital admission or planned admission for routine trial related procedures were not considered to be hospitalizations for the purposes of the trial and were therefore not considered to be SAEs or CEs.

6.1.1.10.5 Hospital Admission or Death Due to Worsening of Heart Failure, Myocardial Infarction, or Stroke

The incidence of CEs (death or hospital admission) caused by worsening of HF, MI or stroke, as adjudicated by the CERC, were of major interest and were considered as secondary endpoints.

When worsening of HF and unstable angina and/or arrhythmia coexisted as cause for hospitalization, worsening of HF took priority as the cause for hospitalization. When an admission was due to both MI and worsening of HF, MI took precedence as the cause.

6.1.1.10.6 Other Assessments

Clinical assessments, laboratory studies, standard 12-lead electrocardiogram (ECG), two-dimensional echocardiogram, assessment of functional capacity by both the New York Heart Association classification and the 6-minute walk test, chest x-ray, and adverse event and clinical event reporting were all done through the course of the trial, as shown in Table 3.

Clinical Assessments

Clinical Assessments included symptom assessment, physical examination, body weight, resting BP (sitting and standing), resting HR, and general cardiovascular examination for signs of heart failure.

Laboratory Studies

Laboratory tests included both blood and urine studies as shown below in Figure 3. All of these parameters were assessed at baseline (T0), 6 months after randomization (M2), and at the Final Follow-Up Visit (FFU). At maintenance visits M4, M6, M8, M10, and M12, only liver function, renal function, and plasma glucose parameters were assessed.

Figure 3: Laboratory Studies

Haematology	Haemoglobin, haematocrit, red blood cell (RBC) count, platelets, white blood cell (WBC) count, leukocyte differentials.
Liver Function	Total bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin.
Renal Function	Blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride.
Metabolic Profile	Glucose (fasting), total cholesterol, triglycerides, uric acid.
Others	Thyroid stimulating hormone (TSH), calcium, phosphorous, magnesium.
Urinalysis	Blood, protein, glucose, and ketones.

[Source: pg 66, Volume 1 of the Forest SENIORS Study Report]

Standard 12-Lead Electrocardiogram

2 copies of a standard lead electrocardiogram were recorded at rest (one for the subject's file and one attached to the CRF) at every titration visit, and at 4 months and 6 months post-randomization and then every 6 months throughout the maintenance phase. The corrected QT interval, or QTc, was calculated using Bazett's formula.

Two-dimensional echocardiogram

2D ECHO was done at baseline and at 12 months post-randomization (or at the EOP in case the 12 month ECHO assessment was not available). These records were stored at the study centers.

Functional Capacity by New York Heart Association Classification

Functional capacity was assessed by the investigator using the NYHA classification (4-grade scale) at every visit during the observation period.

Functional Capacity by 6-Minute Walk Test

The 6-minute walk test was measured at baseline and 6 months after randomization.

Chest X-ray

Chest X-ray was performed at baseline unless it had been performed within the previous 3 months.

Adverse Events

All adverse events that were either observed by the investigator or reported by the subject at any point during the trial were recorded at each visit, up until the FFU visit. The investigator was to follow-up all subjects reporting an AE until either the subject died, the clinical recovery was complete, or the clinical condition had stabilized. These follow-up reports were attached to the CRF.

Serious Adverse Event (SAE) and Clinical Event (CE) Documentation and Reporting

Every SAE and CE had to be reported by the investigator via fax to the CRO's Safety Surveillance Group within one working day of his/her first knowledge of it. The investigator decided whether the event met the criteria of a CE or SAE and then had to fill out and fax the corresponding form. The investigator was to follow-up all subjects reporting SAE/CE until either the subject died, the clinical recovery was complete (i.e. the AE had disappeared), or the clinical condition had stabilized. These follow-up reports were attached to the CRF.

Follow-Up of Clinical Events

The CERC members required objective evidence for worsening of HF at the time of the clinical event (such as result of chest X-ray, ECHO, or ECG at the time of admission). This information was requested if on the CE form "worsening of HF" was checked off. The CRO's Safety Surveillance Group followed-up every event, collected all necessary supporting documents, and, once the case was complete with all necessary documents, batch them into group of approximately 30 cases before sending them to the CERC.

Follow-up of Serious Adverse Events

The follow-up of SAEs was within the responsibility of the sponsor's Drug Safety Unit [DSU], who reported SAEs to the appropriate regulatory authorities or ethics committees, including expedited reporting.

All serious and unexpected AEs other than death or hospital admission which were considered possibly related to the study treatments underwent expedited reporting. Given that deaths and hospital admissions were the efficacy endpoints for the trial, these were not routinely reported in an expedited manner, unless concerned authorities otherwise indicated. If an SAE was subject to expedited reporting, treatment unblinding had to be done via the randomization/call center and needed to be documented in the SAE/CE form.

Table 3: Schedule of Assessments and Events

	Screening	Observation Period*											
		Titration			Maintenance								
Visit		T0	T1-T4	TA1-TA4[1]	M1	M2	M3	M4	M5	M6	M7-M13	EOP[2]	FFU[3]
Month		1-4			4	6	9	12	15	18	21-40	to be defined	
Screening documentation	X												
Informed consent	X												
Eligibility criteria		X											
Demographics		X											
Physical examination		X[4]	X	X	X	X	X	X	X	X	X	X	X
Previous / concomitant illnesses and medication		X											
Changes in concomitant medication			X	X	X	X	X	X	X	X	X	X	X
NYHA classification		X	X	X	X	X	X	X	X	X	X	X	
ECG		X	X	X	X	X		X		X	X[5]	X	
Chest X-ray		X[6]											
Blood sample		X				X		X[7]		X[7]	X[5,7]		X
Urine sample		X				X							X
2-dimensional ECHO		X						X				X[8]	
6-minute walk test		X				X							
Randomisation		X											
AE tracking			X	X	X	X	X	X	X	X	X	X	X
Medication dispense		X	X	X	X	X	X	X	X	X	X	X[9]	
Medication compliance			X	X	X	X	X	X	X	X	X	X	X[9]
Study termination													X

* The average observation period was expected to be 26 months (range 12 – 40 months) (Amendment No. 4).
1 Additional titration visits could be performed if required.
2 EOP = End of Observation Period visit, the date of which was to be defined by the SC.
3 FFU = Final Follow up visit: performed 4-7 weeks after EOP.
4 Detailed physical examination by body systems.
5 Only at visits M8, M10, and M12 (Months 24, 30 and 36) (Amendment No. 4).
6 Unless a chest X-ray had been performed within the previous 3 months.
7 Only liver function tests, renal function tests, and plasma glucose test.
8 Only if a 12 month 2-dimensional ECHO was not available.
9 Down-titration medication.

[Source: Sponsor's Table, pg 64, Volume 1 of the Forest SENIORS Study Report]

6.1.1.11 Statistical Analysis Plan:

Date of the final version of the SAP

The final version of the SAP, version 2, was July 9th, 2004.

Analysis Populations

The analysis populations consisted of the Intention To Treat (ITT) population, comprised of all subjects who were randomized, and the Per Protocol (PP) population, comprised of all

subjects who were randomized, who provided data post-randomization, and who had no major protocol violations. Since the randomization process was considered complete at the first intake of medication, data from all subjects who were randomized and took at least one tablet were included in the ITT population.

Subjects excluded from the ITT population consisted of 6 subjects from center 429 who were excluded due to compliance issues discovered upon audit of the site (significant deviations from the trial protocol and poor quality of data) and one additional subject, from Center 708 (subject 21860), who had enrolled in the trial and then discontinued soon after, taking no study medication in the short intervening time.

The final statistical plan was dated July 9, 2004, which the sponsor states occurred prior to database closure and unblinding.

Reviewer's Comments: *The final statistical plan was dated July 9, 2004, which was after the trial had been completed.*

Time to Event Calculations

All time to event variables were expressed in days and calculated as follows:

1. For subjects who experienced the relevant event during the trial:

Date of adjudicated event minus date of randomization + 1 (i.e. first intake of study medication)

2. For subjects who did not experience the relevant event during the trial and who did not prematurely discontinue the trial, the time to event variables was considered censored. The censoring time was computed as:

Date of EEE minus date of randomization + 1

3. For subjects who did not experience the relevant event during the trial but did prematurely discontinue the trial, it was necessary to distinguish between two types of variables:

- For variables that included "all-cause mortality" either as the sole endpoint or part of a composite
    - Subjects for whom vital status information was available and resulted as 'alive' at or after EEE (or 'death' after EEE). These subjects were considered censored at the date of EEE:

      Date of EEE minus date of randomization + 1
    - Subjects for whom vital status information was available and resulted as 'death' with a complete date of death (i.e. at least month and year) before EEE:

      Date of death minus date of randomization + 1
    - When necessary, a missing day was imputed as 15, i.e. if the date of death was given as "11/2003" this was considered as death on "15/11/2003".
    - Subjects for whom vital status information resulted as 'death' but with incomplete date of death (i.e. only the year or no date given), or subjects for whom no vital status information was obtained, were considered

censored according to the last date available in the CRF (this was the latest date among all study dates available for a subject (e.g. last visit date, collection day of the last laboratory sample, the end date of hospitalization, the end date of an AE, or the date of FFU visit). If this date occurred after EEE, then the subject was censored at the date of EEE:

Last date available minus date of randomization + 1

- For variables that did not include "all-cause mortality":
  - The vital status information was not used in the calculation of these variables. If subjects who prematurely terminated the trial did not experience an adjudicated event prior study termination, they were censored at the study end date:

    Study end date minus date of randomization + 1

Handling of Missing Values

The sponsor states that "*Any replacement of missing values was clearly identified by footnotes or other measures. For dates with missing day of the month, the 15th of the month was used, unless data checks showed that the replacement led to data inconsistencies.*" **[From pg. 85, Volume 1 of the Forest SENIORS Study Report]**

Analyses of Time-to-Event Data

- Number and percentage of events and their odds ratio between the treatment groups
- Quartiles and median time to event and its 95% confidence interval (CI) as well as mean time to event and standard deviation [SD]
- Kaplan-Meier (KM) plots
- The estimated KM event rates at 6, 12, 18, 24, 30 and 36 months

Analysis of Primary Efficacy Variable

- The primary outcome "all-cause mortality or cardiovascular hospital admission" (time to first event)
- The principal analysis of the trial will be the Cox Proportional Hazards Regression Model with a single treatment group covariate. The overall estimated hazard ratio and 95% confidence interval will be derived from this analysis. The analysis will use the intention to treat principle, considering the groups as randomized.
- The overall estimated hazard ratio and 95% CI was derived from this analysis. The analysis used the ITT principle, considering the groups as randomized.
- In the primary analysis, the following hypothesis was tested:

  Null hypothesis H_0: Hazard ratio (nebivolol versus placebo) = 1 for "time from randomization until the occurrence of first event of either all-cause mortality or cardiovascular hospital admission"
- A significance level of 0.05 (two-sided) was used.
- The assumption of proportional hazards was explored by examining a plot of log cumulative hazard against log time.

- As a "further analysis of the primary outcome" in Section 16.8.2 of the protocol, it was noted that "*apart from the Cox Proportional Hazards Regression Model with a single treatment group covariate a further model will be fitted with three further covariates: age, sex, and ejection fraction at baseline. Age and ejection fraction will be included as continuous variables unless there is found to be curvature in their relationship with hazard.*"

Reviewer's Comments: *The primary analysis was pre-specified in the original protocol as being done using a Cox Proportional Hazards Regression Model with a single treatment group covariate, and as a "further analysis" the plan was to use treatment as a major covariate adjusted by age, sex, and LVEF.*

Sensitivity Analysis

- The primary analysis on the PP population encompassing subjects who became major protocol violators after experiencing the primary outcome
- A Cox proportional hazards regression model with a single treatment group covariate on the ITT population
- The primary analysis of subjects while in the trial only (without use of vital status information collected after premature trial discontinuation)

Exploratory Analyses

- The primary analysis on the ITT population with subjects being censored at the earliest date between day of last intake of study medication or EEE (If day of last intake was missing, and the subject did not discontinue prematurely treatment, then EEE was used; if day of last intake was missing and the subject discontinued prematurely treatment then study end date was used.)
- The primary analysis on the PP population
- Three Cox regression models with a single treatment group covariate were fitted with each of the three covariates, age, sex, and LVEF at baseline, in turn. Age and LVEF were included as continuous variables. The interaction between the treatment group effect and the additional covariate was investigated by adding the relevant interaction terms in each model.
- Kaplan-Meier curves by country and geographical area and treatment were presented.
- The primary analysis was re-run on the ITT population including subjects of centre 429.

<u>Analysis of Secondary Efficacy Endpoints (Exploratory)</u>

Time to Event Variables

The time to event secondary variables were analyzed according to the statistical models described in the primary and sensitivity analyses of the primary efficacy variable. The only exception was the sensitivity analysis on the PP population, which did not encompass subjects who became major protocol violators after experiencing the primary outcome. Kaplan-Meier curves by country and/or geographical area and treatment were also presented. Time to all-cause hospital admission was analyzed according to the statistical models described in the primary analysis only.

For the Younger, Low Ejection Fraction Subpopulation [defined as all subjects in the ITT population aged ≤ 75.2 years (the median age) with a baseline LVEF ≤ 35%] , the secondary efficacy endpoints analyzed were:

- All-cause mortality
- Cardiovascular mortality
- Cardiovascular hospital admission

Reviewer's Comments: *All of the secondary endpoints were exploratory in nature, with no pre-specified statistical plan, no hierarchical status for analysis, and no alpha spending.*

Definitions of Endpoints per CERC Charter

1. Mortality
    a. Cardiovascular Mortality
        i. Cardiac Death
            1. Coronary Death

            Death from a new confirmed acute MI, i.e., death within 28 days from the onset of symptoms of a hospital-verified MI, or in cases of death occurring outside the hospital, autopsy findings showing a recent myocardial infarction or a recent occluding coronary thrombus

            Death related to a coronary invasive procedure or surgery and occurring within 28 days from the onset of the procedure

            2. Heart Failure Death

            From worsening of heart failure, even if the terminal event was an arrhythmia

        ii. Vascular Death
            1. Cerebrovascular (stroke) Death

            Causes of cerebrovascular death occurring within 28 days from the onset of symptoms and thought to be due to athero/thrombotic cerebral infarction, stroke with a present source for embolus, or evidence of hemorrhage or stroke for which a distinct etiology cannot be ascertained with any degree of confidence

            2. Other Vascular Death

            Death from a vascular cause not compatible with the previous categories i.e. pulmonary embolism, aortic aneurysm dissection, cardiovascular surgery other than CABG

Bleeding is included in this category[ii]

b. Non-cardiovascular Death
    i. Malignancy

    All cases of death from malignant disease are included in this category
    ii. Suicide, violence or accident
    iii. Other known reasons
    iv. Other unknown reasons

c. Sudden Cardiac Death
    i. Cardiac arrhythmia

    Documented sudden onset of arrhythmias directly leading to death
    ii. Sudden Unexpected Death
        1. Witnessed instantaneous unexpected death occurring without any preceding symptoms
        2. Witnessed cardiac death occurring within one hour after the onset of chest pain, syncope, acute pulmonary edema or cardiogenic shock
        3. Witnessed cardiac death occurring more than one hour but less than 24 hours after the onset of chest pain, syncope, acute pulmonary edema or cardiogenic shock
        4. Non-witnessed unexpected death, if other causes of death can be excluded with reasonable certainty (excluded are those subjects who were known to have signs or symptoms of other fatal disease when last observed)

2. Hospitalizations

a. Definitions of hospital admissions
    i. An admission is defined as a hospital stay of at least 24 hours
    ii. All hospital admissions (except planned hospital admissions for routine study-related procedures) will be recorded and classified
    iii. Cardiovascular hospital admissions include:
        1. worsening heart failure
        2. acute coronary syndromes
        3. stroke and thrombo-embolic events
        4. other cardiovascular causes
    iv. All other causes of hospital admissions will also be documented
    v. All planned and unplanned cardiovascular admissions are to be included in the primary outcome:

[ii] Please see Table 5 (1/19/2002 entry) for further discussion and modification of Bleeding as Vascular Endpoint.

vi. Non-cardiovascular admissions will not be included in the primary outcome but in the secondary outcome

vii. Admission not considered an endpoint of the study

1. All hospital admissions planned before randomization
2. Admissions for routine study-related procedures

b. Hospitalization for worsening heart failure

i. Subjects should have

1. Symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exercise, or peripheral edema, and
2. Objective evidence of heart failure, assessed by either echocardiography, or chest X-ray, or angiography or radionuclide scintigraphy

or

"hard" physical signs (markedly raised jugular venous pressure, and/or pleural effusion and/or ascites in the absence of other causes for these) as diagnosed before or during hospitalization.

ii. Those signs should lead to acute hospitalization of at least 24 hours and should require:

1. Intravenous treatment or an increase of 50% or greater of any medication currently being administered to treat heart failure, including diuretic therapy, or
2. Institution of new drug category

c. Hospitalization for acute myocardial infarction [AMI]

i. Criteria for acute, evolving or recent MI

A rise of biochemical markers exceeding the decision limit of myocardial infarction with at least one of the following:

1. Ischemic symptoms
2. Development of pathologic Q waves
3. ECG changes indicative of ischemia (ST segment elevation or depression)
4. Coronary artery intervention (e.g. coronary angioplasty), or
5. Pathologic findings of an acute MI

ii. Criteria for established MI

1. Development of new pathologic Q waves on serial ECGs
2. The subject may or may not remember previous symptoms
3. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed, or

4. Pathologic findings of a healed or healing MI

d. Hospitalization for unstable angina pectoris
   i. Unstable angina is defined by
      1. Hospitalization with principal presentation of unstable chest discomfort (rest, new onset or worsening of angina) *plus*
      2. Dynamic ECG changes indicating ischemia, *and /or*
      3. A slight rise in biochemical markers (below the decision level), without ECG abnormalities consistent with an AMI, and without a typical rise in biochemical markers of myocardial infarction (exceeding the decision level) and not due to other attributable cause, *and/or*
      4. Acute coronary arteriography showing a critical vulnerable plaque, a culprit lesion, an evolving thrombus or equivalent terms as the most likely cause of the unstable myocardial ischemia.

e. Hospitalization related to cardiac arrest with successful resuscitation
   i. Hospitalization related to cardiac arrest, including in-hospital cardiac arrest, is defined by either
      1. A physical act of cardioversion (except when performed for atrial fibrillation/ flutter or supraventricular tachycardia) *or*
      2. ECG evidence of ventricular fibrillation or asystole, *and*
      3. By survival for at least 28 days
   ii. Cardiac arrests due to non-cardiac causes are excluded as well as those resulting from cardiovascular interventions

f. Hospitalization for cardiac arrhythmias
   i. Documented arrhythmias leading to hospitalization

g. Hospitalization for stroke
   i. The diagnosis of stroke requires
      1. Evidence of a neurological deficit, usually localized, lasting 24 hours or more, or until death (if death occurs <24 hours after the onset of neurological symptoms),
      2. Is usually confirmed by diagnostic testing (e.g., CT-scan).
      3. Clinical Centers will describe
         a. in the Endpoint narrative any physical findings and symptoms with respect to severity and localization as accurately as possible
         b. Other symptoms that may constitute an atypical expression of a stroke and report the results of diagnostic tests

c. Reversible Ischemic Neurological Deficit [RIND] is included in this category.

ii. The clinical characteristics of stroke include

1. The sudden onset of a neurological deficit typically manifested as:

a. Depression of state of consciousness
b. Disturbance of vision
c. Paresis or paralysis of one or more extremities
d. Sensory impairment
e. Speech impairment
f. Central cranial nerve dysfunction
g. Memory defect
h. Ataxia
i. Movement disorder

h. Hospitalization for transient ischemic attacks [TIAs]

i. TIAs are defined as neurological deficits lasting less than 24 hours and will be classified separately

i. Hospitalization for thrombo-embolic events or other vascular causes

i. Admissions for thrombo-embolic events or other vascular causes not compatible with the previous categories, *i.e.*

1. pulmonary embolism
2. aortic aneurysm dissection
3. cardiac surgery

j. Hospitalization for other causes

i. This applies to all hospital admissions not attributable to any of the above categories

3. Endpoint Analysis Conventions

a. Hospitalization

i. Hospital admission includes

1. Acute admission for at least 24 hours
2. For chronic or long-term inpatients, hospital admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit, from the neurological floor to the tuberculosis unit)
3. In addition, hospital admission includes emergency room, observation, and short-stay units of more than 24 hours duration

ii. Hospital admission does not include the following:

1. Outpatient/same-day/ambulatory procedure
2. Planned hospitalization for routine study-related purposes
3. Rehabilitation facilities
4. Hospice facilities
5. Skilled nursing facilities
6. Nursing Homes
7. Custodial care facilities
8. Clinical research/Phase 1 units

b. Prolongation of Hospitalization

i. Strong documented evidence of a new cardiovascular event during a hospital admission for a non-cardiovascular event, leading to prolonged hospital admission, is considered as a new hospital admission for a cardiovascular reason

c. Other conventions

i. If a subject experiences both a cardiovascular admission (except AMI) and death during the same hospitalization, these are counted separately

ii. When worsening of heart failure and unstable angina and/or arrhythmia coexist as a cause for hospitalization, worsening of heart failure takes priority as the cause for hospitalization

iii. Where an admission is due to both myocardial infarction and worsening of heart failure, myocardial infarction takes precedence

iv. Cardiac arrest with successful resuscitation is classified as such only if the subject survives for > 28 days after resuscitation.

1. If the subject dies within 28 days of cardiac arrest, only a single event is classified as a death for the primary endpoint

v. Heart transplantation is classified as worsening heart failure

vi. If a subject is hospitalized for some other reason but experiences a primary or secondary endpoint event during that hospitalization, these are classified as study events

Reviewer's Comments:

1. Sudden cardiac death is being considered as a separate category from CV deaths.

2. Death from any unknown reason is being considered a non-cardiovascular cause, despite the fact that we do not know the cause and therefore cannot rule-out a cardiac etiology.

3. Autopsy findings may alter the results in the cases in which a post-mortem was performed.

4. There is no adjudication rule for bradycardia.

NYHA Classification

NYHA class at each visit was presented along with shift tables displaying changes in NYHA classification at 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, and EOP or last value available versus baseline. Changes were grouped into categories of 'improved', 'no change' and 'worsened' (1,0,-1) and compared per visit between treatments by means of the Cochran-Mantel-Haenszel [CMH] test adjusted for the baseline NYHA class and using the mean score statistics with modified ridit scores.

Six-minute Walk Test

The distance walked in six minutes was compared at baseline and 6 months or last measurement available. In cases where the walk test was performed for less than 6 minutes, the documented distance walked was evaluated. Comparison between the treatment groups was done by means of analysis of covariance [ANCOVA] with baseline distance as covariate. If the outcome of the 6-minutes walk test was reported in more or less discrete data, test results were categorized into 'improved', 'no change', and 'worsened' (1,0,-1) and compared between the treatment groups by means of the CMH test using the mean score statistics with modified ridit scores.

Additional Variables

Worsening of HF, occurrence of stroke, occurrence of MI, cause of death, and cause of hospitalization as attributed by the CERC were analyzed by treatment and by analysis population.

Subgroup Analyses

Subgroup analyses, based on the Cox proportional hazards regression model used in the primary efficacy analysis, were performed for:

- Geographical region and country for subjects in the ITT population
- Males vs. females
- Older vs. younger age (below or equal to the median vs. above the median)
- Reduced LVEF (≤ 35%) vs. "preserved" LVEF (> 35%)
- Diabetes vs. no diabetes
- Prior MI vs. no prior MI
- Maximum tolerated dose - if maximum tolerated dose was missing or if the subject prematurely discontinued treatment, then the last dose dispensed was used
- Creatinine below the median vs. creatinine above the median

These subgroup analyses were performed using descriptive statistics, Kaplan-Meier estimates, and the results based on the Cox proportional hazards regression model used in the primary efficacy analysis. All time-to-event variables were summarized by descriptive statistics and analyzed according to the statistical models described in the primary analysis. For the subgroup reduced vs. preserved LVEF, the statistical model described in the sensitivity analysis were also run.

Safety Analyses

All safety analyses were based on the ITT population. The baseline for each safety parameter was defined as the value at Visit T0 (before intake of the first dose of double-blind study drug).

Clinical laboratory test values, vital sign values, and ECG values were considered potentially clinically significant (PCS) if they met either the low or the high PCS criteria listed in Tables 11.2-1, 11.3-1, 11.4-1 of the Forest Report SAP. The number and percentage of subjects with PCS post-baseline values were tabulated by treatment group. The percentages were calculated relative to the number of subjects with available non-PCS baseline values and at least one post-baseline assessment. The numerator was the total number of subjects with at least one PCS post-baseline value.

AEs in the Menarini Report were coded using Medical Dictionary for Regulatory Activities [MedDRA] Version 4.

The safety analyses (except ECHO, vital signs, and ECG data) were stratified overall, for subjects on drug, and for the following study phases:

- Up-titration period: Between first medication intake and date of dose-fixation (or start of down-titration for subjects terminating study medication before dose fixation).
- Maintenance period: Between date of dose-fixation and EOP visit (or start of down-titration for subjects terminating study medication before EOP).
- Down-titration period: Between EOP visit (or start of down-titration for subjects terminating study medication before EOP) and last intake of study medication.
- Final Follow-up period: Between last intake of study medication and FFU visit (one month after last study drug intake) or date of study discontinuation.

Previous and Concomitant Diseases

Previous and concomitant diseases were coded using the MedDRA.

Previous and Concomitant Medication

Previous and concomitant medications were coded according to the World Health Organization-Anatomical Therapeutic Chemical (WHO-ATC) classification. Data were stratified both by treatment and by study phase (up-titration phase, maintenance phase, merged down-titration and FFU phase), assigning a medication to the study phase according to the starting date of intake. Absolute and relative frequencies were displayed for 1st and 3rd level.

Adverse Events

AEs were coded using MedDRA. Data were stratified by treatment and study phase assigning an event to the study phase according to the starting date of the event. Absolute and relative frequencies were displayed for preferred term and system organ class [SOC]. Furthermore, AEs were displayed overall and stratified by study phase for intensity (mild, moderate, and severe), relationship to study medication (not related, related), AEs leading to discontinuation of study medication (yes, no), seriousness (yes, no), and study phase (up-titration phase, maintenance phase, down-titration phase, FFU phase). SAEs that were not primary and/or secondary outcomes were analyzed analogously. All CE's occurring after the EEE were considered to be AE's.

Furthermore, AE's were stratified as occurring before/after 6 weeks of the first intake of study medication, and before/after 1 year of the first intake of study medication. In addition, AE's that occurred while subjects were on drug were presented.

Laboratory values were categorized as either normal, abnormal but not clinically significant, and abnormal and clinically significant. Laboratory values were flagged as "normal" or "abnormal" based on central laboratory reference ranges. Any abnormal value was categorized as "clinically significant" or "not clinically significant" per the investigator's judgment. The behavior over time was also presented using basic statistics and shift tables.

Extent of Exposure

The extent of exposure (days) was presented overall, by study phase (up-titration, maintenance, down-titration), and by maximum tolerated dose. The number of subjects was presented by both maximum tolerated dose and average treatment dose by titration visit and for every 3 month-interval of the observation period. Compliance (%) was presented overall, for the first 12 months after randomization, by study visit, and by age, sex, baseline LVEF, and maximum tolerated dose.

Interim Analyses

The DSMC undertook 4 formal interim analyses, when approximately 25%, 50% and 75% of the total anticipated patient-years of follow-up had accrued, and after a minimum of 6 months observation for all subjects had occurred (i.e. the minimum observation period as stated in the original study protocol, prior to Amendment No. 4). The study aimed to recruit 2000 patients over 2 years, with an average follow-up of 18 months, yielding a total of 3000 patient-years of observation.

However, of these 4 interim analyses, only the first three were pre-specified in the DSMB Charter: the fourth interim analysis was not pre-specified

Figure 4: Only the first 3 Interim Analyses were pre-specified…

> 3. The DSMC will undertake 3 formal interim analyses, when approximately 25%, 50% and 75% of the total anticipated patient-years of follow-up have accrued. The trial aims to recruit 2000 patients over 2 years, with an average follow-up of 18 months, yielding a total of 3000 patient-years of observation. Thus the interim analyses will occur at approximately 750, 1500 and 2250 patient-years of follow-up (that is, about 1.2, 1.7 and 2.1 years respectively after recruitment begins).

[Source: SENIORS DSMC: Summary of Guidelines and Procedures, Appendix 16.1.9a]

Thus, the first 3 interim analyses occurred at approximately 750, 1500, and 2250 patient-years of follow-up (approximately 1.2, 1.7, and 2.1 years, respectively, after recruitment began).

In order to detect very large early differences without any significant impact on the traditional significance level of 0.05 (at least approximately) at the end of the trial, the significance levels were adjusted following a "Peto design"[iii] to assure an overall significance level of 0.05. Given

iii Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient, I: introduction and design. Br. J Cancer 1976; 34(6): pp. 585-612.

the addition of a fourth interim analysis, the significance level used in the final analysis was 0.048 instead of 0.049.

The interim analyses were performed by an independent statistician, who worked in conjunction with the DSMC statistician in order to provide appropriate tabulations and analyses for the DSMC. Any unblinding of study data had to be requested by the DSMC and could only be performed by the independent statistician.

These interim analyses were restricted to the primary and main secondary time-to-event outcomes and were performed for the ITT population only.

Access to the interim analyses reports were strictly limited to DSMC members and were thus not available to the sponsor or the CRO. Recommendations by the DSMC based on these analyses, however, were provided to the SC, but were done without breaking the SC's blind conditions.

The following data were object of interim DSMC review:

1. Descriptive analyses

- Monthly recruitment, and cumulative recruitment to the trial
- Numbers of subjects (%) by categories of age, sex, country, LVEF group, and NYHA class, by treatment group and overall
- Mean age (SD, minimum, and maximum), by treatment group and overall
- Numbers of subjects (%) by categories of the observation period, by treatment group and overall
- Mean duration of the observation period (SD, minimum, and maximum), by treatment group and overall

2. Analyses for the primary outcome

- Numbers (%) of outcomes, by treatment group and overall
- KM plots of time to outcome, by treatment group and overall, sub-labeled with the number of subjects at risk
- The estimated KM event rates at 6, 12, 18 and 24 months, by treatment group and overall
- Cox regression analysis by treatment group, giving hazard ratio, 95% CI, and p value
- KM plots of time to outcome, by treatment group and overall, sub-labeled with the number of subjects at risk, separately for the two LVEF groups
- A comparison of the treatment effect hazard ratio between the two LVEF groups, using a test for interaction in the Cox regression model
- Numbers (%) of outcomes, according to whether adjudicated or not, by treatment group and overall

With regard to the presence of firewalls implemented for these interim analyses to maintain trial blinding – the sponsor states that Dr. Anthony (Tony) Brady (the SENIORS independent statistician) confirmed that he "*functioned independently; that appropriate firewalls were implemented and adhered to; that interim analyses reports were not available to the sponsor, the CRO, or the SC; that*

access was strictly limited to DSMC members; and that the recommendations by the DSMC based on the analyses were provided to the SC in a separate communication, without breaking the SC's blinding."
[From pg 94, Volume 1 of the Forest SENIORS Study Report]

Reviewer's Comments: *Only the first 3 interim analyses were pre-specified, the fourth analysis was not pre-specified.*

Determination of Sample Size

Sample Size Assumptions

In the control group of the MERIT-HF trial, the estimated annual mortality rate for those ≥ 70 years with HF and LVEF < 40% was 13% in the first year, which was approximately one fifth higher than that of the overall trial population. In CIBIS-II [Cardiac Insufficiency Bisoprolol Study II], the all-cause mortality rate in the control group irrespective of age in the first year was 13%. In the SENIORS trial, given that the average age was expected to be 75 years, an all-cause mortality rate of 15% per year in subjects with LVEF ≤ 35% was estimated. In the preserved LVEF subgroup (those with LVEF > 35%), the mortality rate was estimated to be 10% per year.

The hospital admission rate for HF in CIBIS-II was approximately 14% in the first year (average age 61 years). All-cause hospital admission rates rose steeply with age, and approximately half of all admissions in the elderly were a result of cardiovascular causes. Thus, hospital admission rates for cardiovascular causes in SENIORS was estimated to be 20% per year in the low LVEF group, and about 15% in the preserved LVEF subgroup.

The composite outcome of all-cause mortality and cardiovascular hospital admission was estimated to occur in 30% of subjects per year in subjects with low LVEF, and in 20% of those with preserved LV function. Thus, if the proportions of subjects with low LVEF and preserved LV function entered into the trial were equal (50% in each stratum), the average expected event rate per year would be 25%.

The relative risk reduction in all-cause mortality in both CIBIS-II and MERIT was approximately 34%. The risk reduction for HF admissions in CIBIS-II was 36%. Thus, for each element of the primary outcome a similar risk reduction was expected. In SENIORS, the risk reduction was expected to be in the range of 25 to 30%.

The permanent withdrawal rate of treatment in both CIBIS-II and MERIT was 15% in the active treatment and control groups. Five percent was added to this withdrawal rate to account for non-compliance in the elderly, making the anticipated non-compliance rate 20% in total.

Sample Size Estimates

The sample size calculation was based on the composite outcome of all-cause mortality and cardiovascular hospital admission. The annual event rate was expected to be 25% in the placebo group. The recruitment period was 2 years with a minimum observation period of 0.5 year for the last included subject according to the original trial protocol. Under the assumption of uniform subject entry, the average observation period for an individual subject was to be 1.5 years. Therefore, the control group event rate was expected to be 37.5% for the duration of the trial. The risk reduction (risk reduction = 1-Hazard Ratio) of all-cause mortality and

cardiovascular hospital admission was assumed to be 0.25 for nebivolol treatment compared to placebo, and an overall non-compliance rate of 20% with no loss to observation period was to be expected. With a power of 90% and a two-sided alpha-level of 5%, a risk reduction of 25% could be detected with 1701 subjects (logrank test). Thus, a total of 2000 subjects (i.e. 1000 per treatment group) were to be enrolled.

Amendments to the SAP

Amendment 1 – made February 26th, 2009

This amendment outlines the additional analyses of the SENIORS trial for the Forest report dated July 28th, 2009. These additional analyses are:

- Additional subgroup analyses of subject disposition, demographics and baseline characteristics, adverse events, and clinical laboratory parameters by the presence or absence of diabetes.
- Analyses of certain secondary efficacy parameters (time to all-cause mortality, time to cardiovascular mortality, and time to cardiovascular hospital admission) for the Younger, Low Ejection Fraction Subgroup
- Analyses of efficacy parameters by geographical region and by country
- Revision of the Potentially Clinically Significant [PCS] criteria for clinical laboratory parameters

6.1.1.7 Data Safety and Monitoring Committee (DSMC)

An independent DSMC was established which regularly reviewed unblinded data, provided by an independent statistician (Tony Brady, Sealed Envelope Ltd., London, UK).

The members of the DSMC were:

Professor Alberto Zanchetti (Chairman)	Italy
Professor Basil Lewis	Israel
Professor Markku Nieminen	Finland
Professor Peter Sleight	United Kingdom
Professor Simon Thompson (Statistician)	United Kingdom

6.1.1.8 Clinical Event Review Committee (CERC)

A Clinical Event Review Committee (CERC) was established which was responsible for reviewing and adjudicating all clinical events (CEs) in the trial, i.e. deaths and hospital admissions.

The members of the Clinical Event Review Committee were:

Professor Kristian Thygesen (Chairman)	Denmark
Professor Michael Frenneaux	United Kingdom
Professor Gianfranco Sinagra (consultant)	Italy
Professor Michal Tendera	Poland
Ex-officio: Doctor Marcelo Shibata	Canada

Table 4: DSMC interim analysis meeting dates, analysis information, and timelines

Interim Analysis Meetings	Date of Meeting (Location)	Planned Study Timepoint of the Meeting and Actual Timepoint	Significant Issues Arising from the Meeting
Interim Analysis meeting	May 3rd, 2000 (London)	Prior to study initiation	----------
Finalization of Charter	June 6th, 2000	Prior to study initiation	----------
First analysis (blinded)	09/2/2001 (Stockholm)	Planned: 1000 subjects randomized Actual: 793 subjects randomized	▪ 793 subjects had been evaluated ▪ 81 subjects reached the primary endpoint ▪ The committee noted that cardiovascular mortality was very low. Based on this the meeting minutes states that *"the question was raised whether the inclusion criteria could be too loose, thus meaning that patients that are too well are included, for example in Ukraine."* ▪ No safety concerns were noted ▪ The committee recommended to the SC that *"it would be advisable to have a better proportion of patients recruited from Western and Eastern European countries"*
First interim analysis (unblinded)	03/05/2002	Planned: 25% accrual of anticipated patient years of follow-up (estimated to be 750 patient years) Actual: 1096 patients and 782.8 patient years of follow-up Analysis was repeated* due to missing data Actual: 1087 patients and 699.1 patient years of follow-up	▪ Part of the data originally provided by the CRO was incomplete, so the remaining data was requested by the DSMC and the analysis then repeated. ▪ No safety concerns were noted
Second interim analysis (unblinded)	11/16/2002 (Milan)	Planned: 50% accrual of anticipated patient years of follow-up (estimated to be 1500 patient years) Actual: 1614 patients and 1485 patient years of follow-up	
Third interim analysis (unblinded)	03/05/2003 (Milan)	Planned: 75% accrual of anticipated patient years of follow-up (estimated to be 2250 patient years) Actual: 2133 patients and 2143 patient years of follow-up	▪ No safety concerns were noted ▪ The committee reiterated *"its strong support to any plan of the steering committee to increase the power of the study by extending minimum follow-up from 6 to 12 months."* ▪ The DSMC wanted to *"receive information on how many patients have been re-challenged out of the large number withdrawn from randomized medication"*

*The repeat analysis was required because, per the sponsor's report, the dataset that had been supplied for this first unblinded interim analysis "*did not contain all events. In particular, deaths that occurred after a patient was hospitalized were missing.*"

[Source: Summarized from the Minutes of the DSMC Meetings, Appendix 16.1.9a]

Reviewer's Comments: *The DSMC, after the third interim analysis, reiterated to the Steering Committee "its strong support to any plan of the Steering Committee to increase the power of the trial by extending minimum follow-up from 6 to 12 months"*

Table 5: CERC Meeting Dates and Summary of Issues Arising During Meeting

Meeting Dates	Summary of Meeting Decisions and Adjudications Performed
08/29/2000	▪ In non-English spoken countries, only patient identification and the conclusion of the death report will be translated
09/03/2001	▪ As of August 1rst 844 patients were recruited and 169 events were reported ▪ Package of 30 events would be sent at a time for adjudication
01/19/2002	▪ Majority of Information Requests were made for Clinical Events caused by "worsening of heart failure", so it was decided that objective evidence for heart failure should be sent in at the time of the event ▪ A change in date between admission and discharge was decided to be adequate proof of a hospital stay of more than 24 hours, if not specified otherwise. ▪ "*It was decided by the CERC to modify the adjudication form (see enclosure) by completely deleting the option "bleeding" which can be found under "Cardiovascular". However, the CERC wishes to first receive the Steering Committee chairs' feedback on whether they may proceed in this way. The input leading to this decision is the discussion of a case of "Gastrointestinal bleeding from complete erosion of prepyloric antrum caused slight anaemia with dizziness; this led to admission". The members of the CERC would agree to classify this as a NON cardiovascular event, if it were not for the fact that the option bleeding is given under Cardiovascular.* " ▪ *"Two events occurring simultaneously: When two potential endpoints occur on the same day, (e.g. heart failure and arrhythmia or unstable angina and heart failure), how should these be adjudicated? Should they both be counted separately or should a list of hierarchy be established whereby one event suppresses the other?"* ▪ *"If also approved by the Steering Committee, in the context of acute myocardial infarction (AMI) and another event, e.g. heart failure or arrhythmias, the CERC will only count AMI as THE event. AMI will be given precedence (within a 4-week timeframe)."*
05/24/2002	▪ The CEs adjudicated as "no endpoint" may have to be re-considered by the CERC. ▪ The CEs adjudicated as "cardiovascular reason: bleeding" have to be re-considered by CERC ▪ CERC members would appreciate to receive more and better information (quantity and quality) in supportive documents from the Ukrainian centers ▪ CERC would like to have again clarification from SC whether planned (elective) non-cardiovascular hospital admissions (planned after randomization) have to be adjudicated. ▪ **CE Status:** "562 CEs have been reported, 313 CEs have completed documentation, 283 CEs have been sent to CERC and 205 CEs have been adjudicated, including the meeting on 05/24/2002."
06/10/2002	▪ If a patient dies within 24 hrs of hospitalization only the death should be reported as a CE ▪ *"Ukraine centers are not providing adequate data in about 1/3 of reported cases. For examples, patients dying in military hospitals can't have data retrieved."* ▪ *"Cases of sudden death are being classified as "unknown" due to lack of proper documentation. They feel that these cases should be cases of sudden death."* ▪ **CE Status:** "In the current meeting 60 CEs were assessed. One new CE was disclosed. For 54 cases agreement was found. For 4 cases further information was requested before adjudication is possible. For 2 cases supportive documents were missing. Five CEs were considered not to be an endpoint and were combined with another CE." ▪ **Currently** "603 CEs are reported, 376 have completed documentation. Of these 224 are adjudicated, for 28 CEs further information was requested. Five CEs were considered not to be an endpoint and were combined with other CEs in the same patient."
08/19/2002	▪ *"A case was discussed in which a patient was hospitalized due to acute MI, with death 8 days later. The CERC wonders whether this should be classified as one event (death) or as two separate events (hospitalization and death). This question was addressed to the Steering Committee. However, while waiting for a response it was agreed to handle these cases as two events.* "

	▪ **CE Status:** "In the current meeting 98 CEs were assessed. Two new CEs were disclosed within the meeting. For 70 cases agreement was found. For 2 cases further information was requested before adjudication is possible. Two cases need to go into next CERC meeting again due to missing information on B-Form. Five cases were re-adjudicated and for 19 cases the former adjudication was confirmed." ▪ **Currently** "708 CEs are reported, 491 CEs have complete documentation. Of these 353 are adjudicated, for 31 CEs further information was requested. 15 CEs were considered not to be an endpoint and were combined with other CEs in the same patient or lasted less than 24 hours."
12/05/2002	▪ **CE Status:** "In the current meeting 94 CEs were assessed. For 89 cases agreement was found. Four CEs were considered not to be an endpoint far prolongation of hospitalization. For one case further information was requested before adjudication is possible." ▪ **Currently** "906 CEs are reported, 652 CEs have complete documentation. Of. these 550 are adjudicated, for 17 CEs further information was requested. 21 CEs were considered not to be an endpoint and were combined with other CEs in the same patient or lasted less than 24 hours."
01/30/2003	▪ **During the meeting a question arose whether dementia should be adjudicated as cardiovascular events. This issue should be clarified with the Steering committee and their answer will be forwarded to the CERC members."* ▪ **CE status:** In the current meeting 113 CEs were assessed. For 106 cases agreement was found. Three cases had mistakes on Adjudication Forms and could not be considered as adjudicated after the meeting. Three CEs were considered not to be an endpoint. For four cases further information was requested before adjudication is possible. 17 cases were re-adjudicated in the meeting. ▪ **Currently** 1030 CEs are reported, 788 CEs have complete documentation. Of these 690 are adjudicated, for 18 CEs further information was requested by the CERC members. 26 cases were deleted as they are duplicates of other CEs or for other reasons.
05/21/2003	▪ **CE Status:** In the current meeting 121 CEs were assessed. For 119 cases agreement was found. Eight CEs were considered not to be an endpoint. For two cases further information was requested before adjudication is possible. 7 cases were re-adjudicated in the meeting. ▪ **Currently** 1345 CEs are reported, 989 CEs have complete documentation. Of these 895 are adjudicated, for 16 CEs further information was requested by the CERC members. 34 cases were deleted as they are duplicates of other CEs or for other reasons.
08/6/2003	▪ **CE status:** In the current meeting 108 CE's were assessed. For 90 cases agreement was found. Nine CE's were considered not to be an endpoint. For seven cases further information was requested before adjudication is possible, for two cases the adjudication was postponed. 6 cases were re-adjudicated in the meeting. ▪ Currently 1443 CE's are reported, 1178 CE's have complete documentation. Of these 1097 are adjudicated, for 19 CE's further information was requested by the CERC members. 40 cases were deleted as they are duplicates of other CE's or for other reasons.
01/22/2004	▪ *"It is no longer required to provide a separate CE report form for each case, like defined in the SAE/CE handling manual, if the investigator has reported two events on one CE report form."* ▪ *It should be asked twice for supportive documents in a timeframe of 4 weeks. Thereafter a case has to be closed, if the investigator did not provide the requested documents."* ▪ *"On the last CERC meeting the adjudication form should be supplemented at a new box named "not classifiable" to adjudicate cases without the relevant information."* ▪ *No information from the CRF pages should be used for the adjudication of an event.* ▪ **CE status:** In the current meeting 83 CE's were assessed. For 72 cases agreement was found. Ten CE's were considered not to be an endpoint. For one case further information was requested before adjudication is possible. 12 cases were re-adjudicated in the meeting. ▪ **Currently** 1749 CE's are reported, 61 of these cases with a start date ≥ 16.11.2003. 1459 CE's have complete documentation. Of these 1355 are adjudicated, for 10 CE's further information was requested by the CERC members. 56 cases were marked in the database as deleted as they are duplicates of other CE's or for other reasons. In total, 277 CE's with a start date up to 15.11.2003 remain to be adjudicated by the CERC members.
03/30/2004	▪ The procedure regarding the hospitalization and the death of a patient due to MI will be discussed at the next CERC meeting. It should be clarified whether these are two events or one event if a patient dies <28 days after the hospitalization. ▪ **CE status:** In the current meeting 55 CE's were assessed. For 49 cases agreement was found. Five CE's were considered not to be an endpoint. For one case the relevant documentation was requested

	before adjudication is possible. 4 cases were re-adjudicated in the meeting. ▪ **Currently** 1636 CE's are reported for adjudication (plus 62 cases, that were marked in the database as deleted as they are duplicates of other CE's or for other reasons and 85 cases with a start date ≥ 16.11.2003). 1543 CE's have complete documentation. Of these 1437 are adjudicated, for 8 CE's further information was requested by the CERC members. ▪ In total, 201 CE's with a start date up to 15.11.2003 remain to be adjudicated by the CERC members. 92 cases of these CE's have been adjudicated in the current meeting "without final result".
05/12/2004	▪ **CE status:** In the current meeting 144 CE's were assessed. Another 15 cases were re-adjudicated in the meeting. Of all CE's discussed, 139 cases were assessed as endpoints and twelve cases were considered as "not an endpoint". Three cases have been assessed as "not classifiable" due to the missing of relevant documents/information. Five cases need to be discussed again due to missing information or incorrect data on B-Form.
06/4/2004	▪ **Post Meeting Adjudication via phone:** 18 CE's were assessed. For all cases agreement was found.
07/1/2004	▪ **Post Meeting Adjudication via phone:** 12 CE's were assessed. For all cases agreement was found. ▪ **CE Status:** A total of 1637 cases have been finally adjudicated.

[Source: Summarized from Minutes of the CERC Meetings, Appendix 16.1.9a]

Table 6: Steering Committee Meeting Dates and Summary of Meeting Decisions

SC Meeting Dates	Summary of Meeting Decisions
06/5/2000	▪ Concerns raised regarding the withdrawal of nebivolol at the end of the study i.e. withdrawal and decision made to issue recommendations regarding withdrawal towards the end of the study ▪ *"Substantial evidence for benefits of beta blockers exists already"…"However, it was agreed that there was sufficient uncertainty of the balance of benefit and risk in patients aged more than 70 years and that a randomized trial was both ethically acceptable and clinically important. Furthermore there was no evidence of the effects of beta blocker in patients with clinical heart failure and preserved left ventricular function."* ▪ *"What would the proportion of patients in the impaired and preserved left ventricular function be?"…"It was assumed that a 50:50 split would be useful"* ▪
04/27/2001	▪ Currently randomized approximately one-fourth of the total planned subjects. ▪ 90% of those enrolled up until 04/24/01 were from Eastern Europe ▪ *"It seemed a common practice in Germany to prescribe beta blockers to patients with heart failure regardless of their age. The [SC] agreed that centres that have this practice and doctors who do not agree with the [study design] should be withdrawn from the study]"* ▪ 70 events up until 04/25/2001 ▪ Romania and France had the lowest and highest rate of events per patient randomized, respectively. ▪ "In the light of the results from CAPRICORN, all SC members decided that SENIORS should be continued." ▪ *"Admissions are defined as being in the hospital for at least 24 hours"* ▪ *"Arrhythmias in the presence of heart failure should be classified as a heart failure episode not an arrhythmic episode.* ▪ *"SC should have substantial control over data analysis."*
09/03/2001	▪ Enrollment at 844 up to 08/30/2001 ▪ *"83% of enrolled patients have reached maximum dose fixation rates…"* ▪ *"Clinical Event rates of death and prolongation of hospitalization were felt to be roughly on target for the total number of clinical endpoints expected with the total mean follow-up of 5.8 mths to date."* ▪ "*It has been noted that the high rates of hospitalization to death rates do not match planned expected rates and therefore may affect outcome of results. The breakdown of reasons for hospitalizations shows that most hospitalizations are due to worsening of heart failure with few hospitalizations for bradycardic events. Currently there are ~ 5:1 hospitalizations:deaths. This is likely to be a problem if it is due to the effect of Nebivolol on hospitalization but not on the death rate."*
04/29/2002	▪ "*Discussed the need to know [the] true dropout rates as this appears very high. Agreed that the CRO needs to be more vigilant about getting follow-up data from patients even if they are no longer taking the study medication."* ▪ *"Total annual mortality in SENIORS is currently 8%"* ▪ *"Discussed the lower than expected mortality rate and JSS suggested that this may be because patients who do*

	not have true heart failure may be enrolled in the study. Also expected mortality to be higher based on the age of the patients being enrolled in this study." ▪ *"Discussed the possibility of extra follow-up in order to have actual event rates closer to predicted event rates, and to have meaningful data at the completion of the study. BS stated that there was no need to change the length of the study for regulatory purposes. If a longer follow-up period is agreed [to] then regulatory authorities must be informed prior to the planned end of the study."* ▪ *"Also considered increasing the sample size."* ▪ *"LT discussed the risk of not reaching a positive result and that there is a large commitment with this study to reach a final conclusion, as this is the first study in the elderly with a population with preserved systolic function."* ▪ Enrollment at 1422 patients ▪ "*Discussed the high rate of 'dropouts'. Patients are withdrawing from the study as they no longer wish to take the study medication and do not want observation after stopping the study medication."*
09/03/2002	▪ Current enrollment at 1745 ▪ Study medication discontinued in 236 out of a total of 1553 patients (~ 12%); 50 due to death, 94 due to patient request, 6 lost to follow-up ▪ 736 clinical events reported, with 473 of them sent to the CERC and 377 already adjudicated. ▪ "*Currently combined outcome event rate (July data) is 23% (annualized) and death rate is 8.9% (annualized)…this was a lower death rate than expected and than has been shown in other beta-blocker trials, especially considering the elderly population enrolled in this trial."* ▪ *"Study end needs to be decided. There was agreement that increasing the observation period would increase the power of the study. Many SC members also recommended an extension to the recruitment period until February or March 2003."*
03/25/2003	▪ 2135 patients enrolled with the last patient enrolled 12/31/02 ▪ 3.5% lost to follow-up and 2.3% permanently discontinued study drug ▪ 1119 clinical events, out of which 710 have been adjudicated, and 232 deaths. ▪ "*DSMB Report:…support to increase the power of the study by extension of follow-up to 12 months…if follow-up is extended to 12 months for all patients enrolled then at least 576 composite events will occur, as planned by protocol."*
08/31/2003	▪ 2136 patients enrolled; 1443 clinical events with 1095 hospitalizations reported to date, of which 1079 have been adjudicated. 281 deaths reported to date. ▪ 16.7% (357) patients permanently discontinued study drug, of which 12.3% (263) reached the primary end point. ▪
06/14/2004	▪ 1561 events adjudicated by the CERC, 322 deaths and 1239 hospitalizations. ▪ 696 events (21.6% deaths and 78.4% hospitalizations) contributed to the primary composite outcome giving the study an estimated post hoc power of 95%. 54 SAE's were reported. ▪ Of the 2128 patients included in the ITT analysis, 172 had either not attended the EOP visit or experienced a primary outcome event. Of these, vital status data were confirmed in 76, with 96 patients without further information. In total, 250 patients had unknown vital status on 11/15/03, 172 of which the sponsor had tried to get ethical approval to obtain vital status (133 of these ethical approval requests were granted, 14 denied, and some were still pending). ▪ An amendment was made by the SC to change Handling of Withdrawals and Missing Values as below o Original: *"These data [data from patients who were lost to follow-up and for who vital status information was retrieved] will be considered only as additional information and will be listed and descriptively presented by treatment and overall. These cases of death will not be considered as clinical events in the primary analysis and, therefore, will not be adjudicated by the [CERC]. In addition, only the statistical model of the confirmatory analysis will be re-run for the all-cause mortality outcome on the ITT population including the collected additional information."* o Amendment recommended by the SC (to be decided by the Operations Committee): *"These data will be considered in the primary outcome as long as the information has been obtained from a reliable source and if the date of the death is available (or at the very least month and year of death)."*

[Source: Summarized from the Minutes of the Steering Committee Meetings, Appendix 16.1.9a]

Reviewer's Comments:

1. The primary endpoint, a composite of all-cause mortality and cardiovascular hospitalizations, was primarily driven by hospitalizations (at the conclusion of the study, the adjudicated clinical events contributing to the primary endpoint consisted of approximately 80% hospitalizations and 20% deaths).

2. An amendment was made sometime after 6/2004 to include the information on vital status for those subjects lost to follow-up in analysis of the primary endpoint. Prior to this, the plan was to only include this vital status information in descriptive analyses, and to not include it in the all-cause mortality component of the primary outcome. This constitutes a significant change made to the primary endpoint very late in the trial.

Figure 5: Note to File: Prolongation of the Trial by the Steering Committee

NOTE TO FILE

Dated March 25, 2003

Statement of the SENIORS Steering Committee
Issue: Prolongation of study

On March 25, 2003 the Steering Committee decided to increase the power of the study by prolongation of the minimum observation period for all patients from 6 to 12 months.
Furthermore, it was decided to make all efforts to reinforce compliance and whenever possible to restart study medication intake. Attempts are being made to obtain follow-up data for all patients who withdrawn the trial.

The decision was based on the recommendation of the Data Safety and Monitoring Committee given after the review of the data of the 3rd Interim Analysis (see encl.).

The prolongation of the study is in compliance with the SENIORS study protocol as mentioned in chapter 13.3 Prolongation of Study:
"The study can be prolonged by the Steering Committee until the study is adequately powered."

Professor P. Poole-Wilson
SENIORS Principal Investigator &
Co-Chair of SENIORS Steering Committee

Professor A. Coats
SENIORS Principal Investigator &
Co-Chair of SENIORS Steering Committee

[Source: From the Minutes of the Steering Committee Meetings, Appendix 16.1.9a]

Reviewer's Comments: *In this note to file, the Steering Committee notes that the decision to "increase the power of the trial by prolongation of the minimum observation period for all subjects from 6 to 12 months" was "based on the recommendation of the Data Safety and Monitoring Committee given after the review of the data of the 3rd Interim Analysis"*

6.1.1. Amendments to Protocol

Amendment 1: September 13, 2001

The objectives, procedures and analysis plan of the ECHO substudy is delineated in the first amendment. This substudy was performed on a subset of subjects to assess left ventricular structure and function using two-dimensional (2-D) ECHO. It involved 29 centers and enrolled 112 subjects. The protocol included 2-D and Doppler ECHO at baseline, at 6 months, and at 12 months post-randomization.

Amendment 2: April 30, 2002

The objectives, procedures and analysis plan of the neurohormonal substudy is delineated in the second amendment. This substudy enrolled 106 subjects and involved the collection of blood samples at baseline, at 6 months, and at 12 months post-randomization, and was done for the purpose of evaluating levels of neurohormones, cytokines, and other biomarkers. The biomarkers measured were: N-terminal prohormone of BNP (NT-ProBNP), tumor necrosis factor-alpha (TNF-A), endothelin-1, soluble Fas protein (sFas), atrial natriuretic peptide, uric acid, TNF-beta1 (TNF-B1), arginine, asymmetric dimethylarginine (ADMA), serum ADMA, citrulline, plasma norepinephrine, and Fas ligand.

Amendment 3: September 3, 2002

The third amendment stated that the echocardiograms for the ECHO substudy would be performed at baseline, at 6 months, and at either 12 months or study end of the SENIORS main study, whichever occurred earlier.

Amendment 4: May 26, 2003

The Steering Committee amended the protocol to extend the minimum observation period for all subjects from 6 to 12 months, in an attempt to increase the power of the trial. As a result of this amendment, the individual observation period changed from a range of 6 to 30 months to a new range of 12 to 40 months, and the expected average observation period changed from 18 months to 26 months.

The sponsor states that the protocol had allowed for such a change in its statement that "*the study can be prolonged by the SC until the study is adequately powered*". **[From pg 102, Volume 1 of the Forest SENIORS Study Report]**

Reviewer's Comments: *This amendment, which increased the minimum observation period for efficacy events from 6 to 12 months, thereby attempting to increase the power of the study, was done after the third of four total interim analyses had already occurred.*

Amendment 5: January 20, 2004

Following the request of the SC to obtain follow-up vital status information on all subjects who discontinued the trial prematurely, this amendment implemented a standardized protocol and form for obtaining this information on vital status (whether the subject was alive or not and, in case of death, the date of the death).

Amendment 6: May 18, 2004

Following the rejection of Amendment 5 in the United Kingdom, this amendment states the protocol for collecting vital status information using the British General Register Office.

6.1.2 Demographics

As can be seen in Table 7, Table 8, and Table 9, the subjects were nearly 100% Caucasian, had a low body mass index [BMI] compared to the US population, and 37% were female. With regard to their cardiac history, the subjects were primarily NYHA class II and III, had mean EF of 36% in both groups, and duration of heart failure was approximately 3 years. Three hundred and twelve subjects (14.7%) had an EF of 50 or greater. With regard to the etiology of the CHF, it was largely ischemic, and approximately 80% were on an ACE-Inhibitor.

Table 7: Reviewer's Table of Baseline Demographic Data for ITT Population

	Nebivolol (N=1067)	**Placebo** (N=1061)	**Total ITT** (N=2128)
Age (years)			
Mean ± SD	76.1 ± 4.8	76.1 ± 4.6	76.1 ± 4.7
Median	75.2	75.3	75.2
Range (Min,Max)	69.7, 92.7	69.4, 94.7	69.4, 94.7
Age category n (%)			
Age ≤ median (75.2)	539 (50.5%)	525 (49.5%)	
Age > median (75.2)	528 (49.5%)	536 (50.5%)	
Sex, n (%)			
Male	657 (61.6%)	686 (64.7%)	1343 (63.1%)
Female	410 (38.4%)	375 (35.3%)	785 (36.9%)
Race, n (%)			
N	1038	1030	2068
Caucasian	1031 (99.3%)	1028 (99.8%)	2059 (99.6%)
Black	3 (0.3%)	0 (0.0%)	3 (0.1%)
Asian	2 (0.2%)	0 (0.0%)	2 (0.1%)
Other	2 (0.2%)	2 (0.2%)	4 (0.2%)
Smoking Hx, n (%)			
N	1066	1061	2127
Smoker	52 (4.9%)	57 (5.4%)	109 (5.1%)
Ex-Smoker	355 (33.3%)	355 (33.5%)	710 (33.4%)
Non-smoker	659 (61.8%)	649 (61.2%)	1308 (61.5%)
BMI (kg/m²)			
N	1062	1055	2117

Mean ± SD	26.8 ± 4.2	26.7 ± 3.9	26.8 ± 4.0
Median	26.3	26.3	26.3
Range (Min,Max)	14.7, 45.7	15.0, 50.4	14.7, 50.4

[Source: Clinical Reviewer's Analysis]

Table 8: Reviewer's Table of Baseline History of CHF - ITT Population

	Nebivolol (N=1067)	**Placebo** (N=1061)	**Total ITT** (N=2128)
Subject Status, n (%)			2128
N	1067	1061	
Inpatient	150 (14.1%)	164 (15.5%)	314 (14.8%)
Outpatient	917 (85.9%)	897 (84.5%)	1814 (85.2%)
NYHA Class, n (%)			
N	1067	1061	2128
I	32 (3.0%)	29 (2.7%)	61 (2.9%)
II	603 (56.5%)	597 (56.3%)	1200 (56.4%)
III	413 (38.7%)	411 (38.7%)	824 (38.7%)
IV	19 (1.8%)	24 (2.3%)	43 (2.0%)
Duration of HF (yrs)			
N	783	788	1571
Mean ± SD	2.8 ± 3.4	3.0 ± 3.8	2.9 ± 3.6
Min, Max	0, 20	0, 25	0, 25
Median	2.0	2.0	2.0
LVEF (%)			
N	1058	1053	2111
Mean ± SD	36.0 ± 12.5	36.0 ± 12.1	36.0 ± 12.3
EF Category, n (%)			
N	1063	1058	2121
≤ 35%	683 (64.3%)	686 (64.8%)	1369 (64.5%)
> 35%	380 (35.7%)	372 (35.2%)	752 (35.5%)
Other Diagnoses			
N	1067	1061	2128
CAD	735 (68.9)	717 (67.6%)	1452 (68.2%)
Arrythmia	578 (54.2%)	606 (57.1%)	1184 (55.6%)
Hyperlipidemia	490 (45.9%)	484 (45.6%)	974 (45.8%)
Hypertension	652 (61.1%)	660 (62.2%)	1312 (61.7%)
Diabetes Mellitus	287 (26.9%)	268 (25.3%)	555 (26.1%)
MI	467 (43.8%)	463 (43.6%)	930 (43.7%)

[Source: Clinical Reviewer's Analysis]

Table 9: Etiology and Treatment of Heart Failure

	Nebivolol (N=1067)	**Placebo** (N=1061)	**Total ITT** (N=2128)
Etiology of CHF, n (%)			
N	1066	1061	2127
Ischemic	797 (74.8%)	785 (74.0%)	1582 (74.4%)
Ischemic + ID Cardiomyopathy	3 (0.3%)	7 (0.7%)	10 (0.5%)
Ischemic + Other	12 (1.1%)	17 (1.6%)	29 (1.4%)
ID Cardiomyopathy	162 (15.2%)	157 (14.8%)	319 (15.0%)
ID Cardiomyopathy + Other	1 (0.1%)	3 (0.3%)	4 (0.2%)
Other	91 (8.5%)	92 (8.7%)	183 (8.6%)
Medications Used for CHF, n (%)			
N	1067	1061	2128
Any medication	1058 (99.2%)	1052 (99.2%)	2110 (99.2%)
ACE Inhibitor	872 (81.7%)	876 (82.6%)	1748 (82.1%)
Angiotensin Receptor Blocker	66 (6.2%)	75 (7.1%)	141 (6.6%)
Aldosterone Antagonist	307 (28.8%)	280 (26.4%)	587 (27.6%)
Antiarrhythmic	122 (11.4%)	145 (13.7%)	267 (12.5%)
Cardiac Glycoside	415 (38.9%)	422 (39.8%)	837 (39.3%)
Diuretic	915 (85.8%)	907 (85.5%)	1822 (85.6%)
Other	353 (33.1%)	396 (37.3%)	749 (35.2%)
Prior Revascularization, n (%)			
N	1067	1061	2128
CABG	87 (8.2%)	87 (8.2%)	174 (8.2%)
CABG + PTCA/Stent	13 (1.2%)	7 (0.7%)	20 (0.9%)
CABG + Other	1 (0.1%)	0 (0.0%)	1 (0.0%)
PTCA/Stent	34 (3.2%)	27 (2.5%)	61 (2.9%)
Other	6 (0.6%)	4 (0.4%)	10 (0.5%)

Note: **ID Cardiomyopathy:** **Idiopathic Dilated Cardiomyopathy**
CABG: **Coronary Artery Bypass Graft**
PTCA: **Percutaneous Transluminal Coronary Angioplasty**

[Source: Adapted from Sponsor's Tables, pg 118-119, Volume 1 of the Forest Study Report]

Reviewer's Comments: *Approximately 95% of the trial population had CHF of NYHA class II and III. No imbalances in baseline characteristics were observed.*

6.1.3 Subject Disposition

2135 subjects in total were enrolled in the trial, in 198 centers in 11 European countries. The first subject was enrolled on September 12, 2000, and the last subject completed the trial on

March 12, 2004. Of these subjects, 7 were excluded from the ITT population (6 subjects from center 429, which was excluded due to extensive compliance issues, and 1 subject who never took any study medication and thus never completed the randomization for the trial), leaving 2128 subjects in the ITT population. Subject disposition can be seen in Figure 6.

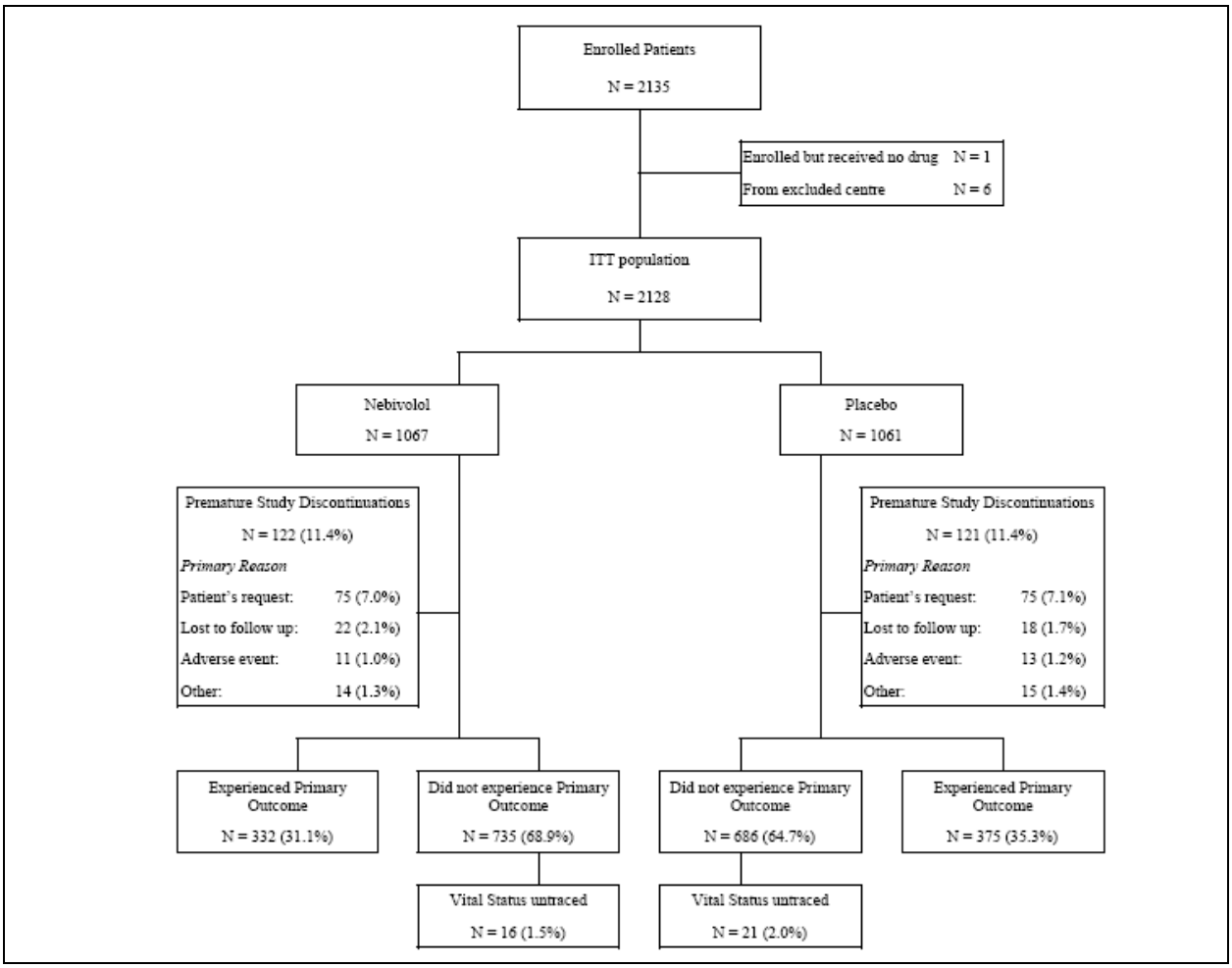
Of these 2128 ITT subjects, 243 subjects (11.4%) prematurely discontinued the trial before the EOP visit for reasons other than "death" – 122 (11.4%) of these were in the nebivolol group and 121 (11.4%) were in the placebo group. The most common reason for premature discontinuation was "patient's request", which was the reported reason for 75 subjects (7.0%) in the nebivolol group and 75 subjects (7.1%) in the placebo group.

Mean duration of follow-up was 20.4 months in the nebivolol group and 19.9 months in the placebo group.

Of the subjects randomized to nebivolol, 332 (31.1%) experienced a primary outcome (death or cardiovascular hospitalization) during the observation period, while 725 subjects (68.9%) did not. In the placebo group, 375 subjects (35.3%) experienced a primary outcome, leaving 686 (64.7%) who did not do so.

Of the subjects who prematurely discontinued the trial prior to experiencing a primary outcome, 16 subjects in the nebivolol group and 21 in the placebo group were left with unknown vital status data due to the unsuccessful attempts (often repeated attempts at contacting the subject, relatives, or healthcare personnel, or reviewing national death registers or practice reports) at obtaining the information, and were thus termed "untraced".

Figure 6: Disposition of subjects



[Sponsor's Figure, pg. 103, Volume 1 of the Forest SENIORS Study Report]

Reviewer's Comments: *Of the 2128 subjects in the ITT, 243 (11.4%) prematurely discontinued the trial before the EOP visit for reasons other than "death" [122 (11.4%) in the nebivolol and 121 (11.4%) in the placebo arms]. The most common reason for premature discontinuation was "patient's request", which was balanced at 75 subjects (7.0%) in the nebivolol group and 75 subjects (7.1%) in the placebo group.*

The treatment allocation code was unblinded for issues of medical necessity for a total of seven subjects, of which two had recurrent atrial fibrillation, two had general deterioration of health status, one subject had an MI, syncope and hypotension, and one subject had abdominal pain, vomiting, and altered liver function, all of whom were found to be on placebo, and one nebivolol-treated subject who sustained bilateral thigh amputation.

Subjects withdrawing from the trial prematurely were divided into those who discontinued from the trial prematurely and those who discontinued permanently from the trial drug treatment. Premature trial and treatment discontinuations are presented in Figure 7.

Figure 7: Premature Study and Treatment Discontinuations

Premature **Study** Discontinuations (including deaths)

Nebivolol Treatment (N = 1067)
n = 273 (25.6%)

Primary reason	
Patient's request:	75 (7.0%)
Lost to follow-up:	22 (2.1%)
Adverse event:	11 (1.0%)
Death:	151 (14.2%)
Other:	14 (1.3%)

Data obtained from final follow up visit/study end CRF (page 99).
Source: Appendix 16.2.1, Table 1.3.2.

Premature **Treatment** Discontinuations (including deaths)

Nebivolol Treatment (N = 1067)
n = 374 (35.1%)

Primary reason	
Patient's request:	110 (10.3%)
Intolerance to lowest dose:	24 (2.2%)
Clear contraindication to beta-blockers:	47 (4.4%)
Mandatory indication for beta-blockers:	17 (1.6%)
Death:	89 (8.3%)
Other:	83 (7.8%)
Unknown:	4 (0.4%)

Data obtained from premature permanent study drug discontinuation CRF (page 72) and adverse event CRF (pages 78-89)
Patients permanently discontinuing study medication were to be observed until the end of the study.
Source: Appendix 16.2.1, Table 1.3.1

Premature **Study** Discontinuations (including deaths)

Placebo Treatment (N = 1061)
n = 289 (27.2%)

Primary reason	
Patient's request:	75 (7.1%)
Lost to follow-up:	18 (1.7%)
Adverse event:	13 (1.2%)
Death:	168 (15.8%)
Other:	15 (1.4%)

Data obtained from final follow up visit/study end CRF (page 99).
Source: Appendix 16.2.1, Table 1.3.2.

Premature **Treatment** Discontinuations (including deaths)

Placebo Treatment (N = 1061)
n = 380 (35.8%)

Primary reason	
Patient's request:	123 (11.6%)
Intolerance to lowest dose:	8 (0.8%)
Clear contraindication to beta-blockers:	29 (2.7%)
Mandatory indication for beta-blockers:	32 (3.0%)
Death:	119 (11.2%)
Other:	67 (6.3%)
Unknown:	2 (0.2%)

Data obtained from premature permanent study drug discontinuation CRF (page 72) and adverse event CRF (pages 78-89).
Source: Appendix 16.2.1, Table 1.3.1.

[Source: Sponsor's Figure, pg. 107, Volume 1 of the Forest SENIORS Study Report]

Subject Disposition by Subgroup

For all the subgroups analyzed, the most common reason for premature discontinuation from the study was "death" and the second most common reason was "patient's request to leave the study."

Protocol Violations

116 subjects (5.5%), with 51 (4.8%) in the nebivolol group and 65 (6.1%) in the placebo group, had major protocol violations, the most common of which was the intake of "prohibited concomitant medication" (such as another beta-blocker).

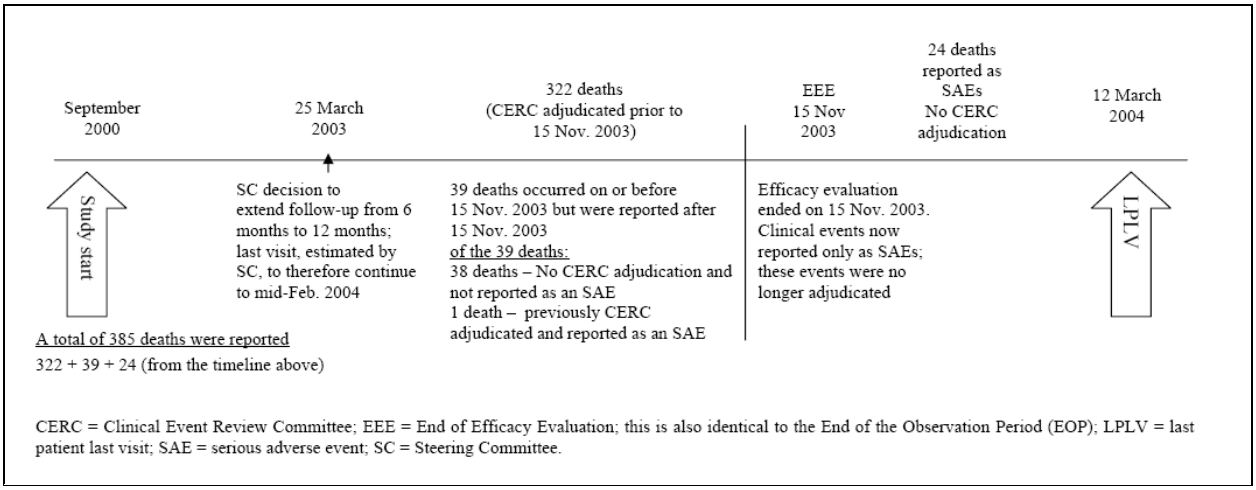
6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Populations to be Analyzed for Efficacy Data

As shown earlier, 2135 subjects were enrolled in the trial, of which 7 were excluded from the ITT population, leaving 2128 subjects in the final ITT group. Of these 2128 ITT subjects (1067 in the nebivolol group and 1061 in the placebo group), 2012 subjects (1016 in the nebivolol arm and 996 in the placebo arm) provided post-randomization data and had no major protocol violations (thus being termed the "Per Protocol", or PP, group).

The final statistical analysis plan, or SAP, was dated July 2004, and included a sensitivity analysis to be done in a "larger" PP population which was to include not only those in the PP population above but also those who committed major protocol violations after experiencing the primary outcome. This larger PP population comprised 2067 subjects, of which 1040 were in the nebivolol arm and 1027 were in the placebo arm.

Figure 8: Timeline of deaths in relation to the trial initiation and completion dates



[Source: pg 11, Volume 1 of the Forest SENIORS Study Report]

6.1.4.2 Analysis of Efficacy

As can be seen in the timeline in Figure 8, the first subject was enrolled in the trial on September 12, 2000 and the last date of follow-up (Last Patient Last Visit, or LPLV) was March 12, 2004. Over the course of these nearly four years, numerous changes were made that effect the efficacy analyses and deserve mention.

The original SENIORS protocol was designed to follow all subjects for a minimum of 6 months, thus resulting in the trial being completed after the last subject finished this 6 month observation period. However, after the second interim analysis, on September 3, 2002, the Steering Committee brought up the question of whether to increase this duration of follow-up (Figure 9).

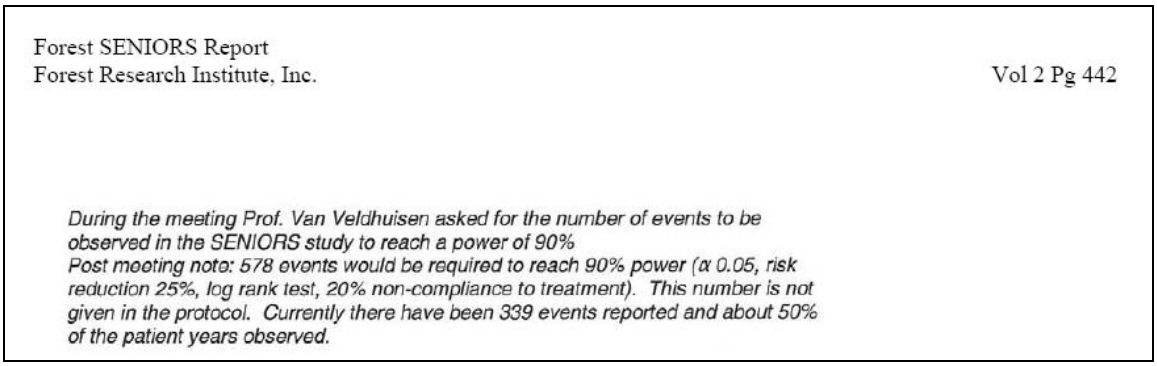
Figure 9: From the Steering Committee Minutes…..

> …Study end needs to be decided. There was agreement that increasing the observation period would increase the power of the study. Many SC members also recommended an extension to the recruitment period until February or March 2003….

[Source: Summarized from the Minutes of the Steering Committee Meetings, Appendix 16.1.9a]

The purpose of such a change, per their report, was to 'increase the power of the study' (Please refer to Figure 5 for the Note to File from the Steering Committee). Per their own post-meeting notes, however, they had calculated that a total of 578 events would be required to achieve 90% power (Figure 10). By this time, approximately 50% of the trial had been completed, and they had accumulated 339 events, which is more than 50% of the events needed to achieve 90% power (578 divided by 2 yields 289 events; thus, they already had more events, at 339, than the number that would be "required" [for 90% power] at the half-way point of the trial – 289 events). Therefore, the trial was well on its way to having an adequate number of events to reach the desired 90% power by the end of the trial as it was already designed (i.e. with the 6 month follow-up period as originally delineated). Yet, the Steering Committee nevertheless decided to increase the duration of follow-up from 6 months to 12 months, but their reasoning, i.e. to increase power, did not make sense given the facts (i.e. number of events). This was the first major change in the trial.

Figure 10: Notes of the Steering Committee – Events required to achieve 90% power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During the meeting Prof. Van Veldhuisen asked for the number of events to be observed in the SENIORS study to reach a power of 90%
Post meeting note: 578 events would be required to reach 90% power (α 0.05, risk reduction 25%, log rank test, 20% non-compliance to treatment). This number is not given in the protocol. Currently there have been 339 events reported and about 50% of the patient years observed.

[Source: Summarized from the Minutes of the Steering Committee Meetings, Appendix 16.1.9a]

The protocol as was originally written specified that the principle analysis would not include adjustments for covariates for the primary endpoint, and that an adjusted analysis would be used only as a sensitivity analysis (Protocol dated May 5, 2000). In the later version of the statistical analysis plan, dated July 9, 2004, this primary analysis was changed to include adjustment for the covariates of age, sex, and LVEF. This was the second of these changes.

Figure 11: Statistical Plan Revisions regarding Adjustment for covariates

Statistical Analysis Plan – May 5, 2000
"The primary outcome, 'all-cause mortality and cardiovascular hospital admissions', will be analyzed in a confirmatory manner. The principal analysis of the trial will be the Cox Proportional Hazards Regression Model with a single treatment group covariate."

Statistical Analysis Plan – July 9, 2004
"The primary outcome 'all-cause mortality or cardiovascular hospital admission' will be analyzed in a confirmatory manner. The principal analysis of the trial will be the Cox proportional hazards regression model with treatment as major covariate adjusted by age, sex and LVEF in compliance with CPMP/EWP/2863/99. Age and LVEF covariates will be inserted in the model as continuous variables."

[Source: Statistical Plan, SENIORS]

The sponsor states that the reason for this modification was a guideline from the European Agency for the Evaluation of Medicine Products (EMEA) Committee for Proprietary Medicinal Products (CPMP) on "points to consider on adjustment for baseline covariates" (Issued 22 May 2003). The sponsor states that the change to using the adjusted analysis as the principle analysis and the unadjusted analysis as a sensitivity analysis was made in compliance with this guideline.

The third major change in the trial was the means by which deaths were captured for the primary endpoint. It had been decided in 2002 that subjects who had 'dropped out' of the trial and were lost to follow-up would be contacted by the local investigators, with the purpose of finding out their 'vital status" – whether or not they were alive (Figure 12). "The investigator will contact by phone all subjects who prematurely terminate the trial or subjects who were

lost to follow up. During the phone call the investigator will obtain information on the vital status of the subjects and fill in this information in a questionnaire…" In the United Kingdom, due to issues with the ethics committees regarding such procedures, the protocol was modified to allow for the investigator to "contact the General Register Office…and ask for death certificates for all subjects who prematurely terminate the trial or subjects who were lost to follow up. The date of the death will be used for the vital status analysis." If no certificate could be provided for a subject by the General Register Office the vital status of these subjects would then be documented as "alive".

Figure 12: Collection of vital status information

April 29, 2002 Steering Committee Minutes

Discussed the high rate of 'dropouts'. Patients are withdrawing from the study as they no longer wish to take the study medication and do not want observation after stopping the study medication. Agreed that as much information as possible needs to be obtained from these patients and most would be likely to respond to a telephone call. SJ to ensure monitors will get study site co-ordinators to make efforts to contact these 'dropouts'. This is also the same for those patients who have gone on to open label beta-blockers.

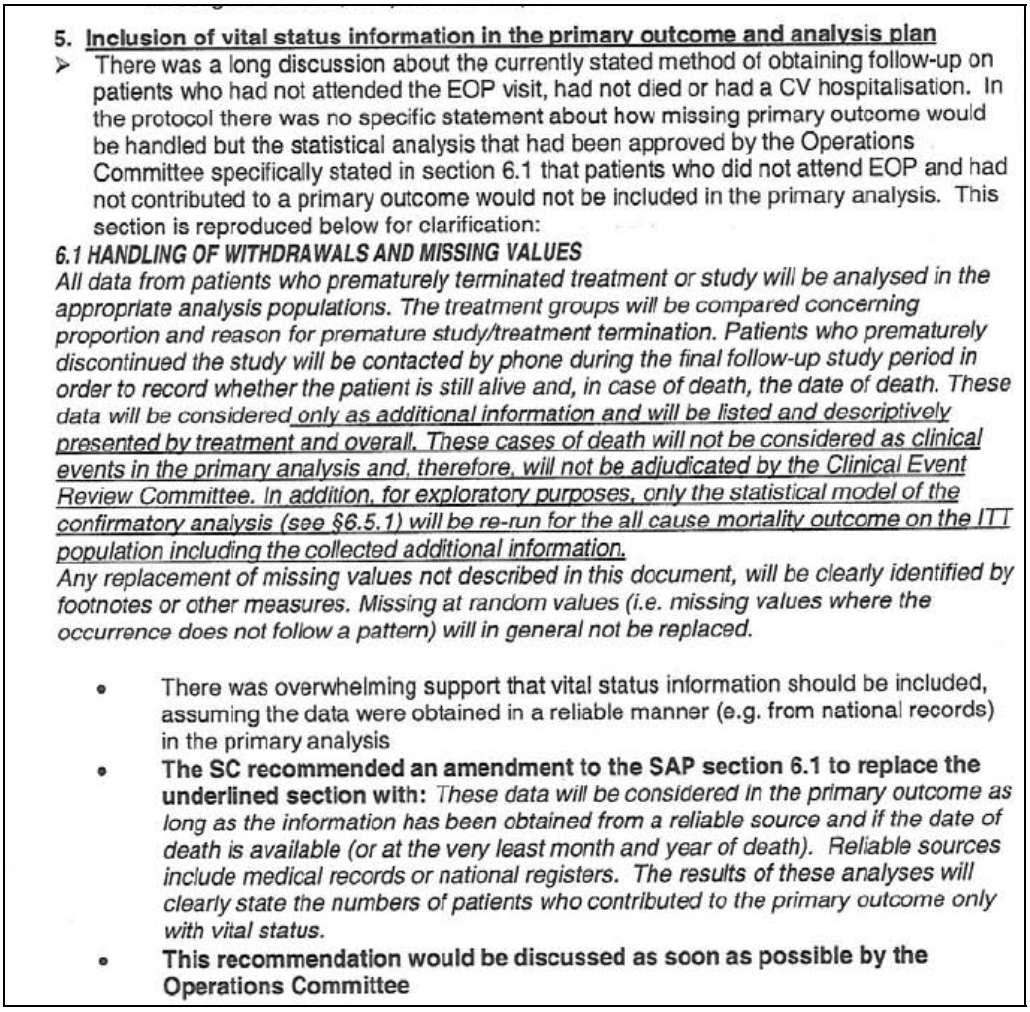
September 3, 2002

Agreed that follow up data needs to be obtained from more patients who have 'been lost' to follow up and that all local investigators have a responsibility to assist the monitors with this. Agreed that monitors are to contact the local Investigators to obtain this information

[Source: Summarized from the Minutes of the Steering Committee Meetings, Appendix 16.1.9a]

Initially, however, it had been decided that this vital status information ["data from patients who were lost to follow-up and for who vital status information was retrieved"] would be "considered only as additional information and will be listed descriptively presented by treatment and overall. These cases of death will not be considered as clinical events in the primary analysis and, therefore, will not be adjudicated…" It was subsequently decided, in 2004, that these deaths would be captured in the primary endpoint. These additional deaths in the all-cause mortality component of the primary endpoint constituted a significant modification to the definition to the primary analysis (Figure 13).

Figure 13: Handling of vital status information in the primary outcome and analysis plan



5. Inclusion of vital status information in the primary outcome and analysis plan

- There was a long discussion about the currently stated method of obtaining follow-up on patients who had not attended the EOP visit, had not died or had a CV hospitalisation. In the protocol there was no specific statement about how missing primary outcome would be handled but the statistical analysis that had been approved by the Operations Committee specifically stated in section 6.1 that patients who did not attend EOP and had not contributed to a primary outcome would not be included in the primary analysis. This section is reproduced below for clarification:

6.1 HANDLING OF WITHDRAWALS AND MISSING VALUES

All data from patients who prematurely terminated treatment or study will be analysed in the appropriate analysis populations. The treatment groups will be compared concerning proportion and reason for premature study/treatment termination. Patients who prematurely discontinued the study will be contacted by phone during the final follow-up study period in order to record whether the patient is still alive and, in case of death, the date of death. These data will be considered only as additional information and will be listed and descriptively presented by treatment and overall. These cases of death will not be considered as clinical events in the primary analysis and, therefore, will not be adjudicated by the Clinical Event Review Committee. In addition, for exploratory purposes, only the statistical model of the confirmatory analysis (see §6.5.1) will be re-run for the all cause mortality outcome on the ITT population including the collected additional information.

Any replacement of missing values not described in this document, will be clearly identified by footnotes or other measures. Missing at random values (i.e. missing values where the occurrence does not follow a pattern) will in general not be replaced.

- There was overwhelming support that vital status information should be included, assuming the data were obtained in a reliable manner (e.g. from national records) in the primary analysis
- **The SC recommended an amendment to the SAP section 6.1 to replace the underlined section with:** *These data will be considered in the primary outcome as long as the information has been obtained from a reliable source and if the date of death is available (or at the very least month and year of death). Reliable sources include medical records or national registers. The results of these analyses will clearly state the numbers of patients who contributed to the primary outcome only with vital status.*
- **This recommendation would be discussed as soon as possible by the Operations Committee**

[Source: Summarized from the Minutes of the Steering Committee Meetings, Appendix 16.1.9a]

Reviewer's Comments: *There were several changes made to the protocol during the course of the trial, including extension of the minimum follow-up period from 6 months to 12 months, adjustment of the primary endpoint for covariates of age, sex, and LVEF, and, finally, adding the deaths collected by phone call/inquiry to the all-cause mortality component of the primary endpoint.*

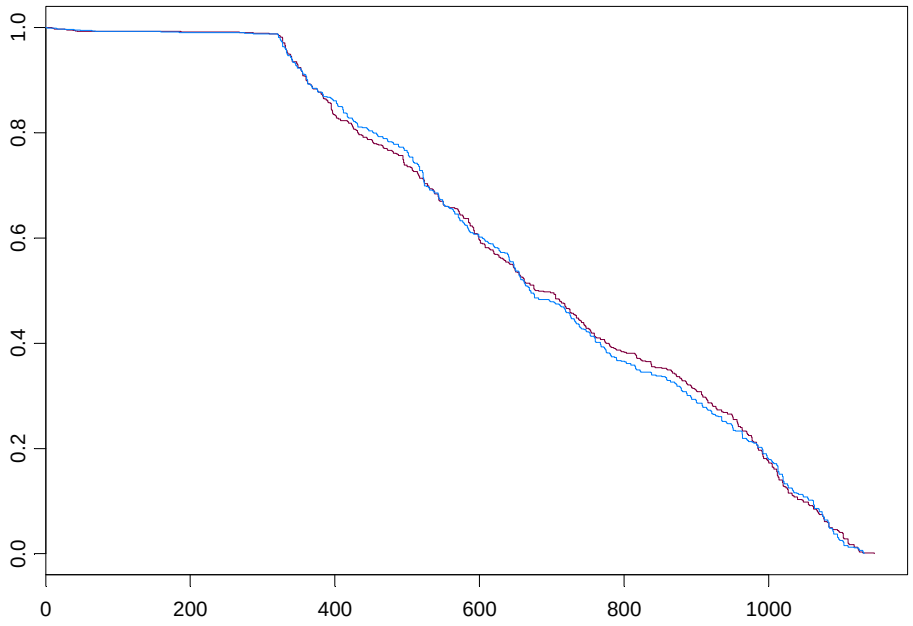
6.1.4.3 Analysis of Primary Endpoint

The primary endpoint was the composite of time to all-cause mortality or first cardiovascular hospitalization analyzed by the Cox proportional hazard regression model adjusted for age, sex and baseline LVEF. The subjects censored were those that did not experience an event during the course of the trial.

Almost all subjects were followed for mortality until the end of the trial, which was a minimum of 12 months for those randomized late during the course of the trial. The censoring

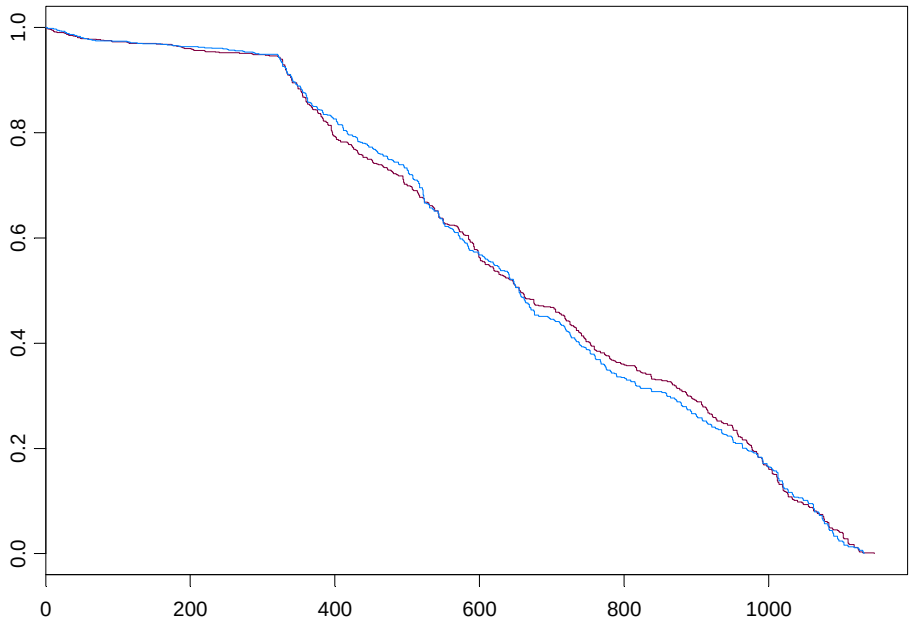
distribution for the primary endpoint (censored at the time of censoring for mortality if later than censoring for hospitalization) and the censoring distribution for hospitalization can be seen in Figure 15 and Figure 19. Nearly 10% of subjects in both groups were censored for CV hospitalization within 12 months.

Figure 14: Censoring distribution for the primary endpoint in the nebivolol and placebo groups (X-axis is represented in days)



[Source: FDA Statistical Reviewer's Analysis]

Figure 15: Censoring distribution for CV hospitalization in the nebivolol and placebo groups (X-axis represented in days)



[Source: FDA Statistical Reviewer's Analysis]

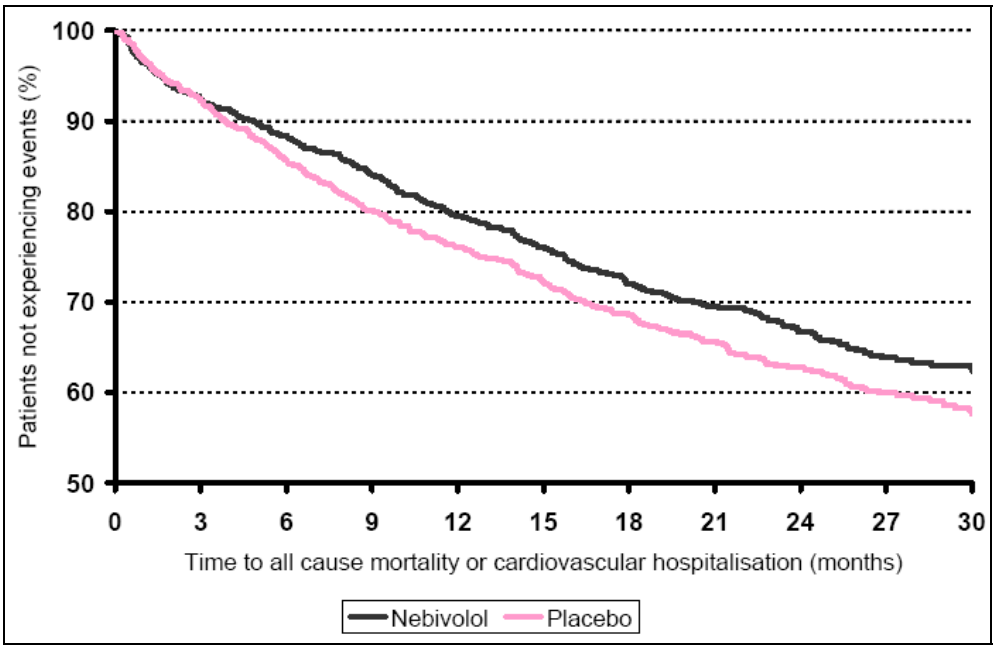
In the ITT population, 332 subjects in the nebivolol group (31.1%) and 375 subjects in the placebo group (35.5%) experienced an event of death or cardiovascular hospitalization during the course of the trial (Table 10). Mean time to event was 796.0 days in the nebivolol group and 774.1 days in the placebo group. The Kaplan-Meier curves for the primary endpoint can be seen in Figure 16. As can be seen, the curves separate after approximately 3 months. Results for the primary analysis for the PP population were similar with respect to the point estimate (HR 0.87, 95% CI [0.74 – 1.01]) but did not reach statistical significance [p=0.071].

Table 10: Primary Endpoint and components using the extended follow-up (minimum of 12 months follow-up)

Endpoint	**Nebivolol (n=1067)**	**Placebo (n=1061)**	**HR**	**P-value**
Primary Endpoint	332	375	0.85	0.034
All-cause mortality (as first event)	76	99		
All-cause mortality (at any time)	169	192	0.87	0.17
CV Hospitalizations	256	276	0.89	0.20

[Source: FDA Statistical Reviewer's Analysis]

Figure 16: Kaplan-Meier curves for the Primary Endpoint of All-cause Mortality or First Cardiovascular Hospitalization during the Course of the Trial (ITT Population)



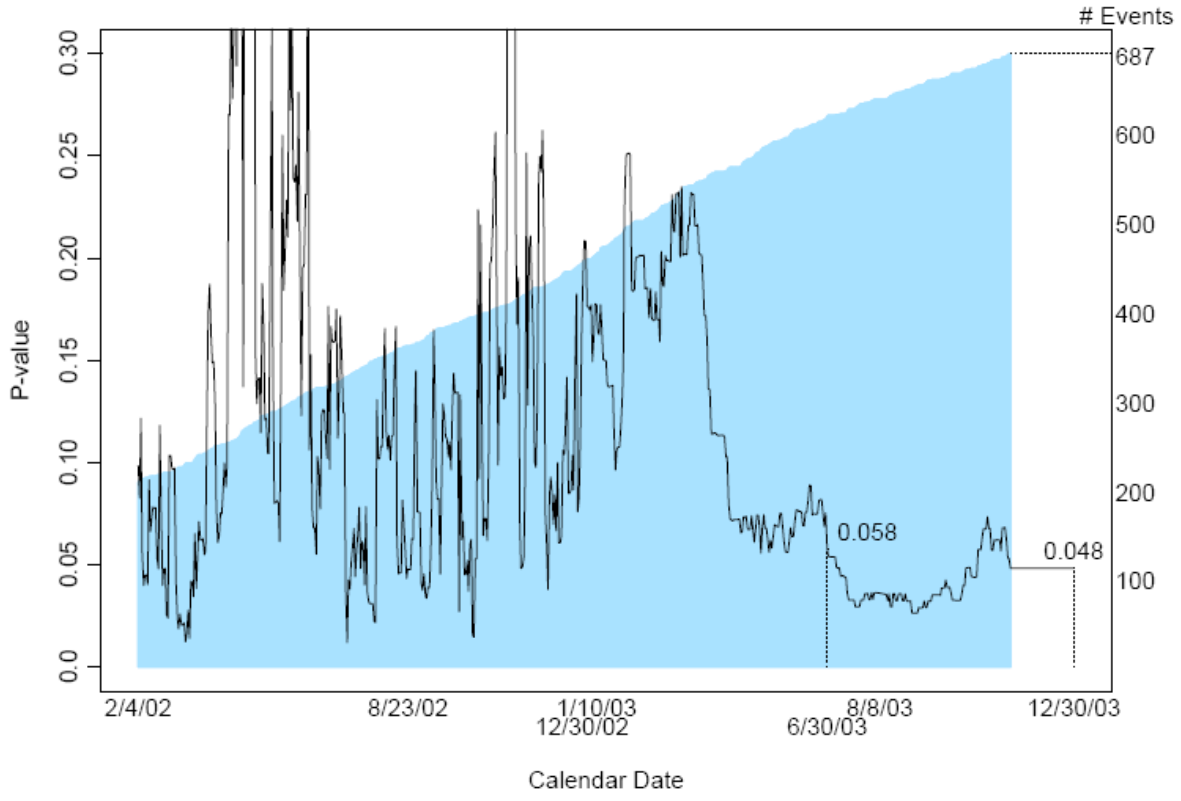
[Source: pg 124, Volume 1 of the Forest SENIORS Study Report]

For the primary analysis, the change to adjusting the analysis for the covariate of LVEF resulted in 17 subjects, 8 from the placebo arm and 9 from nebivolol, being excluded for lack of baseline EF measurement. These subjects included 3 out of the 8 in the placebo group who had an event and 4 subjects with events out of the 9 subjects excluded from the nebivolol group.

The progressive changes in the p-value for the primary endpoint, using the original analysis plan, can be seen in Figure 17 (analyses done by the FDA statistical reviewer). These analyses did not adjust for the covariates of LVEF, sex and age, and did not include deaths that were identified after subjects prematurely discontinued the trial ('vital status' deaths). The dates for which these analyses were done are the cutoff dates for data used for each of the interim analyses – 2/4/02, 8/23/02, 1/10/03, and 8/8/03. These dates are each a few days prior to the dates of their respective DSMB meetings, as they represent the cutoff dates for data collection for the ensuing meeting. Of particular note in these interim analyses is the fact that the last of these interim looks was an unplanned interim analysis added after the Steering committee decided to extend the minimum duration of follow-up from 6 months to 12 months. Other dates of relevance in this timeline are 12/30/02, the dates that the last subject was randomized; 6/30/03, the date that the last randomized subject would be followed-up with a minimum follow-up period of 6 months (as per the original plan); and 12/30/08, the date that the last subject would be follow-up if the minimum follow-up period was 12 months as per the amendment. The blue region corresponds to the cumulative number of events. One point of relevance in this graph is the fact that the p-value essentially hovers around 0.05 after March

2003, sometimes below and sometimes above this value. This means that, if the data collection had stopped either a few days before or after the final date, the p-value could have been greater that 0.05, and thus non-significant. If the data collection is stopped on 6/30/03 as specified in the original protocol, corresponding to a minimum follow-up period of 6 months, the p-value is 0.058. If the data collection is continued until 12/30/03, which corresponds to a minimum follow-up period of 12 months, the p-value is 0.048. Furthermore, despite the fact that this value falls below 0.05, it is not adjusted for any of the 4 interim analyses, including the 3 planned interim looks, that each used an alpha of 0.001. The final time period from mid-November 2003 to end of December 2003 had essentially a straight line, because no data were collected in these last 1.5 months, with no events and no censoring. Thus, the follow-up, despite the extension, was not 12 months but was, in fact, 10.5 months.

Figure 17: P-values for the primary endpoint by calendar time



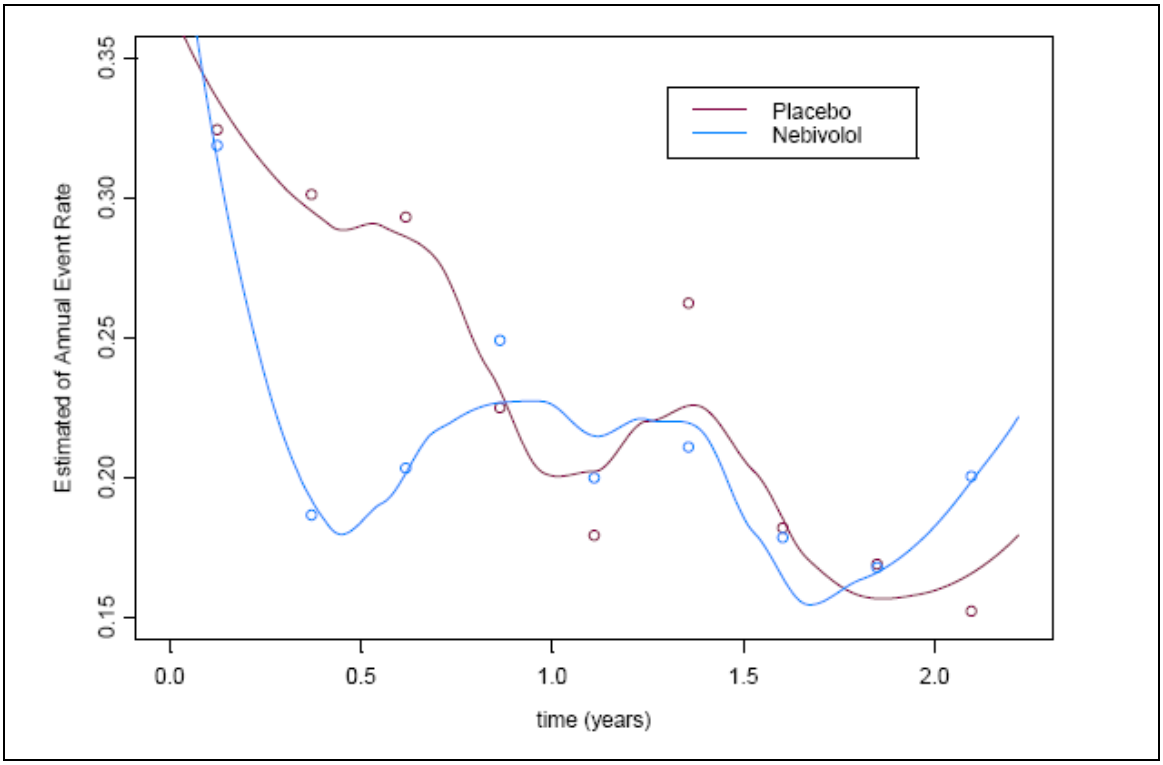
[Source: FDA Statistical Reviewer's Analysis]

Reviewer's Comments: *There were several changes made to the protocol, including extension of the minimum follow-up period from 6 months to 12 months, adjustment of the primary endpoint for covariates of age, sex and LVEF, and, finally, adding the deaths collected by phone call/inquiry to the all-cause mortality component of the primary endpoint. Despite these changes, the p-value for the primary endpoint hovers around 0.05 after March 2003, ranging from 0.058 at the 6 month follow-up time point as originally planned, to 0.048 at the 12 month, extended follow-up time point. These p-values have not been adjusted for the 4 interim analyses, of which 3 were planned and 1 was unplanned.*

One question that arose in our review is the effect of eliminating the additions to the mortality component of the primary endpoint found by 'vital status' inquiries. These additional deaths found after subjects prematurely discontinued the trial amounted to 8 in the nebivolol group (out of a total of 61 subjects in the nebivolol group who had a vital status determination after censoring for other events) and 12 in the placebo group (out of a total of 54 who had vital status known after censoring for other events). If these deaths (found by 'vital status' inquiries) were eliminated, keeping the primary analysis otherwise the same as that utilized by the sponsor (i.e. using the extended follow-up period of 12 months and adjusting for age, sex, and LVEF), the p-value would increase to 0.049 for the treatment effect (after censoring these subjects at the date of loss to follow-up for other events). Further adjusting this value for the 3 pre-specified interim analyses with the Pocock boundary of 0.001, this p-value would then increase to greater than 0.05 (Analysis done by the FDA statistical reviewer).

The estimated hazard functions for both the nebivolol and placebo groups (analysis done by the FDA statistical reviewer) can be seen in Figure 18. The circles represent the estimated annual event rate using the data from intervals of 90 days. For example, in the first 90 days, there were 80 events in the placebo group accumulated during 89,977 subject days of follow-up (the subjects that didn't have an event contribute 90 days each to the subject days, while those who experienced an event contributed the number of days that there passed until the event. The annual event rate based on the data from this interval is calculated as 365*80/89,977, which is approximately 0.325. A red circle with x-coordinate in the middle of the interval (45 days, or 45/365 years) and y coordinate 0.0325. For the generation of the smooth curves, the number of subjects at risk every day and the number of events every day were calculated. A weighted local regression model was then fit with weight proportional to the inverse of the estimated variance. In both the nebivolol and placebo groups, the event rate is higher for the first 6 months of randomization, then decreases, remaining relatively constant after this period. In the initial 90 days, there is little difference between the 2 groups in event rates, after which, over the next 180 days, there is a difference favoring nebivolol. After that, once again the curves return to no difference between the groups. This temporal pattern is similar to that seen in the Kaplan-Meier curves (Figure 16).

Figure 18: Estimated Hazard Functions Over Time



[Source: FDA Statistical Reviewer's Analysis]

Given that one of the components of the primary endpoint in this trial was a relatively 'soft' endpoint of cause-specific hospitalization, one question that arises is the number of subjects needed to be excluded to change the p-value, as it was determined by the sponsor (i.e. with the longer duration of follow-up, the adjustment for covariates, as well as the inclusion of 'vital status' subjects), to greater than 0.05. The number needed to be excluded to change this p-value to a value greater than 0.05 are 2 subjects in the placebo group or 3 subjects in the nebivolol group. In the placebo group, there was one subject who had a CV hospitalization on Day 3 but was alive at the last day of follow-up (day 878) and another who had CV hospitalization on Day 9 and was alive on the last day of follow-up (Day 1081). If we assume those two subjects did not have CV hospitalization and instead censor them for the primary endpoint on the last known date alive, the p-value for the sponsor's primary analysis (adjusted for LVEF, sex, and age) becomes 0.051. In the nebivolol group, among the people lost to follow-up were three people who were lost to follow-up on days 2, 15, and 16. If we assume those 3 people actually had an event at some time after they were lost to follow-up (in the worst case, the next day), the p-value for the sponsor's primary analysis (adjusted for LVEF, sex, and age) becomes 0.051. (Analysis done by the FDA statistical reviewer)

The fact that the number of subjects that need to be excluded to change the result to non-significant is so low begs the question of how the adjudication process was handled with regard to CV versus non-CV hospitalizations. To gain further insight into this process, we reviewed the narratives and CE forms of a sampling of clinical events in the SENIORS trial. From these,

we then identified a sampling of cases in which there were differences between the conclusions of the investigator and that of the CERC. The following example, consisting of 4 cases of bradycardia, each adjudicated differently, suggests that the process of adjudicating cause-specific hospitalization has inherent problems due to the subjective nature of the process.

Table 11: The Adjudication of Cause-Specific Hospitalization - Four Cases of Bradycardia

Group	Case	Adjudicated As…
Nebivolol	88 yo female with NYHA class III HF, and CAD s/p PTCA, s/p MI with thrombolysis who p/w sinus bradycardia. Pacer placed	Non-CV hospitalization
Nebivolol	81 yo female with idiopathic dilated cardiomyopathy, NYHA class II HF, and NIDDM who p/w non-serious AE of hypoglycemia and SAE of sinus bradycardia.	Non-CV hospitalization
Nebivolol	77 yo female with NYHA class II HF, AF, and NIDDM who p/w bradycardia and worsening of HF. Pacer placed.	CV hospitalization
Placebo	79 yo female with NYHA class II HF who p/w mild worsening of HF and elevation in renal parameters due to sinus bradycardia	CV hospitalization

Reviewer's Comments: *In a trial in which the exclusion of a relatively few number of subjects (2-3) can result in the change from a significant to a non-significant result, and in which one of the components of the primary endpoint is cause-specific hospitalization, which inherently depends on the adjudication process for its result (unlike a harder endpoint such as all-cause mortality), the nature of the adjudication process becomes very relevant. We looked at the narratives and CE forms for a sampling of clinical events and identified a sampling of cases in which there were different conclusions between the investigator adjudication and the final adjudication of the CERC. Although the information we had available to us was very limited in nature and thus prevented us from being able to make any conclusions, this process did reveal the somewhat subjective nature of the adjudication process.*

6.1.5 Analysis of Secondary Endpoints(s)

Reviewer's Comments: *All of the secondary endpoints were exploratory in nature, with no pre-specified statistical plan, no hierarchical status for analysis, and no alpha spending.*

6.1.5.1 Cardiovascular Mortality or Cardiovascular Hospital Admission

Of all the secondary endpoints, the only endpoint which was significant was that of the composite of cardiovascular mortality or cardiovascular hospitalization.

As seen in Table 12, 305 subjects in the nebivolol arm (28.6%) and 350 in the placebo arm (33.0%) were hospitalized or died due to cardiovascular reasons during the study. Mean time to the event was 750.9 days (nebivolol) and 782.3 days (placebo).

Table 12: Cardiovascular Mortality or Cardiovascular Hospitalization – ITT and PP Populations

	ITT population		PP population	
	Nebivolol (N = 1067)	Placebo (N = 1061)	Nebivolol (N = 1016)	Placebo (N = 996)
Number of patients at risk	1067	1061	1016	996
Number (%) of events	305 (28.6%)	350 (33.0%)	270 (26.6%)	304 (30.5%)
Number (%) censored[1]	762 (71.4%)	711 (67.0%)	746 (73.4%)	692 (69.5%)
Odds ratio	0.81	-	0.82	-
Time to event (days)				
Mean	750.9	782.3	767.4	804.2
Standard error	10.86	13.23	10.84	13.43
1) Note: Number censored indicates the number of patients without event				

[Source: Sponsor's Table, pg 150, Volume 1 of the Forest SENIORS Study Report]

The hazard ratio for cardiovascular mortality or cardiovascular hospital admission for the ITT population was 0.84, with a 95% CI of 0.72 to 0.98, and this was statistically significant with a p value of 0.027. Analysis of the PP population, however, did not reach significance (hazard ratio of 0.85, 95% CI of 0.72 to 1.00, and a p value of 0.050).

Reviewer's Comments: *Although nebivolol treatment did result in a significant reduction in the composite secondary endpoint of cardiovascular mortality or cardiovascular hospitalization when the analysis was done in the ITT population, (HR 0.84, 95% CI 0.72 to 0.98, and p value of 0.027), it did not win when the analysis was done in the PP population (HR 0.85, 95% CI 0.72 to 1.00, and p value of 0.05).*

6.1.5.2 All-Cause Mortality

There were 169 (15.8%) and 192 (18.1%) all-cause deaths in the ITT nebivolol and placebo groups, respectively. Mean time to death was 986.5 days in the nebivolol arm and 829.9 days in the placebo arm [Table 13]. Kaplan-Meier estimates for survival can be seen in Figure 19.

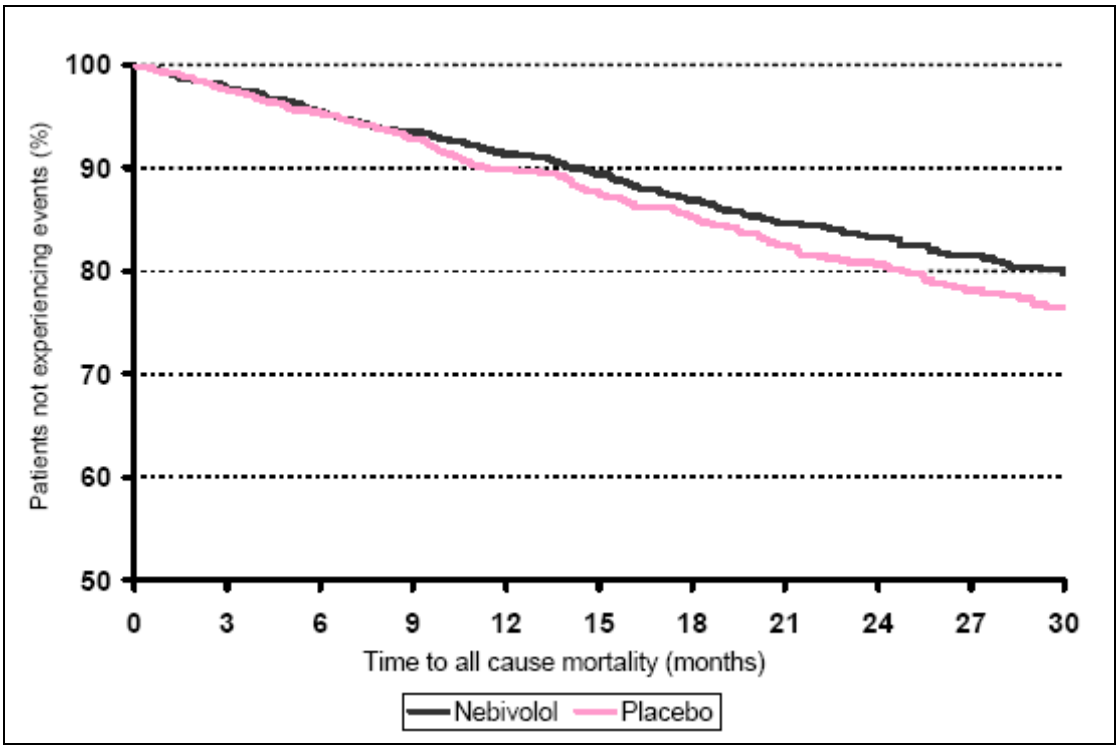
Table 13: All-cause Mortality – ITT and PP Populations

All cause mortality	ITT population		PP population	
	Nebivolol (N = 1067)	Placebo (N = 1061)	Nebivolol (N = 1016)	Placebo (N = 996)
Number of patients at risk	1067	1061	1016	996
Number (%) of events	169 (15.8%)	192 (18.1%)	154 (15.2%)	174 (17.5%)
Number (%) censored[1]	898 (84.2%)	869 (81.9%)	862 (84.8%)	822 (82.5%)
Odds ratio	0.85	-	0.84	-
Time to event (days)				
Mean	986.5	829.9	992.6	833.1
Standard error	10.16	8.11	10.25	8.31

1) Note: Number censored indicates the number of patients without event
Source: Appendix 16.2.1, Table 4.1.1.1

[Source: Sponsor's Table, pg 138, Volume 1 of the Forest SENIORS Study Report]

Figure 19: Kaplan-Meier Survival Plot for All-cause Mortality – ITT Population



[Source: Sponsor's Table, pg 140, Volume 1 of the Forest SENIORS Study Report]

Analysis of time to all-cause mortality for the ITT population yielded a hazard ratio of 0.88 with nebivolol treatment, with a 95% CI of 0.71 to 1.08 and p value of 0.214, and for the PP population the values were HR of 0.87, 95% CI of 0.70 to 1.08, and p value of 0.192.

Reviewer's Comments: *Nebivolol treatment did not result in a significant reduction in either component of the composite endpoint: all-cause mortality (HR 0.88, 95% CI 0.71 to 1.08, and p value of 0.214), or cardiovascular hospitalizations (HR 0.90, 95% CI 0.76 to 1.06, and p value of 0.204).*

6.1.5.3 Cardiovascular Mortality

There were 123 deaths attributed to cardiovascular causes in the nebivolol group (11.5%) and 145 deaths (13.7%) in the placebo group. Mean time to cardiovascular death was 953.0 days and 807.8 days in the nebivolol and placebo groups, respectively [Table 14].

Table 14: Cardiovascular Mortality – ITT and PP Populations

Cardiovascular mortality	ITT population		PP population	
	Nebivolol (N = 1067)	Placebo (N = 1061)	Nebivolol (N = 1016)	Placebo (N = 996)
Number of patients at risk	1067	1061	1016	996
Number (%) of events	123 (11.5%)	145 (13.7%)	111 (10.9%)	130 (13.1%)
Number (%) censored[1]	944 (88.5%)	916 (86.3%)	905 (89.1%)	866 (86.9%)
Odds ratio	0.82	-	0.82	-
Time to event (days)				
Mean	953.0	807.8	958.1	811.0
Standard error	8.47	7.01	8.50	7.15

1) Note: Number censored indicates the number of patients without event
Source: Appendix 16.2.1, Table 4.2.1.1

[Source: Sponsor's Table, pg 141, Volume 1 of the Forest SENIORS Study Report]

Of these 268 subjects adjudicated to the secondary endpoint of cardiovascular mortality, 154 were attributed by the CERC to "cardiovascular cause" and 114 deaths were attributed to "sudden cardiac death of unknown origin".

The hazard ratio for time to cardiovascular mortality for the ITT population was 0.84 with a 95% confidence interval of 0.66 to 1.07, but this did not reach significance (p = 0.165). In the PP population, hazard ratio was 0.83, with a 95% confidence interval of 0.65 to 1.07, and a similar p value of 0.155.

Reviewer's Comments: *Nebivolol treatment did not result in a significant reduction in cardiovascular mortality (HR 0.84, 95% CI of 0.66 to 1.07, and a p value of 0.165).*

6.1.5.4 Cardiovascular Hospital Admission

In the ITT population, 256 nebivolol-treated subjects (24.0%) and 276 placebo-treated subjects (26.0%) underwent cardiovascular hospitalization. Mean time to cardiovascular hospitalization was 781.2 days in the nebivolol arm and 836.7 days in the placebo arm [Table 15].

Table 15: Cardiovascular Hospitalizations – ITT and PP Populations

	ITT population		PP population	
	Nebivolol (N = 1067)	Placebo (N = 1061)	Nebivolol (N = 1016)	Placebo (N = 996)
Number of patients at risk	1067	1061	1016	996
Number (%) of events	256 (24.0%)	276 (26.0%)	223 (21.9%)	234 (23.5%)
Number (%) censored[1]	811 (76.0%)	785 (74.0%)	793 (78.1%)	762 (76.5%)
Odds ratio	0.90	-	0.92	-
Time to event (days)				
Mean	781.2	836.7	798.2	860.3
Standard error	10.47	12.85	10.38	12.88

1) Note: Number censored indicates the number of patients without event

[Source: Sponsor's Table, pg 144, Volume 1 of the Forest SENIORS Study Report]

The hazard ratio for cardiovascular hospitalization in the ITT population was 0.90 with a 95% confidence interval of 0.76 to 1.06, and a p value which did not reach statistical significance at 0.204. For the PP population, the values were similar at HR 0.91, 95% CI [0.76-1.09], and p value of 0.312.

Reviewer's Comments: *Nebivolol treatment did not result in a significant reduction in either component of the composite endpoint: all-cause mortality (HR 0.88, 95% CI 0.71 to 1.08, and p value of 0.214), or cardiovascular hospitalizations (HR 0.90, 95% CI 0.76 to 1.06, and a p value of 0.204).*

6.1.5.5 All-Cause Hospital Admission

In the ITT population, 359 nebivolol-treated subjects (33.6%) and 364 placebo-treated subjects (34.3%) were hospitalized for any cause during the duration of the study. Mean time to all-cause hospitalization was 742.7 days in the nebivolol arm and 758.2 days in the placebo arm [Table 16].

Table 16: All-cause Hospitalization – ITT and PP Populations

All cause hospital admission	ITT population		PP population	
	Nebivolol (N = 1067)	Placebo (N = 1061)	Nebivolol (N = 1016)	Placebo (N = 996)
Number of patients at risk	1067	1061	1016	996
Number (%) of events	359 (33.6%)	364 (34.3%)	322 (31.7%)	318 (31.9%)
Number (%) censored[1]	708 (66.4%)	697 (65.7%)	694 (68.3%)	678 (68.1%)
Odds ratio	0.97	-	0.99	-
Time to event (days)				
Mean	742.7	758.2	760.4	780.0
Standard error	12.58	13.71	12.69	13.98
1) Note: Number censored indicates the number of patients without event				

[Source: Sponsor's Table, pg 146, Volume 1 of the Forest SENIORS Study Report]

The hazard ratio for all-cause hospitalization was 0.95 with a 95% CI of 0.82 to 1.10, but did not reach statistical significance (p = 0.473).

Reviewer's Comments: *Nebivolol treatment did not result in a significant reduction in all-cause hospitalization (HR 0.95, 95% CI of 0.82 to 1.10, and a p value of 0.473).*

6.1.5.6 All-Cause Mortality or All-Cause Hospital Admission

408 nebivolol-treated subjects (38.2%) and 443 placebo-treated subjects (41.8%) were hospitalized or died for any reason during the course of the trial. Mean time to all-cause mortality or all-cause hospitalization was 720.0 days in the nebivolol group and 714.5 days in the placebo group [Table 17].

Table 17: All-Cause Mortality or All-Cause Hospitalization – ITT and PP Populations

	ITT population		PP population	
	Nebivolol (N = 1067)	Placebo (N = 1061)	Nebivolol (N = 1016)	Placebo (N = 996)
Number of patients at risk	1067	1061	1016	996
Number (%) of events	408 (38.2%)	443 (41.8%)	369 (36.3%)	394 (39.6%)
Number (%) censored[1]	659 (61.8%)	618 (58.2%)	647 (63.7%)	602 (60.4%)
Odds ratio	0.86	-	0.87	-
Time to event (days)				
Mean	720.0	714.5	736.8	733.5
Standard error	12.47	13.47	12.61	13.81
1) Note: Number censored indicates the number of patients without event				

[Source: Sponsor's Table, pg 148, Volume 1 of the Forest SENIORS Study Report]

The hazard ratio for all-cause mortality or all-cause hospitalization for the ITT population was 0.89, with a 95% CI of 0.78 to 1.02 and a p value which did not reach statistical significance at 0.082. Analysis of the PP population revealed similar results, with a hazard ratio of 0.90, 95% CI of 0.78 to 1.03, and a p value of 0.131.

Reviewer's Comments: *Nebivolol treatment did not result in a significant reduction in the composite secondary endpoint of all-cause mortality or all-cause hospitalization (HR 0.89, 95% CI of 0.78 to 1.02, and a p value of 0.082).*

6.1.5.7 Functional Capacity by NYHA Class

There were no significant changes between the number of shifts in NYHA classes between the nebivolol and placebo treated groups. At EOP, there was no change in the NYHA class in 72.1% and 70.0% of the nebivolol- and placebo-treated subjects, respectively. NYHA class had worsened in 6.4% and 6.0%, and had improved in 21.6% and 24.0%, of the nebivolol and placebo groups, respectively. There were also no significant changes noted between baseline NYHA class and that at the last observation available (LOA). NYHA class remained unchanged in 73.0% and 71.3%, had worsened in 7.9% and 7.2%, and had improved in 19.1% and 21.5% (nebivolol- and placebo-treated subjects, respectively).

Reviewer's Comments: *There was no significant changes between the number of shifts in NYHA classes between the nebivolol and placebo treated groups.*

6.1.5.8 Functional Capacity by 6-Minute Walk Test

There were no significant changes noted in 6-minute walk test between the nebivolol- and placebo-treated groups. Median walking distance increased from 275 m and 260 m at baseline in the nebivolol and placebo arms, respectively, to 300 m in both arms at 6 months post randomization (visit M2). Mean improvement was +25.4 m and +24.8 m in the nebivolol and placebo groups, respectively. The proportion of nebivolol-treated subjects experiencing angina symptoms during the 6-minute walk test decreased from 16.0% at baseline to 9.8% at 6 months post-randomization, while in the placebo-treated subjects the proportion was 14.9% as baseline to 10.9% at 6 months.

Reviewer's Comments: *There was no significant difference between the 6 minute walk in the nebivolol and placebo treated groups, though one can see evidence of a placebo effect.*

6.1.5.9 Cause of Death

As shown in Table 18, 154 out of the 361 deaths in the trial (deaths that occurred up to and including the EEE date, November 15, 2003) were attributed to cardiovascular causes (79 in the nebivolol group and 75 in the placebo group) and 46 were attributed to non-cardiovascular causes, (26 in the nebivolol group and 20 in the placebo group). There were 114 sudden cardiac deaths of unknown origin in the trial (44 in the nebivolol group and 70 in the placebo group) which were adjudicated as cardiovascular deaths per the decision of the CERC. The cause of

death was not recorded for 39 subjects who prematurely terminated the trial and for whom vital status information was collected at end of the trial (16 nebivolol-treated subjects and 23 placebo-treated subjects). Of these, 28 subjects had a complete post hoc date of death recorded while 11 had an imputed post hoc date of death which, per report of the sponsor, was derived from *"less complete, but definitive, information."* Of the 39 deaths documented by vital sign status, 38 deaths were not adjudicated by the CERC (by the decision of the SC) and 1 death was adjudicated, subject 21985.

These 39 deaths documented by vital status information were included in the all-cause mortality efficacy analyses, including analysis of the primary efficacy endpoint, but not in any of the analyses involving cardiovascular mortality.

Table 18: Cause of Death - ITT Population

Cause of Death	Nebivolol	Placebo	Total
CV Death	79	75	154
Non CV Death	26	20	46
Unknown, Sudden Cardiac Death	44	70	114
Unknown, No Sudden Cardiac Death	3	1	4
Not Classifiable According to CERC	1	3	4
Complete Post-Hoc Date of Death	12	16	28
Imputed Incomplete Post-Hoc Date	4	7	11
Total Deaths	169	192	361

[Source: Clinical Reviewer's Analysis]

Reviewer's Comments: *It appears from Table 18 that sudden cardiac death is not considered a cardiovascular [CV] death, but instead is being considered as a separate category.*

6.1.5.10 Cause of Hospitalization

As shown in Table 19, 532 subjects were hospitalized for a cardiovascular causes (256 in the nebivolol group and 276 in the placebo group), while 308 subjects were hospitalized for non-cardiovascular causes (160 in the nebivolol group and 148 in the placebo group).

Table 19: Summary of Cause of Hospitalizations: CV, Non-CV, and Unknown

Cause for Admission	Nebivolol (n=1067)	Placebo (n=1061)	Total (n=2128)
Cardiovascular	256 (24.0%)	276 (26.0%)	532 (25.0%)
Non-cardiovascular	160 (15.0%)	148 (13.9%)	308 (14.5%)
Unknown	4 (.38%)	0	4 (.19%)

6.1.5.11 Hospital Admission or Death due to Worsening of Heart Failure, Stroke or Myocardial Infarction

As shown in Table 20, 422 subjects (213 in the nebivolol arm and 209 in the placebo arm) had either hospital admission or death due to worsening of HF (304 subjects), occurrence of stroke (71 subjects) or of MI (81 subjects). Reasons for hospital admission or death were adjudicated to 11 classifications of potential cardiovascular causes, including "Other", of which three of these classified events (worsening of HF, occurrence of stroke, or occurrence of MI) were considered pre-specified, secondary endpoints. There was no difference between the treatment groups with respect to the incidence of hospital admission or death due to either worsening of HF, occurrence of MI, or occurrence of stroke.

Table 20: Worsening of Heart Failure, Occurrence of Stroke/Myocardial Infarction – ITT Population

	Nebivolol (n=1067)	**Placebo (n=1061)**	**Total (n=2128)**
Worsening of Heart Failure	152 (14.2%)	152 (14.3%)	304 (14.3%)
Stroke	37 (3.5%)	34 (3.2%)	71 (3.3%)
Myocardial Infarction	41 (3.8%)	40 (3.8%)	81 (3.8%)

[Source: Clinical Reviewer's Analysis]

6.1.6 Other Endpoints

There were no other endpoints.

6.1.7 Subpopulations

6.1.7.1 Primary Efficacy Variable

In males, there were 224 events out of 657 subjects in the nebivolol group and 241 events out of 686 subjects in the placebo group, corresponding to an estimated odds ratio of 0.96. In females, there were 100 events out of 410 subjects (nebivolol) and 121 events out of 375 subjects (placebo), resulting in an estimated odds ratio of 0.68.
With regard to race, there were only 9 subjects of non-Caucasian race in the entire trial, making it difficult to make any substantive conclusions.
With regard to age, in subjects at or younger than the median age in the trial, there were 145 events out of 539 subjects in the nebivolol group and 170 events out of 525 subjects in the placebo group, corresponding to an estimated odds ratio of 0.77. In subjects older than the median age, there were 179 events out of 528 subjects (nebivolol) and 192 events out of 536 subjects (placebo), corresponding to an estimated odds ratio of 0.92.
With regard to LVEF, the point estimate of the odds ratio was 0.84 in subjects with low (≤35%) baseline LVEF and 0.83 in subjects with high (> 35%) baseline EF.
In Western European sites, there were 121 events out of 382 subjects in the nebivolol group and 134 events out of 376 subjects in the placebo group. In Central Europe, there were 90 events out of 274 subjects in the nebivolol group and 94 events out of 269 subjects in the

placebo group. Finally, in Eastern Europe, there were 121 events out of 411 subjects in the nebivolol group and 147 events out of 416 subjects in the placebo group. This shows that the difference between the groups was slightly in favor of nebivolol in both Western and Central European centers (a difference between groups of 13 and 4 events respectively), but was much greater in Eastern European centers (a difference of 26 events) [FDA Statistical Reviewer]. Subgroup analysis of those subjects with diabetes versus those without diabetes showed the hazard ratio for nebivolol treatment in non-diabetic subjects to be 0.79, with a 95% confidence interval of 0.66 to 0.95, while in subjects with diabetes, the hazard ratio was 1.02, with a 95% confidence interval of 0.78 to 1.34. This suggests the possibility of an increase in risk of reaching the composite endpoint with nebivolol treatment. In diabetic subjects, 115 subjects in the nebivolol group and 108 subjects in the placebo group experienced an event of death or of cardiovascular hospital admission during the course of the trial. In the non-diabetic cohort, 217 subjects in the nebivolol group and 267 subjects in the placebo group experienced an event of death or of cardiovascular hospital admission during the course of the trial.

Table 21 presents the results of subgroup analysis of the composite primary endpoint of all-cause mortality and cardiovascular hospitalizations.

Table 21: Subgroup Analysis of the Primary Endpoint of All Cause Mortality or Cardiovascular Hospitalizations

		95% CI		*Number of Events[a]/ Patients at Risk*	
	Hazard Ratio	*Lower Limit*	*Upper Limit*	*Nebivolol*	*Placebo*
ITT population[b]	0.86	0.74	0.99	332/1067	375/1061
Subgroups					
Male	0.93	0.78	1.11	231/657	250/686
Female	0.72	0.55	0.94	101/410	125/375
Age ≤ median age	0.79	0.63	0.98	148/539	176/525
Age > median age	0.92	0.75	1.12	184/528	199/536
Baseline LVEF ≤ 35%	0.87	0.73	1.05	219/683	249/686
Baseline LVEF > 35%	0.82	0.63	1.05	110/380	125/372
Western centers	0.84	0.66	1.08	121/382	134/376
Central centers	0.93	0.70	1.25	90/274	94/269
Eastern centers	0.80	0.63	1.02	121/411	147/416
Diabetes	1.02	0.78	1.34	115/287	108/268
No diabetes	0.79	0.66	0.95	217/780	267/793
Prior MI	0.89	0.72	1.09	176/467	187/463
No prior MI	0.81	0.65	1.00	156/600	188/597
Dose = none	1.25	0.74	2.10	36/62	23/45
1.25 mg	0.80	0.43	1.49	26/76	17/41
2.5 mg	0.77	0.45	1.32	31/85	29/64
5.0 mg	0.91	0.56	1.47	44/140	28/84
10.0 mg	0.80	0.67	0.96	192/692	272/812
Creatinine ≤ 95.472 µmol/L	0.88	0.70	1.10	152/568	155/519
Creatinine > 95.472 µmol/L	0.85	0.69	1.03	178/492	217/533
Ukraine	0.82	0.59	1.13	70/232	81/225
Romania	0.80	0.55	1.15	51/179	66/191
The Netherlands	0.82	0.57	1.19	54/170	64/171
Czech Republic	1.05	0.70	1.57	51/157	48/155
Hungary	0.69	0.42	1.15	27/88	35/87
United Kingdom	1.22	0.66	2.26	24/78	18/69
Spain	0.85	0.48	1.51	22/67	25/70
Italy-Switzerland	0.80	0.27	2.39	7/36	9/35
France	0.70	0.34	1.45	14/31	18/31
Germany	0.95	0.41	2.23	12/29	11/27

Source: Menarini SENIORS CSR, Appendix 16.2.1, Tables, 3.1.1.1, 3.1.1.1.1, 3.1.1.1.2, 3.1.1.1.3, 3.1.1.1.4, 3.2, 6.1.1.1, 6.1.1.2, 6.1.1.3, 6.1.1.4, 6.1.3.1, 6.1.3.2, 6.1.3.3, 6.1.3.4, 6.1.3.5, 6.1.3.6, 6.1.3.7; Forest CSR, Appendix 14, Tables 14.4.1.4, 14.4.1.5, and 14.4.1.7

a Number of first events of all cause mortality or cardiovascular hospital admission.

b The ITT population encompassed 2111 patients (nebivolol: N = 1058, placebo: N = 1053) because 17 patients did not provide baseline LVEF.

ITT = intention to treat; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

[Source: Sponsor's Table, pg 136-137, Volume 1 of the Forest SENIORS Study Report]

Reviewer's Comments: *The hazard ratio in diabetic subjects was 1.02, with a 95% confidence interval of 0.78 to 1.34, suggesting the possibility of an increase in risk of reaching the composite primary endpoint with nebivolol treatment in those subjects with diabetes.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Given that the majority of subjects in the SENIORS trial reached the highest maintenance dose of 10 mg/day, there was insufficient data in this trial to make any conclusions regarding dosing recommendations

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There was not adequate data to make conclusions as to persistence of efficacy and/or tolerance effects

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses

7 Review of Safety

Safety Summary

With regard to the safety database for nebivolol during the development program for heart failure, the population analyzed was adequate, consisting of 1067 subjects receiving nebivolol and 1061 subjects receiving placebo. Of these treated subjects, approximately 11% in each arm discontinued the trial for reasons other than death, the most common of which was subject's desire to withdraw. With regard to dose of exposure, 67.9% of the nebivolol-treated subjects reached the maximum maintenance dose of 10 mg/day, while 80.4% reached a dose of ≥5 mg/day. The estimated exposure in total for the trial was 606,376 days, amounting to approximately 1660 patient-years.

There were 1539 subjects with treatment-emergent serious adverse events [SAEs] in the trial, of which the most common, in both the nebivolol and placebo arms, was worsening of heart failure, with 143 events in the nebivolol group (13.4%) and 153 events in the placebo group (14.4%). The next most common SAEs (listed in descending order by frequency in the nebivolol arm) were those related to cerebrovascular disorder (36 events or 3.4% and 21 events or 2.9% in the nebivolol and placebo arms, respectively), myocardial infarction (34 events or 3.2 % and 26 events or 2.5% in the nebivolol and placebo arms, respectively), and then sudden death, pneumonia, and unstable angina. The SAEs found at a higher incidence in the nebivolol compared with the placebo group were anemia (13[1.2%] and 4[0.4%] in the nebivolol and placebo arms, respectively), renal dysfunction (12[1.1%] and 6[0.6%], in the nebivolol and placebo groups, respectively), and edema (5[0.5%] vs. 1 [0.1%] in the two groups, respectively). Overall, however, the numbers of these SAEs in the two groups were two small to make any significant conclusions.

Adverse events that were seen in the trial that were expected based on the drug-class of beta adrenergic blockers were bradycardia (which was the most commonly seen of these in the nebivolol group – noted in 14.3% of the nebivolol-treated subjects compared with 3.6% of the placebo subjects), hypotension, orthostasis, dizziness, syncope, and fatigue and weakness.

Finally, with regard to all AEs, the most commonly seen treatment-emergent AE seen at a greater frequency in the nebivolol group compared with placebo were renal dysfunction (present in 108 subjects, or 10.1%, in the nebivolol group compared with 78, or 7.4%, in the placebo group), edema (present in 103 subjects, or 9.7%, in the nebivolol-treated subjects compared with 61, or 5.7%, in the placebo-treated subjects), and hyperuricemia (present in 79 subjects, or 7.4% of the nebivolol group compared with 41 subjects, or 3.9%, in the placebo group).

Thus, analysis of the safety profile of nebivolol does not reveal any specific causes for concern.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary trial utilized in the safety analysis of nebivolol administration in the setting of heart failure is SENIORS. This is a single, randomized, double blind, placebo-controlled, parallel-group, titrated-dose trial designed to evaluate the effects of nebivolol as add-on therapy to already optimized CHF treatment (i.e. ACE Inhibitors, diuretics, cardiac glycosides), on the combined endpoint of all-cause mortality or cardiovascular hospitalization in clinical stable elderly subjects (70 years of age or older) with chronic congestive heart failure with or without impairment of LV systolic function. The sponsor also has included five subjects with heart failure enrolled in three controlled clinical trials of hypertension (Studies NEB-302, NEB-305, and NEB-321). In addition, the sponsor also included a series of small legacy studies of nebivolol administration in the setting of heart failure in their analysis, some of which were only available in the published literature. However, given that these were of differing trial designs, had differing levels of details about adverse events, were small studies, and were non-randomized and without adequate control groups, we will not focus on these in our review. Hence, the primary focus of this review will be the SENIORS trial.

7.1.2 Categorization of Adverse Events

The coding of the sponsor was assessed by comparison of the verbatim terms of the adverse events with the MedDRA preferred terms, along with review of the submitted Case Report Forms. In general, the coding was deemed to be adequate, though there were a few instances with incorrect coding (example noted in Table 22 below). We did note, however, a systematic issue of splitting similar medical concepts into different preferred terms. In this application, this was of particular relevance with adverse events such as heart failure exacerbation, unstable angina, and dizziness. Thus, we analyzed the adverse events both as coded by the sponsor and after pooling into categories of clinically relevant medical concepts (herein labeled as "recoded by the reviewer" in this review). To do this, we recoded every adverse event in the AE dataset to make the categories more clinically relevant.

Table 22: Reviewer's Table of Incorrect Coding in Submission

Verbatim Term	**Coded as:**	**Recoded as:**
Potassium Depletion	Blood Potassium Increased	Hypokalemia
Dizziness, Vertigo	Dizziness (Excl Vertigo)	Vertigo
Hypotension	Blood Urea Increased	Low BP
Obstructive Chronic Bronchitis	Rib Fracture	Bronchitis

[Source: Clinical Reviewer's Analysis]

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

At the time of the Pre-IND review of nebivolol treatment for heart failure, we had requested a separate analysis combining subjects with heart failure from the hypertension program with the SENIORS trial population to increase power for safety evaluation. However, because only five subjects had heart failure in the 2464 subjects in the hypertension trials, it was agreed that the data would not be pooled with the SENIORS data set and only subject profiles would be provided for these additional five subjects. Likewise, the legacy studies of nebivolol administration in heart failure were also summarized in the sponsor's safety evaluation, but the data were not pooled with the SENIORS trial data.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Extent of Exposure

In the SENIORS trial, the intent to treat population consisted of 1067 subjects who received nebivolol and 1061 subjects who received placebo. Of these treated subjects, 122 (11.4%) in the nebivolol group and 121 (11.4%) in the placebo group discontinued participation in the trial for reasons other than death, the most common of which was the subject's desire to withdraw. There were 776 completers in the nebivolol group and 748 completers in the placebo group. Among the secondary legacy trials, the discontinuation rate was 13/166 (7.8%) for nebivolol compared with 1/77 (1.3%) for placebo. Finally, for the trials in the published literature, the discontinuation rate for nebivolol was 3/87 (3.4%).

As can be seen in Table 23 and Table 24, the SENIORS trial contributed the highest amount of exposure data for nebivolol administration in the setting of heart failure. 67.9% of the nebivolol-treated subjects reached the maximum maintenance dose of 10 mg/day, while 80.4% reached a dose ≥ 5 mg/day. The mean duration of treatment in the SENIORS trial was 568.3 days, and estimated exposure in total for the trial was 606,376 days, amounting to 1660.2 patient-years, of exposure. A total of 740 subjects in the SENIORS trial (457 males and 283 females) were treated for more than 1 year and, of these, 329 (195 males and 134 females) were treated for more than 2 years.

Table 23: Estimated Extent of Exposure to Nebivolol in Subjects with Heart Failure – Across All Studies

Study	*Nebivolol Dosage Range*	*No. of Patients*	*Duration of Treatment*	*Estimated Exposure*[a]	*Estimated Exposure*
Primary Sources					
SENIORS[b]	1.25-10 mg	1067	568.3 days	606376 days	1660.2 years
NDA 21-742 (Studies NEB-302, NEB-305, NEB-306, and NEB-321)[c]	5-20 mg	5	15-108 days	289 days	0.8 years
Secondary Sources					
Study USA-6[d]	0.5-5 mg	19	27.8 days	528.2 days	1.4 years
Study BEL-46[d]	2.5-5 mg	20	8-10 weeks	180 weeks	3.5 years
Study RSA-8[d]	1-5 mg	11	3 months	33 months	2.8 years
Study TCH-4[d]	2.5-5 mg	62	3 months	186 months	15.5 years
Study BEL-33[d]	5 mg	12	10 days	120 days	0.25 years
Study BEL-34[d]	5 mg	5	1 month	5 months	0.41 years
Study FRA-3[d]	1-5 mg	6	6.5 weeks	39 weeks	0.75 years
Study GER-1[d]	5 mg	10	7 days	70 days	0.19 years
Study TCH-3[d]	5 mg	20	4 weeks	80 weeks	1.5 years
Edes et al, 2005[d]	1.25-10 mg	134	10.5 months	1407 months	117.3 years
Lombardo et al, 2006[d]	1.25-5 mg	35	6 months	210 months	17.5 years
Triposkiadis et al, 2007[d]	5 mg	10	1 day	10 days	0.03 years
Erdogan et al, 2007[d]	1.25-5 mg	21	1.5 months	31.5 months	2.6 years
Brehm et al, 2002[d]	2.5-5 mg	6	3 months	18 months	1.5 years
Nodari et al, 2003[d]	2.5-5 mg	15	6 months	90 months	7.5 years

[Source: pg 36-37, Integrated Summary of Safety]

Table 24: Duration of Exposure during Maintenance Phase and Maximum Dosage Level Reached in the ITT Population of the SENIORS Trial

	Nebivolol (N = 1014)	*Placebo (N = 1012)*	*Overall[a] (N = 2026)*
Duration of Follow-up On Drug During Maintenance			
≤ 3 months	11	21	32
> 3-6 months	27	27	54
> 6-9 months	32	35	67
> 9-12 months	113	118	231
> 12-18 months	250	229	479
> 18-24 months	207	210	417
> 24-30 months	157	149	306
> 30-36 months	194	189	383
> 36-40 months	23	34	57
Maintenance Dosage Reached			
None, n (%)	57 (5.6)	42 (4.2)	99 (4.9)
1.25 mg/d, n (%)	69 (6.8)	36 (3.6)	105 (5.2)
2.5 mg/d, n (%)	73 (7.2)	53 (5.2)	126 (6.2)
5 mg/d, n (%)	127 (12.5)	76 (7.5)	203 (10.0)
10 mg/d, n (%)	688 (67.9)	805 (79.5)	1493 (73.7)
≥ 5 mg/d, n (%)	815 (80.4)	881 (87.1)	1696 (83.7)

a Excluding patients who terminated the study before the end of the titration phase (n = 102).
On drug = patient status during double-blind study drug administration (including up- and down-titration).

[Source: pg 45, Integrated Summary of Safety]

Table 25: Duration of Exposure during Maintenance Phase in the ITT Population of the SENIORS Trial

Duration of Follow-Up	Nebivolol N = 1014	Placebo N = 1012	Total N = 2026
≤ 3 months	11 (1.1%)	21 (2.1%)	32 (1.6%)
> 3-6 months	27 (2.7%)	27 (2.7%)	54 (2.7%)
> 6-9 months	32 (3.2%)	35 (3.5%)	67 (3.3%)
> 9-12 months	113 (11.1%)	118 (11.7%)	231 (11.4%)
>12-18 months	250 (24.7%)	229 (22.6%)	479 (23.6%)
>18-24 months	207 (20.4%)	210 (20.8%)	417 (20.6%)
> 24-30 months	157 (15.5%)	149 (14.7%)	306 (15.1%)
> 30-36 months	194 (19.1%)	189 (18.7%)	383 (18.9%)
> 36-40 months	23 (2.3%)	34 (3.4%)	57 (2.8%)

[Source: Adapted from Sponsor's Table, pg 45, Integrated Summary of Safety]

7.2.1.2 Demographics

The ITT population of the SENIORS trial consisted of 2128 subjects, of which 1343 were male and 785 were female. The median age of subjects was 75.2 years with a range of 69.4 to 94.7 years. The subjects were primarily Caucasian (2059 subjects, or 99.6%), with 3 Black subjects (0.3%), all of whom were in the nebivolol group, and 2 subjects of Asian descent (0.2%), both of whom were also in the nebivolol arm. Finally, there were 2 subjects in each of the two arms who had race classified as '*other*'. The trial population came from 198 centers in 11 European countries. The most common diagnoses related to the development of heart failure were myocardial ischemia (1582 subjects, or 74.4%) and idiopathic dilated cardiomyopathy (319 subjects, or 15.0%). The majority of subjects were of NYHA class II or III at the time of trial enrollment.

7.2.2 Explorations for Dose Response

Given that the majority of subjects in the SENIORS trial reached the highest maintenance dose of 10 mg/day, there was insufficient data in this trial to make any conclusions on the other, lower dose levels (1.25, 2.5 and 5.0 mg/day).

7.2.3 Special Animal and/or *In Vitro* Testing

For this supplemental NDA application of an already approved drug, special animal testing and/or *in vitro* testing was not indicated.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate in the trial, with monitoring of vital signs including blood pressure and heart rate and appropriate collection and monitoring of laboratory data.

7.2.5 Metabolic, Clearance, and Interaction Workup

For this supplemental NDA application of an already approved drug, there were no significant metabolic, clearance, or interaction studies.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The primary adverse events of relevance for beta-adrenergic blockers are fluid retention and exacerbation of heart failure, bradycardia, fatigue, heart block, and hypotension. Also relevant are hyperglycemia, bronchospasm, cerebrovascular accidents, and myocardial infarction.

7.3 Major Safety Results

Overview of Adverse Events

During the course of the trial, including the post-treatment following up period, 911 nebivolol-treated subjects (85.4%) and 900 placebo-treated subjects (84.8%) experienced at least one AE. Of these, 861 nebivolol-treated (80.7%) and 846 placebo-treated subjects (79.7%) experienced at least 1 AE while receiving trial drug. Of the nebivolol and placebo treated subjects, 432 subjects (40.5%) and 468 subjects (44.1%) experienced an SAE, respectively.

Table 26: Overview of Adverse Events in the SENIORS Trial - ITT Population

Category	*No. (%) of Patients Experiencing an Adverse Event*		
	Nebivolol (N = 1067)	*Placebo (N = 1061)*	*Overall (N = 2128)*
At least 1 AE	911 (85.4)	900 (84.8)	1811 (85.1)
Any mild AE	701 (65.7)	658 (62.0)	1359 (63.9)
Any moderate AE	674 (63.2)	646 (60.9)	1320 (62.0)
Any severe AE	328 (30.7)	347 (32.7)	675 (31.7)
Any AE related to study drug	573 (53.7)	472 (44.5)	1045 (49.1)
Any AE causing discontinuation	165 (15.5)	136 (12.8)	301 (14.1)
Any SAE	432 (40.5)	468 (44.1)	900 (42.3)
Any SAE related to study drug	113 (10.6)	118 (11.1)	231 (10.9)
Deaths reported as an SAE	165 (15.5)	182 (17.2)	347 (16.3)

[Source: pg 48, Integrated Summary of Safety]

7.3.1 Deaths

There were a total of 402 deaths in the trial. Of these, 17 (9 nebivolol- and 8 placebo-treated subjects) did not contribute to the efficacy analysis (4 of these subjects were excluded from the

efficacy analysis because only the year of death was known, while the other 13 were excluded because they occurred after the end of the observation period (EOP), which concluded on November 15, 2003).

There were 427 adverse events which resulted in deaths per the adverse event dataset [please see Table 27]. This discrepancy between the number of deaths (402) and the number of AE resulting in deaths (427) arises as a result of the fact that multiple adverse events may have been associated with one death (thus resulting in a greater number of AEs associated with deaths than the number of deaths themselves). Of these, worsening of heart failure was the adverse event most often associated with death as the outcome (36 occurrences or 3.4% in the nebivolol group and 42 occurrences or 4.0% in the placebo group), followed by the adverse event of sudden death (34 events or 3.2% and 40 events or 3.8% in the nebivolol and placebo groups, respectively). These were then followed by (in descending order by frequency in the nebivolol group) the AEs of myocardial infarction and cerebrovascular disorder.

Table 27: Treatment Emergent Adverse Events (Recoded by the Reviewer) listing Death as the Outcome, Listed in Descending Order by Frequency in the Nebivolol Arm

Adverse Event	**Nebivolol (n=1067)**	**Placebo (n=1061)**	**Total (n=2128)**
Worsening Of Heart Failure	36 (3.4%)	42 (4.0%)	78 (3.7%)
Sudden Death	34 (3.2%)	40 (3.8%)	74 (3.5%)
Myocardial Infarction	15 (1.4%)	10 (0.9%)	25 (1.2%)
Cerebrovascular Disorder	12 (1.1)	8 (0.8%)	20 (0.9%)
Cardiac Arrest	9 (0.8%)	12 (1.1%)	21 (1.0%)
Cancer	7 (0.7%)	8 (0.8%)	15 (0.7%)
Pneumonia	6 (0.6%)	6 (0.6%)	12 (0.6%)
Gastrointestinal Hemorrhage	4 (0.4%)	2 (0.2%)	6 (0.3%)
Sepsis	4 (0.4%)	1 (0.1%)	5 (0.2%)
Arrhythmia	3 (0.3%)	1 (0.1%)	4 (0.2%)
Cardiogenic Shock	3 (0.3%)	4 (0.4%)	7 (0.3%)
Dyspnea	3 (0.3%)	3 (0.3%)	6 (0.3%)
Multi-Organ Failure	3 (0.3%)	0 (0.0%)	3 (0.1%)
Abdominal Pain	2 (0.2%)	0 (0.0%)	2 (0.1%)
Cardiorespiratory Insufficiency	2 (0.2%)	1 (0.1%)	3 (0.1%)
Cerebrovascular Disease	2 (0.2%)	2 (0.2%)	4 (0.2%)
Pulmonary Edema	2 (0.2%)	6 (0.6%)	8 (0.4%)
Shock, Non-Cardiogenic	2 (0.2%)	0 (0.0%)	2 (0.1%)
Sudden Cardiac Death	2 (0.2%)	14 (1.3%)	16 (0.8%)
Unstable Angina	2 (0.2%)	2 (0.2%)	4 (0.2%)
Ventricular Arrhythmia	2 (0.2%)	4 (0.4%)	6 (0.3%)
Aortic Aneurysm Rupture/Dissection	1 (0.1%)	1 (0.1%)	2 (0.1%)
Arterial Thrombo-Embolic Disease	1 (0.1%)	0 (0.0%)	1 (0.1%)
Cerebral Edema	1 (0.1%)	0 (0.0%)	1 (0.1%)
Cirrhosis	1 (0.1%)	0 (0.0%)	1 (0.1%)

Adverse Event	Nebivolol (n=1067)	Placebo (n=1061)	Total (n=2128)
Death	1 (0.1%)	1 (0.1%)	2 (0.1%)
Edema	1 (0.1%)	0 (0.0%)	1 (0.1%)
Gastroenteritis	1 (0.1%)	0 (0.0%)	1 (0.1%)
Hepatorenal Syndrome	1 (0.1%)	0 (0.0%)	1 (0.1%)
Ileus	1 (0.1%)	0 (0.0%)	1 (0.1%)
Intestinal Obstruction/Perforation	1 (0.1%)	0 (0.0%)	1 (0.1%)
Malaise	1 (0.1%)	1 (0.1%)	2 (0.1%)
Mesenteric Thrombus	1 (0.1%)	0 (0.0%)	1 (0.1%)
Myocardial Ischemia	1 (0.1%)	8 (0.8%)	9 (0.4%)
Pulmonary Embolism	1 (0.1%)	1 (0.1%)	2 (0.1%)
Respiratory Tract Infection	1 (0.1%)	1 (0.1%)	2 (0.1%)
Spinal Cord Lesion	1 (0.1%)	0 (0.0%)	1 (0.1%)
Supra-Ventricular Arrhythmia	1 (0.1%)	1 (0.1%)	2 (0.1%)
Thoracic Injury And Death	1 (0.1%)	0 (0.0%)	1 (0.1%)
Weakness	1 (0.1%)	0 (0.0%)	1 (0.1%)
Weight Gain	1 (0.1%)	0 (0.0%)	1 (0.1%)
Anemia	0 (0.0%)	1 (0.1%)	1 (0.1%)
Angina	0 (0.0%)	1 (0.1%)	1 (0.1%)
Asphyxia	0 (0.0%)	1 (0.1%)	1 (0.1%)
BP Increased	0 (0.0%)	3 (0.3%)	3 (0.1%)
Chest Pain	0 (0.0%)	1 (0.1%)	1 (0.1%)
Fever/Chills	0 (0.0%)	1 (0.1%)	1 (0.1%)
Fracture	0 (0.0%)	1 (0.1%)	1 (0.1%)
Hepatic Dysfunction	0 (0.0%)	1 (0.1%)	1 (0.1%)
Intestinal Ischemia/Infarction	0 (0.0%)	2 (0.2%)	2 (0.1%)
Lymphadenopathy	0 (0.0%)	1 (0.1%)	1 (0.1%)
MVR	0 (0.0%)	1 (0.1%)	1 (0.1%)
Pulmonary Hypertension	0 (0.0%)	1 (0.1%)	1 (0.1%)
Renal Dysfunction	0 (0.0%)	3 (0.3%)	3 (0.1%)
Syncope	0 (0.0%)	1 (0.1%)	1 (0.1%)

[Source: Clinical Reviewer's Analysis]

7.3.2 Nonfatal Serious Adverse Events

There were 2159 serious adverse events (fatal, nonfatal and those with unknown outcome) throughout the course of the trial. When duplicate SAE terms occurring more than once per subject were removed, there were1539 subjects with fatal and nonfatal treatment emergent SAEs [Table 28]. As can be seen, worsening of heart failure was the most common SAE in both the nebivolol and placebo arms, with 143 events in the nebivolol group (13.4%) and 153 events in the placebo group (14.4%). The next most common serious adverse events (listed in descending order by frequency in the nebivolol arm) were those related to cerebrovascular disorder (36 events or 3.4% and 21 events or 2.9% in the nebivolol and placebo arms,

respectively), myocardial infarction (34 events or 3.2 % and 26 events or 2.5% in the nebivolol and placebo arms, respectively), and then sudden death, pneumonia, and unstable angina.

The SAEs found at a higher incidence in the nebivolol compared with the placebo group were anemia (13[1.2%] and 4[0.4%] in the nebivolol and placebo arms, respectively), renal dysfunction (12[1.1%] and 6[0.6%], in the nebivolol and placebo groups, respectively), and edema (5[0.5%] vs. 1 [0.1%] in the two groups, respectively). Overall, however, the numbers of these SAEs in the two groups were two small to make any significant conclusions.

Table 28: All Treatment Emergent Serious Adverse Events (Recoded by the Reviewer), Listed in Descending Order by Frequency in the Nebivolol arm (Fatal, Nonfatal, and those of unknown outcome)

Adverse Event	**Nebivolol (n=1067)**	**Placebo (n=1061)**	**Total (n=2128)**
Worsening Of Heart Failure	143 (13.4%)	153 (14.4%)	296 (13.9%)
Cerebrovascular Disorder	36 (3.4%)	31 (2.9%)	67 (3.1%)
Myocardial Infarction	34 (3.2%)	26 (2.5%)	60 (2.8%)
Sudden Death	34 (3.2%)	40 (3.8%)	74 (3.5%)
Pneumonia	33 (3.1%)	26 (2.5%)	59 (2.8%)
Unstable Angina	32 (3.0%)	52 (4.9%)	84 (3.9%)
Cancer	29 (2.7%)	23 (2.2%)	52 (2.4%)
Dyspnea	20 (1.9%)	16 (1.5%)	36 (1.7%)
Pulmonary Edema	16 (1.5%)	24 (2.3%)	40 (1.9%)
Supra-Ventricular Arrhythmia	16 (1.5%)	27 (2.5%)	43 (2.0%)
Anemia	13 (1.2%)	4 (0.4%)	17 (0.8%)
Cardiac Pacemaker Implantation/Dysfunction/Battery Change	13 (1.2%)	9 (0.8%)	22 (1.0%)
Renal Dysfunction	12 (1.1%)	6 (0.6%)	18 (0.8%)
Ventricular Arrhythmia	11 (1.0%)	11 (1.0%)	22 (1.0%)
Cardiac Arrest	10 (0.9%)	13 (1.2%)	23 (1.1%)
Chest Pain	10 (0.9%)	12 (1.1%)	22 (1.0%)
Bradycardia	9 (0.8%)	6 (0.6%)	15 (0.7%)
Fracture	9 (0.8%)	17 (1.6%)	26 (1.2)
Respiratory Tract Infection	9 (0.8%)	4 (0.4%)	13 (0.6%)
Syncope	9 (0.8%)	10 (0.9%)	19 (0.9%)
Arrhythmia	8 (0.7%)	8 (0.8%)	16 (0.8%)
BP Increased	8 (0.7%)	17 (1.6%)	25 (1.2%)
Bronchitis	8 (0.7%)	8 (0.8%)	16 (0.8%)
Gastrointestinal Hemorrhage	8 (0.7%)	10 (0.9%)	18 (0.8%)
Sepsis	7 (0.7%)	2 (0.2%)	9 (0.4%)
Urinary Tract Infection	7 (0.7%)	6 (0.6%)	13 (0.6%)
Angiography	6 (0.6%)	9 (0.8%)	15 (0.7%)
Cholecystitis	6 (0.6%)	3 (0.3%)	9 (0.4%)

Adverse Event	Nebivolol (n=1067)	Placebo (n=1061)	Total (n=2128)
Hernia	6 (0.6%)	4 (0.4%)	10 (0.5%)
Low BP	6 (0.6%)	5 (0.5%)	11 (0.5%)
Abdominal Pain	5 (0.5%)	9 (0.8%)	14 (0.7%)
Edema	5 (0.5%)	1 (0.1%)	6 (0.3%)
Glucose Intolerance	5 (0.5%)	3 (0.3%)	8 (0.4%)
Pleural Effusion	5 (0.5%)	2 (0.2%)	7 (0.3%)
Arthritis	4 (0.4%)	2 (0.2%)	6 (0.3%)
Dizziness	4 (0.4%)	4 (0.4%)	8 (0.4%)
Gastric/Duodenal Ulcers	4 (0.4%)	5 (0.5%)	9 (0.4%)
Intestinal Obstruction/Perforation	4 (0.4%)	2 (0.2%)	6 (0.3%)
Myocardial Ischemia	4 (0.4%)	11 (1.0%)	15 (0.7%)
Pancreatitis	4 (0.4%)	2 (0.2%)	6 (0.3%)
Pulmonary Embolism	4 (0.4%)	5 (0.5%)	9 (0.4%)
Venous Thrombosis	4 (0.4%)	2 (0.2%)	6 (0.3%)
Volume Depletion	4 (0.4%)	2 (0.2%)	6 (0.3%)
Weakness	4 (0.4%)	1 (0.1%)	5 (0.2%)
Biliary Stones/Colic	3 (0.3%)	0 (0.0%)	3 (0.1%)
Cardiogenic Shock	3 (0.3%)	4 (0.4%)	7 (0.3%)
Cataract	3 (0.3%)	9 (0.8%)	12 (0.6%)
Cholecystectomy	3 (0.3%)	3 (0.3%)	6 (0.3%)
Complete Heart Block	3 (0.3%)	6 (0.6%)	9 (0.4%)
Fall	3 (0.3%)	7 (0.7%)	10 (0.5%)

Each subject was counted only once per row; however, an individual subject could be in more than one row.

[Source: Clinical Reviewer's Analysis]

There were 1675 serious adverse events which were nonfatal throughout the course of the trial (this analysis excludes both AEs listing death as the outcome and those with the outcome unknown). When duplicate SAE terms occurring more than once per subject were removed, there were 1157 subjects with nonfatal treatment emergent SAEs [Table 29]. As can be seen, worsening of heart failure was the most common SAE in both the nebivolol and placebo arms. The next most common serious adverse events (listed in descending order by frequency in the nebivolol arm) were those related to unstable angina, pneumonia, cerebrovascular disorder, and finally myocardial infarction.

The nonfatal SAEs found at a higher incidence in the nebivolol compared with the placebo group were anemia (13[1.2%] and 2[0.2%] in the nebivolol and placebo arms, respectively), renal dysfunction (11[1.0%] and 3[0.3%], in the nebivolol and placebo groups, respectively), and edema (4[0.4%] vs. 1 [0.1%] in the two groups, respectively). Overall, however, the numbers of these nonfatal SAEs in the two groups were too small to make any significant conclusions.

Table 29: Nonfatal Treatment Emergent Serious Adverse Events (Recoded by the Reviewer), Listed in Descending Order by Frequency in the Nebivolol arm

Adverse Event	**Nebivolol (n=1067)**	**Placebo (n=1061)**	**Total (n=2128)**
Worsening Of Heart Failure	107 (10.0%)	117 (11.0%)	224 (10.5%)
Unstable Angina	30 (2.8%)	47 (4.4%)	77 (3.6%)
Pneumonia	26 (2.4%)	17 (1.6%)	43 (2.0%)
Cerebrovascular Disorder	23 (2.2%)	23 (2.2%)	46 (2.2%)
Myocardial Infarction	21 (2.0%)	18 (1.7%)	39 (1.8%)
Cancer	18 (1.7%)	15 (1.4%)	33 (1.6%)
Dyspnea	15 (1.4%)	12 (1.1%)	27 (1.3%)
Supra-Ventricular Arrhythmia	15 (1.4%)	26 (2.5%)	41 (1.9%)
Pulmonary Edema	14 (1.3%)	18 (1.7%)	32 (1.5%)
Anemia	13 (1.2%)	2 (0.2%)	15 (0.7%)
Cardiac Pacemaker Implantation/Dysfunction/Battery Change	13 (1.2%)	9 (0.8%)	22 (1.0%)
Renal Dysfunction	11 (1.0%)	3 (0.3%)	14 (0.7%)
Chest Pain	10 (0.9%)	11 (1.0%)	21 (1.0%)
Bradycardia	9 (0.8%)	5 (0.5%)	14 (0.7%)
BP Increased	8 (0.7%)	13 (1.2%)	21 (1.0%)
Bronchitis	8 (0.7%)	8 (0.8%)	16 (0.8%)
Fracture	8 (0.7%)	14 (1.3%)	22 (1.0%)
Ventricular Arrhythmia	8 (0.7%)	6 (0.6%)	14 (0.7%)
Respiratory Tract Infection	7 (0.7%)	3 (0.3%)	10 (0.5%)
Syncope	7 (0.7%)	9 (0.8%)	16 (0.8%)
Urinary Tract Infection	7 (0.7%)	6 (0.6%)	13 (0.6%)
Angiography	6 (0.6%)	9 (0.8%)	15 (0.7%)
Cholecystitis	6 (0.6%)	3 (0.3%)	9 (0.4%)
Hernia	6 (0.6%)	3 (0.3%)	9 (0.4%)
Arrhythmia	5 (0.5%)	7 (0.7%)	12 (0.6%)
Gastrointestinal Hemorrhage	5 (0.5%)	9 (0.8%)	14 (0.7%)
Glucose Intolerance	5 (0.5%)	3 (0.3%)	8 (0.4%)
Pleural Effusion	5 (0.5%)	2 (0.2%)	7 (0.3%)
Arthritis	4 (0.4%)	2 (0.2%)	6 (0.3%)
Dizziness	4 (0.4%)	4 (0.4%)	8 (0.4%)
Edema	4 (0.4%)	1 (0.1%)	5 (0.2%)
Gastric/Duodenal Ulcers	4 (0.4%)	5 (0.5%)	9 (0.4%)
Low BP	4 (0.4%)	5 (0.5%)	9 (0.4%)
Pancreatitis	4 (0.4%)	2 (0.2%)	6 (0.3%)
Venous Thrombosis	4 (0.4%)	2 (0.2%)	6 (0.3%)

Each subject was counted only once per row; however, an individual subject could be in more than one row.

[Source: Clinical Reviewer's Analysis]

7.3.3 Dropouts and/or Discontinuations

There were 288 and 307 discontinuations in the nebivolol and placebo arms, respectively. The number of subjects discontinuing the trial for reasons of subject request, loss to follow-up, adverse event, and death were fairly well balanced between the nebivolol- and placebo-treated arms, as can be seen in Table 30. We reviewed all of the narratives of subjects discontinuing the trial due to the reason of adverse event, which can be found in Table 31, below. There were a total of 13 such cases in the nebivolol group and 14 in the placebo group. Of these, four of the case report forms, or (CRFs) didn't specify which AE resulted in the discontinuation and 1 of the CRFs (that of a nebivolol-treated subject) was not submitted to us by the sponsor. For all of these subjects, there was an AE which had 'discontinued study' checked off on the AE page, but not all of them had AE written as the reason for discontinuation on the investigator's discontinuation page, which presented somewhat of a discrepancy.

Looking at the nature of the adverse events associated with these premature discontinuations, bradycardia accounted for 4 discontinuations in the nebivolol group and 1 discontinuation in the placebo group. There were 2 subjects in the nebivolol arm and 3 subjects in the placebo arm who discontinued for reasons pertaining to heart failure/pulmonary edema. Of note, in the nebivolol arm, two subjects discontinued due to dizziness and 1 subject discontinued for the reason of symptomatic postural hypotension. In the placebo arm, there were three discontinuations related to rhythm disturbances other than bradycardia, one for third degree AVB with junctional rhythm, one subject who prematurely stopped the trial due to atrial fibrillation, and one who stopped due to RBBB.

Table 30: Primary Reason for Discontinuation from Trial

	Nebivolol (N=1067)	**Placebo (N=1061)**
Per Subject Request	76	78
Lost to Follow-up	24	19
Adverse Event	13	14
Death	160	178
Other Reason	15	18
Total Discontinuations	288	307

[Source: Clinical Reviewer's Analysis]

Table 31: Table of Treatment Emergent Adverse Events Resulting in Permanent Discontinuation from Trial

	D/C Due to	Adverse Event	SAE	D/C Narrative
Nebivolol				
210/20850	AE /Pt Request	Symptomatic Postural Hypotension, BP 90/60	No	*"Due to symptomatic postural hypotension, the patient refused to continue participation. The last visit that she accepted…was M2"*
226/20806	AE	Bradycardia to 40 bpm	No	*None*
325/21192	AE/Death	Worsening of Heart Failure	Yes	*None*
331/21229	CRF not provided			
422/21473	AE	Headache/Dizziness /SOB Esophageal Ca	No No Yes	*"AE of Esophageal Ca"*
603/21934	AE and other reason	* Not Specified		*"end of study is discharge date hospitalization 21-01-2004-no FFU planned"*
615/22523	AE	Dizziness Tiredness/Fatigue Intolerance to higher dose	No No No	*"Patient developed bradycardia accompanied by hypotension and excessive tiredness and FFU not done by mistake"*
616/22527	AE	Bradycardia	No	*None*
616/22738	AE/Pt Request	Sleeping Disturbance Contraindication to BBl	No No	*None*
621/22568	AE/Death	Bradycardia	No	*None*
621/22570	AE/Death	Bradycardia	No	*None*
920/22373	AE	* Not Specified		*None*
920/22374	Other reason	Worsening Heart Failure (listed as AE)	Yes	*"Mandatory Indication for BBl has developed"*
Placebo				
113/20298	AE/Pt request	Worsening Heart Failure	Yes	*"After worsening of heart failure and repeating adverse events the patient decided to stop his participation in the study"*
202/20616	AE	Pulmonary Edema	Yes	*None*
212/20693	AE	Third degree AVB with Junctional Rhythm	No	*"Two or more visits were performed for trying retitration, which was not possible due to 3rd degree AVB"*
226/20808	Death	Atrial Fibrillation (listed as AE)	Yes	*None*
322/21160	AE	* Not Specified		*"The FFU visit was not performed due to documented severe adverse events…"(rest is illegible)*
325/20937	AE	* Not Specified		*None*

	D/C Due to	Adverse Event	SAE	D/C Narrative
331/21231	AE	Bradycardia	Yes	*None*
403/21321	AE	Acute Myocardial Infarction	Yes	*"Patient withdrawn due to…[illegible]…of adverse events"*
410/21373	AE	Tired and lethargic	No	*"Increasing tiredness reported on page 82"*
616/22526	AE/Pt request	Fatigue	No	*None*
		Dyspnea	No	
626/22076	Other reason	Bronchial Carcinoma (listed as AE)	Yes	*"Patient died on 24-06-2003"*
711/21883	AE	Right BBB	Yes	*None*
802/22189	Other reason	Vertebral Fracture (listed as AE)	Yes	*"The patient was hospitalized due to fracture vertebrae. Further participation was not able [to be] allowed"*
920/22376	AE	Heart Failure	Yes	*None*

* Not Specified – CRF does not specify which AE resulted in the premature discontinuation

[Source: Clinical Reviewer's Analysis]

7.3.4 Significant Adverse Events

The adverse events which have been described in the CRFs as severe in intensity are shown in Table 32. The most common serious adverse events, in descending order of frequency, were worsening of heart failure, sudden death, cancer, myocardial infarction, and cerebrovascular disorder. The numbers of subjects with these adverse events in each treatment group are too small to make any valid conclusions about the differences between the groups.

Table 32: Treatment Emergent Adverse Events with Intensity Described as Severe (Recoded by the Reviewer), Listed in Descending Order by Frequency in the Nebivolol Arm

Adverse Event	Nebivolol (n=1067)	Placebo (n=1061)	Total (n=2128)
Worsening Of Heart Failure	79 (7.4%)	94 (8.9%)	173 (8.1%)
Sudden Death	33 (3.1%)	35 (3.3%)	68 3.2%)
Cancer	25 (2.3%)	16 (1.5%)	41 (1.9%)
Myocardial Infarction	24 (2.2%)	19 (1.8%)	43 (2.0%)
Cerebrovascular Disorder	23 (2.2%)	18 (1.7%)	41 (1.9%)
Unstable Angina	20 (1.9%)	19 (1.8%)	39 (1.8%)
Dyspnea	17 (1.6%)	16 (1.5%)	33 (1.6%)
Pneumonia	17 (1.6%)	17 (1.6%)	34 (1.6%)
Pulmonary Edema	14 (1.3%)	17 (1.6%)	31 (1.5%)
Anemia	10 (0.9%)	4 (0.4%)	14 (0.7%)
BP Increased	10 (0.9%)	10 (0.9%)	20 (0.9%)
Cardiac Arrest	9 (0.8%)	13 (1.2%)	22 (1.0%)
Ventricular Arrhythmia	9 (0.8%)	7 (0.7%)	16 (0.8%)
Dizziness	8 (0.7%)	5 (0.5%)	13 (0.6%)
Renal Dysfunction	8 (0.7%)	4 (0.4%)	12 (0.6%)

Sepsis	7 (0.7%)	1 (0.1%)	8 (0.4%)
Syncope	7 (0.7%)	9 (0.8%)	16 (0.8%)
Abdominal Pain	6 (0.6%)	4 (0.4%)	10 (0.5%)
Arrhythmia	6 (0.6%)	3 (0.3%)	9 (0.4%)
Chest Pain	6 (0.6%)	2 (0.2%)	8 (0.4%)
Headache	6 (0.6%)	3 (0.3%)	9 (0.4%)
Respiratory Tract Infection	6 (0.6%)	2 (0.2%)	8 (0.4%)
Supra-Ventricular Arrhythmia	6 (0.6%)	10 (0.9%)	16 (0.8%)
Back Pain	5 (0.5%)	2 (0.2%)	7 (0.3%)
Bradycardia	5 (0.5%)	1 (0.1%)	6 (0.3%)
Gastrointestinal Hemorrhage	5 (0.5%)	6 (0.6%)	11 (0.5%)
Hyperuricemia	5 (0.5%)	3 (0.3%)	8 (0.4%)
Cholecystitis	4 (0.4%)	2 (0.2%)	6 (0.3%)
Fracture	4 (0.4%)	12 (1.1%)	16 (0.8%)

Each subject was counted only once per row; however, an individual subject could be in more than one row.

[Source: Clinical Reviewer's Analysis]

7.3.5 Submission Specific Primary Safety Concerns

Submission specific primary safety concerns include adverse events related to the spectrum of bradycardia/heart block and that of hypotension/dizziness/orthostasis/syncope, both of which were indeed found at greater frequency in the nebivolol-treated subjects compared to the placebo-treated subjects in the SENIORS trial.

Of all of these beta-blocker associated 'expected' adverse events, the difference between the two treatment groups was by far the most dramatic with regard to bradycardia. In the nebivolol-treated subjects, bradycardia was noted in 153, or 14.3%, of subjects, compared with 38, or 3.6%, of placebo-treated subjects. AV Block (not including complete heart block) was found in 26 subjects in the nebivolol group (2.4%), compared with 23 subjects in the placebo group (2.2%).

Hypotension was found in 105 (9.8%) of the nebivolol-treated subjects compared with 88 (8.3%) of the placebo-treated subjects. Dizziness was also found at a higher frequency in the nebivolol compared to the placebo groups (169 [15.8%] versus 145 [13.7%]). Similarly, orthostatic hypotension was also found at a greater frequency in the nebivolol group, at 49 subjects (4.6%), compared with 30 subjects (2.8%), in the placebo group. Along the same spectrum, syncope was found in 29 (2.7%) of the nebivolol subjects, compared with 21 (2.0%) of the placebo treated subjects.

Fatigue and weakness are other adverse events frequently noted with beta-blocker therapy. In the SENIORS trial, both fatigue and weakness were found at higher frequencies in the treatment group compared with placebo (fatigue was noted in 92, or 8.6%, of the nebivolol-treated subjects, compared with 77, or 7.3%, of the placebo-treated subjects, and weakness was seen in 34, or 3.2%, and 20, or 1.9%, of nebivolol and placebo-treated subjects, respectively.)

Table 33: Adverse Events Expected with Nebivolol

Adverse Event	Nebivolol (n=1067)	Placebo (n=1061)
Bradycardia	153 (14.3%)	38 (3.6%)
Hypotension	105 (9.8%)	88 (8.3%)
Orthostasis	49 (4.6%)	30 (2.8%)
Dizziness	169 (15.8%)	145 (13.7%)
Syncope	29 (2.7%)	21 (2.0%)
Fatigue and weakness	126 (11.8%)	97 (9.1%)

[Source: Clinical Reviewer's Analysis]

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 911 subjects, or 85.4%, in the nebivolol group and 900 subjects, or 84.8%, in the placebo group experienced at least one AE while enrolled in the trial [Table 34]. All of these subjects had received study medication at some point in the trial, but not all were on treatment at the time of the occurrence of the AE. Of these individuals, 861 nebivolol-treated subjects and 846 placebo-treated subjects reported at least one AE during the time period in which they were actually receiving study drug.

Table 34: Overview of Adverse Events in the SENIORS Trial - ITT Population

Category	*No. (%) of Patients Experiencing an Adverse Event*		
	Nebivolol (N = 1067)	*Placebo (N = 1061)*	*Overall (N = 2128)*
At least 1 AE	911 (85.4)	900 (84.8)	1811 (85.1)
Any mild AE	701 (65.7)	658 (62.0)	1359 (63.9)
Any moderate AE	674 (63.2)	646 (60.9)	1320 (62.0)
Any severe AE	328 (30.7)	347 (32.7)	675 (31.7)
Any AE related to study drug	573 (53.7)	472 (44.5)	1045 (49.1)
Any AE causing discontinuation	165 (15.5)	136 (12.8)	301 (14.1)
Any SAE	432 (40.5)	468 (44.1)	900 (42.3)
Any SAE related to study drug	113 (10.6)	118 (11.1)	231 (10.9)
Deaths reported as an SAE	165 (15.5)	182 (17.2)	347 (16.3)

[Source: pg, Integrated Summary of Safety]

Table 35 presents the most commonly occurring AEs in the trial as per the reviewer's analysis, after recoding by the reviewer to allow for categorization of the AEs into more clinically meaningful terms (see Section 7.1.2). The most common adverse events in the trial were worsening of heart failure, dizziness, bradycardia, and dyspnea, which is expected given that the trial involves subjects with heart failure (and thus the AEs of worsening of heart failure and dyspnea) and treatment with a beta-blocker (dizziness and bradycardia). Nebivolol was also associated with an increased frequency of some other, unexpected treatment emergent adverse effects. These include renal dysfunction (present in108 subjects, or 10.1%, in the nebivolol group compared with 78, or 7.4%, in the placebo group), edema (present in 103 subjects, or 9.7%, in the nebivolol-treated subjects compared with 61, or 5.7%, in the placebo-treated subjects), and hyperuricemia (present in 79 subjects, or 7.4% of the nebivolol group compared with 41 subjects, or 3.9%, in the placebo group). Also seen at higher frequencies in the nebivolol group compared with placebo were the GI effects of nausea/vomiting and diarrhea, though the numbers of subjects was too low to see significant differences. Elevated BUN and hyperkalemia were also present in a greater number of subjects in the nebivolol group compared with placebo, which is likely related to the effects of nebivolol on renal function.

Table 35: Reviewer's Analysis of Treatment-Emergent Adverse Events with Reviewer's Coding (≥ 2% in the Nebivolol Subjects) by Treatment Group – ITT Population

Adverse Event	**Nebivolol (n=1067)**	**Placebo (n=1061)**	**Total (n=2128)**
Worsening Of Heart Failure	289 (27.1%)	304 (28.7%)	593 (27.9%)
Dizziness	169 (15.8%)	145 (13.7%)	314 (14.8%)
Bradycardia	153 (14.3%)	38 (3.6%)	191 (9.0%)
Dyspnea	138 (12.9%)	147 (13.9%)	285 (13.4%)
Elevated BP	128 (12.0%)	122 (11.5%)	250 (11.7%)
Renal Dysfunction	108 (10.1%)	78 (7.4%)	186 (8.7%)
Decreased BP	105 (9.8%)	88 (8.3%)	193 (9.1%)
Respiratory Tract Infection	104 (9.7%)	90 (8.5%)	194 (9.1%)
Edema	103 (9.7%)	61 (5.7%)	164 (7.7%)
Supra-Ventricular Arrhythmia	101 (9.5%)	109 (10.3%)	210 (9.9%)
Fatigue	92 (8.6%)	77 (7.3%)	169 (7.9%)
Unstable Angina	91 (8.5%)	116 (10.9%)	207 (9.7%)
Hyperuricemia	79 (7.4%)	41 (3.9%)	120 (5.6%)
Headache	63 (5.9%)	56 (5.3%)	119 (5.6%)
Bronchitis	59 (5.5%)	66 (6.2%)	125 (5.9%)
Glucose Intolerance	55 (5.2%)	58 (5.5%)	113 (5.3%)
Urinary Tract Infection	53 (5.0%)	57 (5.4%)	110 (5.2%)
Orthostasis	49 (4.6%)	30 (2.8%)	79 (3.7%)
Anemia	47 (4.4%)	46 (4.3%)	93 (4.4%)
Chest Pain	47 (4.4%)	26 (2.5%)	73 (3.4%)
Nausea And Vomiting	47 (4.4%)	31 (2.9%)	78 (3.7%)
Pneumonia	46 (4.3%)	43 (4.1%)	89 (4.2%)
Ventricular Arrhythmia	42 (3.9%)	58 (5.5%)	100 (4.7%)

Adverse Event	Nebivolol (n=1067)	Placebo (n=1061)	Total (n=2128)
Cerebrovascular Disorder	39 (3.7%)	38 (3.6%)	77 (3.6%)
Myocardial Ischemia	39 (3.7%)	41 (3.9%)	80 (3.8%)
Diarrhea	35 (3.3%)	21 (2.0%)	56 (2.6%)
Hypercholesterolemia	34 (3.2%)	31 (2.9%)	65 (3.1%)
Myocardial Infarction	34 (3.2%)	28 (2.6%)	62 (2.9%)
Sudden Death	34 (3.2%)	40 (3.8%)	74 (3.5%)
Weakness	34 (3.2%)	20 (1.9%)	54 (2.5%)
Hyperlipidemia	32 (3.0%)	20 (1.9%)	52 (2.4%)
Tachycardia	32 (3.0%)	42 (4.0%)	74 (3.5%)
Back Pain	30 (2.8%)	21 (2.0%)	51 (2.4%)
Cancer	30 (2.8%)	29 (2.7%)	59 (2.8%)
Syncope	29 (2.7%)	21 (2.0%)	50 (2.3%)
Abdominal Pain	28 (2.6%)	30 (2.8%)	58 (2.7%)
Constipation	28 (2.6%)	23 (2.2%)	51 (2.4%)
Elevated Bun	28 (2.6%)	20 (1.9%)	48 (2.3%)
AV Block	26 (2.4%)	23 (2.2%)	49 (2.3%)
Traumatic Injury	26 (2.4%)	20 (1.9%)	46 (2.2%)
Arthritis	25 (2.3%)	19 (1.8%)	44 (2.1%)
Intolerance to Study Drug/Beta Blocker	24 (2.2%)	14 (1.3%)	38 (1.8%)
Pulmonary Edema	24 (2.2%)	28 (2.6%)	52 (2.4%)
Arrhythmia	23 (2.2%)	34 (3.2%)	57 (2.7%)
Arthralgia	23 (2.2%)	22 (2.1%)	45 (2.1%)
Cough	23 (2.2%)	33 (3.1%)	56 (2.6%)
Rash	23 (2.2%)	22 (2.1%)	45 (2.1%)
Hyperkalemia	21 (2.0%)	9 (0.8%)	30 (1.4%)
Pain In Limbs	21 (2.0%)	11 (1.0%)	32 (1.5%)

Each subject was counted only once per row; however, an individual subject could be in more than one row.

[Source: Clinical Reviewer's Analysis]

Table 36 shows the reviewer's analysis of treatment-emergent adverse events in the SENIORS ITT population by system organ class (SOC). By far, the greatest numbers of adverse events in the trial were related to the cardiac disorders SOC, for both the nebivolol and placebo arms, which is to be expected given that the subjects were enrolled on the basis of having heart failure. Adverse events related to the vascular and infectious diseases SOCs were also observed at high frequencies in both arms of the trial. Adverse events in the gastrointestinal, general disorders and administration site conditions, metabolism, nervous system, and renal and urinary disorders SOCs were seen at greater frequency in the nebivolol-treated subjects than those treated with placebo.

Table 36: Reviewer's Analysis of Treatment-Emergent Adverse Events by System Organ Class – ITT Population

System Organ Class (SOC)	Nebivolol (n=1067)	Placebo (n=1061)	Total (n=2128)
Blood And Lymphatic System Disorders	59 (5.5%)	56 (5.3%)	115 (5.4%)
Cardiac Disorders	568 (53.2%)	561 (52.9%)	1129 (53.1%)
Congenital, Familial And Genetic Disorders	0 (0.0%)	1 (0.1%)	1 (0.0%)
Ear And Labyrinth Disorders	23 (2.2%)	19 (1.8%)	42 (2.0%)
Endocrine Disorders	18 (1.7%)	19 (1.8%)	37 (1.7%)
Eye Disorders	29 (2.7%)	27 (2.5%)	56 (2.6%)
Gastrointestinal Disorders	195 (18.3%)	155 (14.6%)	350 (16.4%)
General Disorders And Administration Site Conditions	297 (27.8%)	252 (23.8%)	549 (25.8%)
Hepatobiliary Disorders	46 (4.3%)	37 (3.5%)	83 (3.9%)
Immune System Disorders	4 (0.4%)	5 (0.5%)	9 (0.4%)
Infections And Infestations	284 (26.6%)	272 (25.6%)	556 (26.1%)
Injury, Poisoning And Procedural Complications	48 (4.5%)	56 (5.3%)	104 (4.9%)
Investigations	208 (19.5%)	182 (17.2%)	390 (18.3%)
Metabolism And Nutrition Disorders	175 (16.4%)	132 (12.4%)	307 (14.4%)
Musculoskeletal And Connective Tissue Disorders	123 (11.5%)	115 (10.8%)	238 (11.2%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	41 (3.8%)	40 (3.8%)	81 (3.8%)
Nervous System Disorders	279 (26.1%)	252 (23.8%)	531 (25.0%)
Psychiatric Disorders	46 (4.3%)	52 (4.9%)	98 (4.6%)
Renal And Urinary Disorders	124 (11.6%)	108 (10.2%)	232 (10.9%)
Reproductive System And Breast Disorders	25 (2.3%)	17 (1.6%)	42 (2.0%)
Respiratory, Thoracic And Mediastinal Disorders	201 (18.8%)	221 (20.8%)	422 (19.8%)
Skin And Subcutaneous Tissue Disorders	59 (5.5%)	62 (5.8%)	121 (5.7%)
Social Circumstances	1 (0.1%)	2 (0.2%)	3 (0.1%)
Surgical And Medical Procedures	63 (5.9%)	61 (5.7%)	124 (5.8%)
Vascular Disorders	294 (27.6%)	268 (25.3%)	562 (26.4%)

[Source: Clinical Reviewer's Analysis]

7.4.2 Laboratory Findings

With regard to laboratory data, the tests of interest for nebivolol were those of renal function, hepatic function, and uric acid. As can be seen in Table 37 and Table 38, there were greater number of subjects with laboratory values out of the reference range in the nebivolol group

than the placebo group for creatinine, potassium, AST, and Uric Acid, but the differences in mean laboratory values were not significant.

Table 37: Subjects with Laboratory Data out of the Reference Range for the Nebivolol and Placebo groups

Laboratory Test	Nebivolol	Placebo
Creatinine	621	604
Potassium	457	412
AST	189	162
ALT	171	175
Uric Acid	714	683

[Source: Clinical Reviewer's Analysis]

Table 38: Mean Laboratory Values for the Nebivolol and Placebo groups

Laboratory Test	Nebivolol	Placebo
	Mean ± SD	**Mean ± SD**
Creatinine	144.2 ± 42.0	144.5 ± 99.7
Potassium	5.50 ± 0.39	5.50 ± 0.41
AST	59.5 ± 41.9	68.9 ± 52.4
ALT	66.3 ± 44.2	78.1 ± 83.6
Uric Acid	497.7 ± 96.5	504.0 ± 96.5
Hemoglobin	17.5 ± 1.6	17.9 ± 1.5
Hematocrit	51.5 ± 4.0	51.6 ± 3.9

[Source: Clinical Reviewer's Analysis]

7.4.3 Vital Signs

Table 39 shows the heart rate and blood pressure values at baseline and with treatment in both arms of the trial. The only caveat to this is that all of the post-baseline visits have been combined to obtain the mean treated value, so the temporal effect of progressive treatment on blood pressure and heart rate are not able to be discerned from these data. The data does reveal an effect on heart rate with nebivolol treatment, from a mean HR of 78.9 ± 13.7 at baseline to 70.6 ± 12.7 with nebivolol treatment. With placebo treatment, as expected, the heart rate remains relatively unchanged, from a mean of 78.9 ± 13.5 at baseline to 77.4 ± 13.3 upon treatment with placebo. Overall, no significant change in blood pressure was noted with nebivolol treatment compared with placebo.

Table 39: Heart Rate and Blood Pressure (Sitting/Standing) at Baseline and with Treatment (All post-baseline visits combined for the treated values) – ITT Population

	Nebivolol	**Placebo**	**Total ITT**
Baseline Heart Rate (bpm)			
N	1067	1061	2128
Mean ± SD	78.9 ± 13.7	78.9 ± 13.5	78.9 ± 13.6
Median	76	76	76
Range (Min,Max)	43, 150	48, 159	43, 159
Heart Rate with Treatment (bpm)			
N	1067	1061	2128
Mean ± SD	70.6 ± 12.7	77.4 ± 13.3	74.0 ± 13.5
Median	69	76	72
Range (Min,Max)	37, 158	40, 165	37, 165
Baseline Sitting Systolic BP (mmHg)			
N	1067	1061	2128
Mean ± SD	139.4 ± 20.0	140.5 ± 21.2	139.9 ± 20.6
Median	140	140	140
Range (Min,Max)	88, 230	94, 240	88, 240
Baseline Sitting Diastolic BP (mmHg)			
N	1067	1061	2128
Mean ± SD	80.9 ± 10.8	81.1 ± 11.2	81.0 ± 11.0
Median	80	80	80
Range (Min,Max)	42.5, 121	50, 120	42.5, 121
Sitting Systolic BP with			

	Nebivolol	Placebo	Total ITT
Treatment (mmHg)			
N	1067	1061	2128
Mean ± SD	133.6 ± 19.0	135.6 ± 19.4	134.6 ± 19.3
Median	132.5	135	135
Range (Min,Max)	71, 260	73, 240	71, 260
Sitting Diastolic BP with Treatment (mmHg)			
N	1067	1061	2128
Mean ± SD	77.1 ± 10.1	78.5 ± 10.2	77.8 ± 10.2
Median	80	80	80
Range (Min,Max)	37, 130	37.5, 137	37, 137
Baseline Standing Systolic BP (mmHg)			
N	1066	1061	2127
Mean ± SD	137.8 ± 20.5	138.3 ± 21.2	138.1 ± 20.8
Median	138	140	140
Range (Min,Max)	73, 240	90, 220	73, 240
Baseline Standing Diastolic BP (mmHg)			
N	1066	1061	2127
Mean ± SD	80.7 ± 10.9	81.3 ± 11.3	81.0 ± 11.1
Median	80	80	80
Range (Min,Max)	40, 120	50, 125	40, 125
Standing Systolic BP with Treatment (mmHg)			
N	1066	1061	2127
Mean ± SD	131.4 ± 19.4	133.4 ± 19.6	132.4 ± 19.5
Median	130	131	130
Range (Min,Max)	67, 240	71, 280	67, 280
Standing Diastolic BP with Treatment (mmHg)			
N	1066	1061	2127
Mean ± SD	77.0 ± 10.3	78.4 ± 10.4	77.7 ± 10.4
Median	80	80	80
Range (Min,Max)	36, 151	35, 125	35, 151

[Source: Clinical Reviewer's Analysis]

Table 40 shows the weight at baseline and with treatment (nebivolol versus placebo), though again all post baseline weight measurements have been combined, and their average taken, for the treatment value. As can be seen in the table, there is no significant change in weight with either treatment per this analysis.

Table 40: Weight at Baseline and with Treatment (All post-baseline visits combined for the treated values) - ITT Population only

	Nebivolol	**Placebo**	**Total ITT**
Baseline Weight (kg)	1067	1061	2128
Mean ± SD	75.0 ± 13.2	75.2 ± 12.8	75.1 ± 13.0
Median	74	75	75
Range (Min,Max)	31, 126	43, 129	31, 129
Weight with Treatment(kg)			
N	1058	1048	2106
Mean ± SD	75.5 ± 13.2	75.1 ± 12.8	75.3 ± 13.0
Median	75	75	75
Range (Min,Max)	28, 141	39, 138	28, 141

[Source: Clinical Reviewer's Analysis]

7.4.4 Electrocardiograms (ECGs)

There were minor differences between the treatment groups in the percentage of patients having post-baseline changes in PR or QT intervals [Table 41]. A slightly lower percentage of subjects in the nebivolol group compared to the placebo group had post-baseline changes of prolongation of the QT interval (corrected for time) [26.7% (231 subjects) versus 28.0% (235 subjects), respectively]. A slightly higher percentage of subjects in the nebivolol group compared to the placebo group had post-baseline changes of prolongation of the PR interval [10.2% (71 subjects) versus 9.3%, (63 subjects), respectively].

Table 41: Incidence of Potentially Clinically Significant Post-baseline ECG Values – ITT population

ECG Parameter(Unit) PCS Criterion	*Nebivlol (N = 1067) n / N1 (%)*	*Placebo (N = 1061) n / N1 (%)*
PR interval ≥ 250 msec	71/695 (10.2%)	63/678 (9.3%)
QTcB > 500 msec	231/865 (26.7%)	235/838 (28.0%)

Source: Forest CSR, Appendix 14, Table 14.5.4.1
ECG = electrocardiogram; ITT = intent to treat; n = number of patients (of the N1 patients) who met the criterion at least once during the study; N1 = number of patients with available non-PCS baseline and at least one postbaseline assessments; PCS = potentially clinically significant; QTcB = QT/Square root of RR.

[Source: pg 207, Volume 1 of the Forest SENIORS Study Report]

7.4.5 Special Safety Studies/Clinical Trials

Special safety studies/clinical trials were not indicated for this supplemental NDA for an already approved agent.

7.4.6 Immunogenicity

Given that this product is not a biologic and furthermore is an already approved agent, immunogenicity studies were not indicated.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The adverse events were not adequately characterized to determine dose dependency for the adverse events.

7.5.2 Time Dependency for Adverse Events

The adverse events were not adequately characterized to determine time dependency for the adverse events.

7.5.3 Drug-Demographic Interactions

Race
With regard to race, there were only 9 subjects in the trial who were not Caucasian, and thus there was insufficient data to make any conclusions about the effect of race on the safety results.

Gender
Table 42 shows the most common treatment-emergent adverse events in SENIORS subgrouped by treatment and by gender. From this table, one can see that females had a higher

incidence of hypertension which was seen in both nebivolol and placebo but was more pronounced in the nebivolol group (11.9% vs. 29.0% in the nebivolol group and 14.3% vs. 24.8% in the placebo group, males and females respectively). Headache was also more commonly seen in the female subgroup for both nebivolol and placebo (6.8% vs. 12.4% in the nebivolol group and 7.4% vs. 10.4% in the placebo group, males and females respectively).

Table 42: Reviewer's Analysis of Treatment-Emergent Adverse Events with Reviewer's Coding (≥ 2% in the Nebivolol Subjects) by Treatment Group and subgrouped by gender – ITT Population

Adverse Events	**Nebivolol**		**Placebo**	
	Males	**Females**	**Males**	**Females**
CHF	284 (43.2%)	157 (38.3%)	325 (47.4%)	168 (44.8%)
Dizziness	194 (29.5%)	110 (26.8%)	139 (20.3%)	91 (24.3%)
Dyspnea	174 (26.5%)	81 (19.8%)	153 (22.3%)	79 (21.1%)
Bradycardia	164 (25.0%)	82 (20.0%)	40 (5.8%)	17 (4.5%)
Low BP	120 (18.3%)	72 (17.6%)	110 (16.0%)	46 (12.3%)
Edema	97 (14.8%)	46 (11.2%)	67 (9.8%)	22 (5.9%)
Fatigue	94 (14.3%)	60 (14.6%)	67 (9.8%)	51 (13.6%)
Resp Tract Infection	87 (13.2%)	57 (13.9%)	87 (12.7%)	29 (7.7%)
Unstable Angina	86 (13.1%)	66 (16.1%)	118 (17.2%)	57 (15.2%)
BP Increased	78 (11.9%)	119 (29.0%)	98 (14.3%)	93 (24.8%)
Renal Dysfunction	67 (10.2%)	49 (12.0%)	60 (8.7%)	26 (6.9%)
Orthostasis	62 (9.4%)	38 (9.3%)	43 (6.3%)	24 (6.4%)
Atrial Fibrillation	58 (8.8%)	50 (12.2%)	79 (11.5%)	34 (9.1%)
Hyperuricemia	53 (8.1%)	48 (11.7%)	38 (5.5%)	15 (4.0%)
Chest Pain	46 (7.0%)	17 (4.1%)	28 (4.1%)	13 (3.5%)
Headache	45 (6.8%)	51 (12.4%)	51 (7.4%)	39 (10.4%)
Bronchitis	44 (6.7%)	28 (6.8%)	55 (8.0%)	37 (9.9%)
Glucose Intolerance	44 (6.7%)	19 (4.6%)	48 (7.0%)	14 (3.7%)
Weakness	44 (6.7%)	18 (4.4%)	25 (3.6%)	6 (1.6%)
Pneumonia	43 (6.5%)	13 (3.2%)	38 (5.5%)	13 (3.5%)

Age
Given that all subjects in the trial were 70 years of age or older, already resulting in a narrowing of the spread of age in the enrolled population, it would be difficult to make any conclusions about the age subgroups in the trial.

7.5.4 Drug-Disease Interactions

The adverse events were not adequately characterized to determine drug-disease interactions.

7.5.5 Drug-Drug Interactions

The adverse events were not adequately characterized to determine drug-drug interactions.

7.6 Additional Safety Evaluations

There were no additional safety evaluations.

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed for this supplemental NDA for an already approved agent.

7.6.2 Human Reproduction and Pregnancy Data

Human Reproduction and pregnancy studies were not performed for this supplemental NDA.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not-applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were insufficient data to make any conclusions regarding Overdose, Drug Abuse Potential, Withdrawal and Rebound.

7.7 Additional Submissions / Safety Issues

No other safety issues

8 Postmarket Experience

8.1 AERS Reports

Evaluation of the AERS database (done by Office of Surveillance and Epidemiology, CDER, FDA) yielded dyspnea, drug interaction, bradycardia, heart rate decreased, hypotension, dizziness, fatigue, and edema peripheral as the 8 most frequent Preferred Terms in postmarket safety reports (see Table 43).

Table 43: AERS Crude Counts of PTs Reported for Nebivolol from Approval to May 31, 2009

Rank	Preferred Term	Count of PTs	Percent of Total
1	Dyspnea	25	7.20
2	Drug Interaction	21	6.05
3	Bradycardia	19	5.48
4	Heart Rate Decreased	19	5.48
5	Hypotension	17	4.90
6	Dizziness	16	4.61
7	Fatigue	16	4.61
8	Edema Peripheral	16	4.61
9	Rash	16	4.61
10	BP Increased	15	4.32

[Source: Office of Surveillance and Epidemiology Reviewer's Analysis]

Table 44 lists the Designated Medical Events (DMEs) which have been reported for this NME and the crude counts for each DME, as per analyses from AERS done by the Office of Surveillance and Epidemiology, CDER, FDA.

Table 44: Designated Medical Event Terms Reported for Nebivolol from Approval to May 31, 2009

DME Preferred Term	Total Case/Event Count	Number of Deaths
Acute Renal Failure	8	2
Hepatic Failure	6	6
Toxic Epidermal Necrolysis	7	0
Hepatic Necrosis	5	5
Stevens-Johnson Syndrome	6	0
Respiratory Failure	2	0
Hemolytic Anemia	2	0
Angranulocytosis	2	0
Torsade de pointes	1	0
Ventricular Fibrillation	1	0
Blindness	1	0
Convulsions	2	0

[Source: Office of Surveillance and Epidemiology Reviewer's Analysis]

Table 45 lists the most frequent preferred terms reported for nebivolol which were coded with death as the outcome (as per analysis done by the Office of Surveillance and Epidemiology, CDER, FDA). As can be seen in this table, the top 3 most frequently reported PTs resulting in death involved injury to the liver.

Table 45: AERS Crude Counts of all PTs that Comprise >5% of all PT's Reported for Nebivolol in Cases Coded with "Death" as an Outcome

Rank	Preferred Term	Count of PTs	Percent of Total
1	Hepatic Failure	6	42.86
2	Hepatic Necrosis	5	35.71
3	Acute Hepatic Failure	4	28.57
4	Arteriosclerosis Coronary Artery	3	21.43
5	Death	3	21.43
6	Hepatic Congestion	3	21.43
7	Hepatic Encephalopathy	3	21.43
8	Arteriosclerosis	2	14.29
9	Bronchopneumonia	2	14.29
10	Drug Interaction	2	14.29

[Source: Office of Surveillance and Epidemiology Reviewer's Analysis]

8.2 Data-mining of the Empirica Database

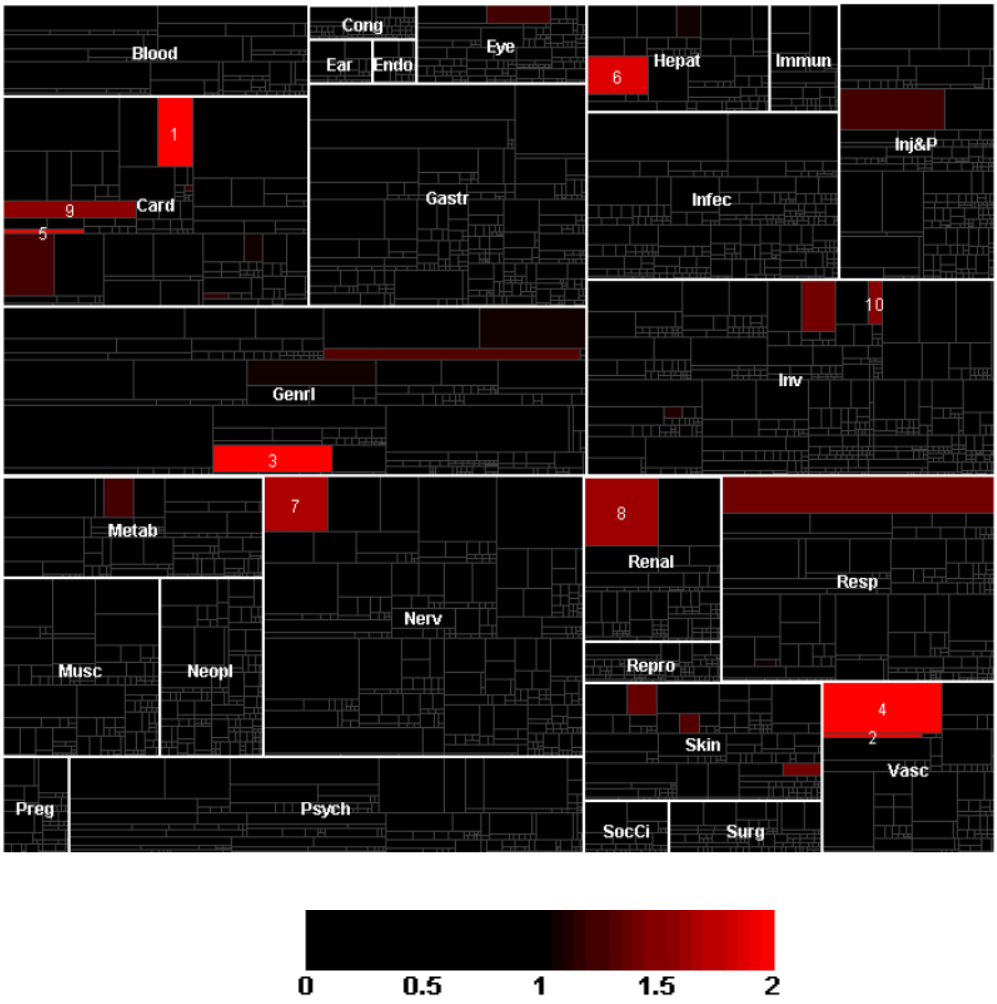
Table 46, Table 47, and Table 48 show the results of data-mining of the Empirica database conducted by the Office of Surveillance and Epidemiology, CDER, FDA. As can be seen, bradycardia, orthostatic hypotension, drug interaction, and hypotension are the preferred terms associated with nebivolol with the highest EB05 scores in the database.

Table 46: Data Mining Results for Nebivolol, by Decreasing EB05 Score

Preferred Term	SOC	N	EB05	EBGM	EB95
Bradycardia	Cardiac	21	6.845	11.836	18.249
Orthostatic Hypotension	Vascular	10	6.039	16.592	30.927
Drug Interaction	General	28	5.032	7.144	10.313
Hypotension	Vascular	18	2.524	3.755	5.426
Sinus Bradycardia	Cardiac	5	2.002	5.288	22.181
Hepatic Failure	Hepatic	6	1.899	3.847	7.446
Loss of Consciousness	Nervous	10	1.679	2.859	4.621
Renal Failure	Renal	10	1.642	2.795	4.516
Atrial Fibrillation	Cardiac	8	1.579	2.86	4.862

[Source: Office of Surveillance and Epidemiology Reviewer's Analysis]

Table 47: Data Mining Sector Map for Nebivolol, Colored by EB05 Value



[Source: Office of Surveillance and Epidemiology Reviewer's Analysis]

Table 48: Preferred Terms that Match the Above Data Mining Sector Map (by Rank Scores)

Rank	System Organ Class	Preferred Term	EB05
1	Cardiac	Bradycardia	6.845
2	Vascular	Orthostatic Hypotension	6.039
3	General	Drug Interaction	5.032
4	Vascular	Hypotension	2.524
5	Cardiac	Sinus Bradycardia	2.002
6	Hepatic	Hepatic Failure	1.899
7	Nervous	Loss of Consciousness	1.679
8	Renal	Renal Failure	1.642
9	Cardiac	Atrial Fibrillation	1.579
10	Inv	Heart Rate Decreased	1.480

[Source: Office of Surveillance and Epidemiology Reviewer's Analysis]

9 Appendices

9.1 Literature Review/References

1. Armstrong and Alexander. Nebivolol in Older Adults with Heart Failure: Reduced Rates for SENIORS? JACC. 2009; 53; pp. 2159-2161.
2. van Veldhuisen et al. Beta-Blockade with Nebivolol in Elderly Heart Failure Patients With Impaired Left Ventricular Ejection Fraction: Data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). JACC. 2009; 53; pp. 2150-2158.
3. Lainscak et al. Beta-Blockers in Elderly Patients with Heart Failure – Ready for Prime Time? JACC. 2009; 54. (Editorial)
4. Munzel and Gori. Nebivolol: The Somewhat-different Adrenergic Receptor Blocker. JACC. 2009; 54; pp. 1491-1499.
5. Flather et al. Randomized Trial to Determine the Effect of Nebivolol on Mortality and Cardiovascular Hospital Admission in Elderly Patients with Heart Failure (SENIORS). European Heart Journal. 2005; 26; pp. 215-225.
6. McMurray. Making Sense of SENIORS. European Heart Journal. 2005; 26; pp. 203-206.

9.2 Labeling Recommendations

Given that the efficacy results are inadequate to support the claim for treatment of heart failure, we cannot provide recommendations for the efficacy segment of the label.

With regard to the safety portion of the draft label, would recommend that Table 2 be changed to include the higher frequency of AEs seen when the AE terms are grouped into clinically-relevant categories (as opposed to the very fine granular terms in MedDRA), as in Table 35 of this review.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting is scheduled for January 11, 2010.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21742	SUPPL-7	FOREST LABORATORIES INC	NEBIVOLOL TABLETS 1.25/2.5/5/10/20MG

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/s/

SHONA S PENDSE
12/11/2009