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*APPLICATION NUMBER:*

**21-742**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**Pharmacometrics Review  
Office of Clinical Pharmacology**

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<b>NDA:</b>	<b>21-742</b>
<b>Compound:</b>	<b>Nebivolol</b>
<b>Submission Dates:</b>	<b>May 31, 2007</b>
<b>Applicant:</b>	<b>Mylan Bertek</b>
<b>Type of submission:</b>	<b>2nd cycle review (Standard)</b>
<b>Pharmacometrics Reviewer:</b>	<b>Yaning Wang, Ph.D.</b>
<b>Secondary Reviewer:</b>	<b>Jogarao Gobburu, Ph.D.</b>

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Is higher exposure of nebivolol, e.g. observed in poor metabolizers (PM), associated with more suppression of adrenal function, luteinizing hormone, or testosterone levels in male?

No. Exposure response analyses were performed for nebivolol based on data from Study NEB-PK-03 (Effects of Nebivolol on Adrenal Function, Luteinizing Hormone, and Testosterone Levels in Healthy Male Volunteers). Detailed study design is referred to Dr. Keren Hicks' review. Nine safety endpoints were measured in Study NEB-PK-03, which included area under the curve from time zero to 120 minutes (AUC<sub>0-120 min</sub>) of ACTH-stimulated (IV dose of 250 µg) serum cortisol levels, AUC<sub>0-120 min</sub> of serum aldosterone levels after the IV administration of ACTH (250 µg), sex hormone binding globulin, total testosterone level, free testosterone level, mean luteinizing hormone value, peak post-ACTH cortisol level, peak post-ACTH aldosterone above basal level, and peak post-ACTH cortisol above basal level. Under nebivolol 10 mg QD regimen, steady state trough concentration for either l-nebivolol or d-nebivolol was not found to be related to change in any of the 9 safety endpoint after 7 weeks of treatment in healthy male volunteers despite that 4 poor metabolizers achieved significantly higher exposure of l-nebivolol or d-nebivolol (Table 1, Figure 1 and Figure 2). The exposure of l-nebivolol or d-nebivolol was set to be zero for subjects taking placebo. No significant difference was observed between placebo and nebivolol groups in terms of change from baseline for any of the 9 endpoints (Table 2). The only endpoint suggesting a relationship with nebivolol exposure is free testosterone level as indicated by the marginal significant p-values in both regression analysis and t-test. However, the direction of this relationship is opposite of hormone suppression, which is highly influenced by one outlier observation in nebivolol group (patient 59038 with 18 unit increase in free testosterone level at the end of study). The same influence was also observed for total testosterone level. Four poor metabolizers had higher peak post-ACTH aldosterone above basal level compared to either extensive metabolizers (EM) or placebo subjects (Table 3). Overall, these results do not support the observation from animal data which suggested suppression of male hormone by nebivolol.

Endpoint	Group	N	Mean	Lower	Upper	P-value
Area Under Curve (0-120 min) Aldosterone	Nebivolol	42	-0.58	-2.87	1.72	0.21
	Placebo	48	1.01	-0.30	2.33	
	Difference (Nebivolol-Placebo)		-1.59	-4.12	0.94	
Area Under Curve (0-120 min) Cortisol	Nebivolol	42	0.44	-0.93	1.80	0.73
	Placebo	48	0.77	-0.54	2.07	
	Difference (Nebivolol-Placebo)		-0.33	-2.19	1.53	
Free Testosterone Level	Nebivolol	42	1.00	-0.10	2.10	0.07
	Placebo	48	-0.25	-1.10	0.60	
	Difference (Nebivolol-Placebo)		1.25	-0.10	2.60	
Free Testosterone Level*	Nebivolol	41	0.59	-0.14	1.32	0.14
	Placebo	48	-0.25	-1.10	0.60	
	Difference (Nebivolol-Placebo)		0.84	-0.29	1.97	
Mean Luetinizing Hormone Value	Nebivolol	42	0.04	-0.44	0.52	0.80
	Placebo	48	0.11	-0.23	0.45	
	Difference (Nebivolol-Placebo)		-0.07	-0.64	0.49	
Peak Post-ACTH Aldosterone Above Basal	Nebivolol	42	-0.20	-1.77	1.37	0.91
	Placebo	48	-0.32	-1.68	1.05	
	Difference (Nebivolol-Placebo)		0.12	-1.93	2.16	
Peak Post-ACTH Cortisol	Nebivolol	42	0.20	-0.56	0.96	0.87
	Placebo	48	0.28	-0.40	0.96	
	Difference (Nebivolol-Placebo)		-0.08	-1.08	0.92	
Peak Post-ACTH Cortisol Above Basal	Nebivolol	42	0.11	-1.41	1.64	0.23
	Placebo	48	-1.08	-2.41	0.24	
	Difference (Nebivolol-Placebo)		1.20	-0.79	3.18	
Sex Hormone Binding Globulin	Nebivolol	42	-0.57	-1.93	0.80	0.18
	Placebo	48	0.60	-0.50	1.70	
	Difference (Nebivolol-Placebo)		-1.17	-2.88	0.54	
Testosterone, Total	Nebivolol	42	26.64	-6.66	59.95	0.18
	Placebo	48	-2.90	-31.74	25.95	
	Difference (Nebivolol-Placebo)		29.54	-13.67	72.75	

\* Without an influential point in nebivolol group

*Table 3. ANOVA comparison results for peak post-ACTH aldosterone above basal level*

Group	Estimate	N	95% CI		P-value*
			Lower	Upper	
Nebivolol (PM)	6.90	4	2.30	11.50	
Nebivolol (EM)	-0.94	38	-2.44	0.55	
Placebo	-0.31	48	-1.64	1.01	
Difference (PM-Placebo)	7.21		2.43	12.00	0.004
Difference (PM-EM)	7.84		3.01	12.68	0.002
Difference (EM-Placebo)	-0.63		-2.63	1.37	0.532

\* Not adjusted for multiple comparisons; PM, poor metabolizers; EM, extensive metabolizers.

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**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW**


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<b>NDA:</b>	<b>21-742</b>	<b>N000</b>
<b>Submission Dates:</b>	2/21, 2/22 2005	
<b>Generic Name:</b>	Nebivolol	
<b>Dosage Form &amp; Strength:</b>	Tablets 2.5, 5, and 10 mg	
<b>Indication:</b>	Hypertension	
<b>Applicant:</b>	Bertek Pharmaceuticals Inc.	
<b>Submission:</b>	Original NDA, responses to the FDA comments	
<b>Primary Reviewers:</b>	Elena V. Mishina, Ph.D.	

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**Background**

Reference is made to the NDA 21-742, nebivolol tablets, which is currently under review. In the February 10, 2005 letter the Agency provided the OCPB comments to the sponsor. The submission contains the sponsor's responses to the OCPB comments.

**Response to comment 1.**

The sponsor is satisfied with comment 1 regarding the granting the requested biowaiver for the 2.5 mg dosage strength of the nebivolol tablet.

**Response to comment 2.**

The dissolution data for nebivolol tablets was reevaluated based on the available data to date. The dissolution specification of NLT — (Q) in 30 minutes is recommended for the 2.5, 5, and 10 mg tablets strength.

**Response to comment 3.**

The FDA pointed out that due to a failure to assess the active metabolites in the clinical studies, the sponsor could not explain why the striking differences in the levels of the parent drug in extensive (EM) and poor metabolizers (PM) of CYP 2D6 did not show any differences in the drug effect.

The sponsor argued that the pharmacokinetics of the active metabolites was assessed in this NDA. This argument was based on the mass-balance study (reports NEBI-0136 and NEBI-0142) where the metabolism of nebivolol was characterized in 3 EM and 3 PM healthy subjects. In this study performed in healthy subjects, the total radioactivity was detectable in urine and feces up to 17 days, and it was detected up to 7 days in whole blood and plasma. The half-life of the total radioactivity in whole blood in EMs blood was calculated as 86 hours (2 subjects, 39 and 132 hours) and in PMs 73 hours (N=3) and 44 hours (1 EM subject) and 60 hours (3PMs) in plasma. The distribution and excretion of the active metabolites (4-hydroxy (A8), 8- and 5-hydroxy (A6), 4,8- and 4,5-dihydroxy (A3) and their corresponding glucuronides (G8, G6, and G3) were properly assessed. In general, all these active metabolites and their glucuronides were formed in EM subjects and not in PM subjects. However, their contribution to the pharmacodynamic

effects was not assessed and the final conclusions only speculated that the similar effect in PMs and EMs is possibly due to the effect of the active metabolites in EMs which substituted the effect of the parent drug in PMs.

#### Glucuronide Conjugates

The mass balance study showed that the major metabolites of nebivolol are glucuronides of the unchanged drug, which was reported as GUD. The drug is represented by two stereoisomers, d- and l-nebivolol, from which only d-nebivolol has beta-blocking activity. Moreover, the 5-, and 8-hydroxy metabolites of both stereoisomers can form glucuronides as well. In the clinical pharmacology studies, the sponsor assayed in bulk all glucuronides and reported that 'the main active metabolite, glucuronide of the unchanged parent drug, was measured in studies NEBI 126, 127, 270, 136, 142, 124, 125, 2118, and 302'. In the above mentioned studies glucuronide conjugates (bulk measurements) were assessed up to 24 (majority of studies) and up to 96 hours in studies 125 (5 patients) and 124 (7 patients). The attempt to describe the pharmacokinetic properties of the mixture of more than a dozen substances which have different chemical and physiologic properties does not make any sense. Moreover, in all these studies (except for the mass balance studies (136 and 142), the half life of the 'glucuronides' was calculated in the range of 3 to 15 hours (EMs) and up to 30 hours in PMs while the total radioactivity was detected in plasma up to 7 days. This indicates that the characterization of the pharmacokinetic profile was not complete. In addition, when the AUC values measured to the last data point were compared to the extrapolated AUC values, the measured part represented less than 50%. Therefore based on these data, the characterization of the terminal phase of the plasma concentrations vs time profile was impossible and the half-life, clearance, and volume of distribution values calculated by the sponsor for the glucuronides cannot be considered reliable. Therefore, the Agency concluded that the pharmacokinetics of the main metabolites of nebivolol (glucuronide conjugates) was not properly characterized.

In conclusion,

1. The mass balance study properly characterized the metabolic profiles of d- and l-nebivolol in 3 EM and 3PM healthy subjects; however, the described groups were very small to adequately describe the variability and only 2 out of 3 subjects in the EM group had similar results.
2. None of the active metabolites (4-hydroxy, 8- and 5-hydroxy, 4,8- and 4,5-dihydroxy-nebivolol and their corresponding glucuronides were measured in the clinical studies to evaluate their impact into the overall pharmacodynamic effect.
3. The sponsor attempted to describe the pharmacokinetics of the major metabolite of nebivolol, namely, glucuronide of unchanged drug. However, the assay measured the sum of glucuronide conjugates of d- and l-nebivolol and above mentioned active metabolites. This approach is not acceptable and the pharmacokinetic parameters calculated by the sponsor do not reflect the properties of any specific metabolite.

#### Response to comment 4.

The relationship between pharmacokinetics and pharmacodynamics of nebivolol was not established. The reasons include poor study design and inability to measure all pharmacologically active moieties.

*Sponsor:*

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*The estimated placebo-subtracted trough-to-peak ratio of diastolic blood pressure was approximately 0.9 or greater at all doses. Although this limited degree in fluctuation is ideal with respect to clinical efficacy it makes pharmacokinetic modeling extremely difficult. Since patients maintained on nebivolol appear to have a relatively stable reduction in blood pressure, efforts to construct a pharmacodynamic relationship are somewhat limited.*

**FDA comment:**

The sponsor claims that the obtained data do not show a proper pattern for the relationship between PK and PD.

*Sponsor: The PK/PD analysis conducted previously is believed to adequately reflect the pharmacodynamic performance of nebivolol for the following reasons:*

- a. The pharmacokinetics of nebivolol and related moieties is well understood and was taken into account*

**FDA comment:**

The pharmacokinetics of d- and l-nebivolol was previously described in studies NEBI-126 and NEBI-127. In these studies, the limitation of the assay for the low doses of drug and failure to obtain plasma samples at least up to 3 half-lives led to poor characterization of the nebivolol pharmacokinetics particularly for the low doses and for the PM subjects. Nevertheless, the parameters estimated in these studies by the non-compartmental method were used by the sponsor as a comparator of the population model estimated parameters. Moreover, all parameters (except for clearance (CL) and volume of distribution of the central compartment, (Vd)) obtained in healthy subjects were fixed for the patient population data analysis in order to estimate the patient's CL and V. The sponsor assumed that the pharmacokinetics of d- and l-nebivolol in healthy subjects and patients were similar but this assumption was never tested. Although the pharmacokinetic parameters estimated for d- and l-nebivolol were cited as "comparable" for the healthy and patient population, the clearance in the patient population was reduced for d-nebivolol by 20%, in EMs and 55% in PMs; and for l-nebivolol, no change for EMs and increased 2.5 times for PMs).

- b. Nebivolol-related moieties follow a similar plasma concentration versus time profile as nebivolol and its glucuronides and as such correlate with nebivolol as well as one another*

**FDA comment:**

Pharmacokinetics of all three moieties measured in the clinical studies: d-, l- nebivolol and nebivolol glucuronides were quite different with respect to all parameters. D- and l-nebivolol plasma concentrations were added at all sampling times and this combined quantity was used for the PK and PK/PD modeling; however, only d-nebivolol has a pronounced beta-blocking activity. The exposure to d-nebivolol was much smaller (both AUC and C<sub>max</sub>) and the half-life shorter compared to l-nebivolol. In studies in healthy subjects (NEBI-126 and NEBI-127), nebivolol glucuronides were inadequately characterized for the low doses of nebivolol (2.5 and 5 mg). The sponsor failed to measure the plasma concentrations of the nebivolol glucuronides for EMs (not enough assay sensitivity) and for PMs, the plasma concentrations of nebivolol glucuronides were not measured long enough to characterize the terminal phase of elimination

and the estimations of the AUC values and clearance values were deemed not acceptable. Therefore, the sponsor's claim regarding the similarity in pharmacokinetics of the measured nebivolol moieties in plasma is not supported by the submitted results.

- c. *Sampling measurements were designed to be clinically practical within the confines of the study and to assess both maximal and minimal responses of concentrations and effects*
- d. *The data was based on a population PK data set, providing a large number of measures over a broad range of dosage regimens (1.25 to 40mg/day) and clinical scenarios in mild-to-moderate hypertensive patients.*

**FDA comment:**

The plasma sampling in this study was poorly designed. Although the number of samples (3-4 per subject) was sufficient, the sampling occurred only at the peak and trough plasma concentrations and there was no information about the plasma concentration profiles in between these points. The Population PK Guidance for the industry recommends having 3-4 plasma samples per patients which are obtained in a few intervals to properly characterize the full plasma concentration time profile.

In conclusion, the population model described the pharmacokinetics of d- and l-nebivolol with a lot of assumptions and particularly was based on the parameters obtained from healthy subjects. Due to poor study design, the pharmacokinetic profiles were not properly characterized and the effects of the important covariates were not assessable.

*Sponsor: Our analysis suggests that a saturable effect model best describes the relationship between nebivolol plasma concentration and diastolic blood pressure [NEB-302PKPD], which may explain the relatively high trough-to-peak ratio for blood pressures and may in part explain nebivolol's similar effectiveness in patients classified as either EMs or PMs.*

**FDA comments:**

1. The sponsor's estimated EC50 values (50% of the drug concentration responsible for the maximal effect) are not correlated with the activity of  $\beta_1$ -adrenoceptor ( $K_i$  7-8 mol/L or 5-15 ng/mL, Maack et al 2001). The sponsor's estimation of EC50 for the sitting diastolic blood pressure was 0.068 ng/mL. This value is 220 fold higher than  $K_i$ . Moreover, the average d-nebivolol plasma concentrations measured in Study NEBI-302 was about 6 ng/mL, this value was the same order of magnitude as the  $K_i$  value. The EC50 values estimated by the sponsor do not reflect the  $K_i$  for  $\beta$ -adrenoceptor activity of nebivolol. The EC50 value for heart rate was estimated by the sponsor as 0.016 ng/mL. The same comments as above for DBP are applicable for the heart rate response model.
2. The data available in this study did not allow to evaluate if there is a lag time between the pharmacokinetics and pharmacodynamics of the drug. The model proposed by the sponsor is not able to rule this out. The hysteresis could only be assessed if the full plasma concentration vs. time profile with the corresponding PD measurements was taken into consideration.

3. Based on all of the above, the PK/PD model proposed by the sponsor is not acceptable. The attempt to describe the data with a linear PK/PD model (FDA reviewer) did not lead to a better model fit.

**Response to comment 5.**

The Agency recommended to evaluate the PK/PD relationship in African-American patients. The sponsor's response to perform a small single dose study in African-American and Caucasian patients is acceptable. The protocol of this study should be submitted for review.

**RECOMMENDATION**

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the sponsor's response. The following dissolution method specifications and method are recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	— in 30 minutes

The sponsor's responses to the original FDA comments 3 and 4 are not acceptable. The FDA comments to the sponsor responses should be conveyed to the sponsor.

Date \_\_\_\_\_

\_\_\_\_\_  
Elena Mishina, Ph. D.  
Clinical Pharmacology Reviewer

\_\_\_\_\_  
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Cardio-Renal Team Leader

cc list: NDA 21-742, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

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**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW**

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<b>NDA:</b>	<b>21-742</b>	<b>N000</b>
<b>Submission Dates:</b>	4/30, 6/24, 7/9, 7/14, 7/15, 10/27, 11/12, 11/16, 11/19, 11/23, 11/30, 12/15, 12/21 2004	
<b>Brand Name:</b>	_____	
<b>Generic Name:</b>	Nebivolol	
<b>Dosage Form &amp; Strength:</b>	Tablets 2.5, 5, and 10 mg	
<b>Indication:</b>	Hypertension	
<b>Applicant:</b>	Bertek Pharmaceuticals Inc.	
<b>Submission:</b>	Original NDA	
<b>Divisions:</b>	DPEI and Cardio-Renal Drug Products, HFD-110	
<b>Primary Reviewers:</b>	Elena V. Mishina, Ph.D. Robert Kumi, Ph.D.	
<b>Pharmacometrics Consult:</b>	Elena V. Mishina, Ph.D.	
<b>Team Leaders:</b>	Patrick Marroum, Ph.D.	

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## Table of Contents

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>14</b>
1.1	RECOMMENDATIONS: .....	14
1.2	COMMENTS: .....	14
1.3	SUMMARY OF OCBP FINDINGS .....	16
1.3.1	Background .....	16
1.3.2	Current Submission .....	16
<b>2</b>	<b>QUESTION BASED REVIEW.....</b>	<b>24</b>
2.1	GENERAL ATTRIBUTES .....	24
2.2	GENERAL CLINICAL PHARMACOLOGY .....	25
2.3	INTRINSIC FACTORS.....	41
2.4	EXTRINSIC FACTORS.....	45
2.5	GENERAL BIOPHARMACEUTICS .....	46
2.6	ANALYTICAL SECTION .....	49
<b>3</b>	<b>DETAILED LABELING RECOMMENDATIONS.....</b>	<b>51</b>
<b>4</b>	<b>APPENDICES.....</b>	<b>55</b>
4.1	OCPB PROPOSED LABEL .....	55
4.2	INDIVIDUAL STUDY REVIEWS.....	67
4.2.1	Single Dose, Dose-Proportionality Pharmacokinetic Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status (NEBI- 0126) .....	67
4.2.2	Single-Dose, Relative Bioavailability and Food Effect Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status (NEBI- 0127) .....	81
4.2.3	A Phase I Open-Label Single-Dose Study Assessing the Pharmacokinetics of Nebivolol HCL and the Formation of Metabolites in Healthy Volunteers (NEBI- 0223).....	92
4.2.4	A Phase I Open Label Multiple Dose Study Assessing the Pharmacokinetics of Nebivolol HCL and the Formation of Metabolites in Healthy Volunteers (NEBI- 0270).....	98
4.2.5	The plasma protein binding and distribution in blood of rac- nebivolol and of its two enantiomers in rats, dogs and humans.....	109
4.2.6	A Phase I, Open Label Study Investigating the Effects of Hepatic Impairment on the Single Dose Pharmacokinetics of Nebivolol Hydrochloride (NEBI- 0124) .....	111
4.2.7	A Phase I, Open- Label Study Investigating the Effects of Renal Impairment on the Single Dose Pharmacokinetics of Nebivolol Hydrochloride (NEBI-125).....	118
4.2.8	Absorption, Metabolism, and Excretion of Nebivolol in Healthy Male Volunteers after a Single Oral Dose of 15mg <sup>14</sup> C- Nebivolol HCL (NEBI- 0136).....	127
4.2.9	Metabolism of [ <sup>14</sup> C]- Nebivolol in Human: Mass Balance and Metabolite Profiling/Identification in Plasma and Excreta (NEBI-142).....	131
4.2.10	An in vitro Study on the Microsomal Metabolism of d- and l-Nebivolol in Human Liver Microsomes (NEBI- 0157).....	144
4.2.11	An in vitro Evaluation of Nebivolol as an Inhibitor of Human Cytochrome P450 Enzymes (NEBI-158) .....	153
4.2.12	A Randomized, Parallel Group Safety Evaluation of Electrocardiographic Intervals And Blood Pressure in Normal Healthy Volunteers after Nebivolol, Atenolol, Moxifloxacin, or Placebo Administration after Single and Repeated Doses (NEBI22) .....	159
4.2.13	A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Dosing Evaluating the Effects of Nebivolol on Blood Pressure in Patients with Mild to Moderate Hypertension (NEB-302) .....	170
4.2.14	Population Pharmacokinetic Data Analysis NEBI-302 .....	172
4.2.15	Pharmacokinetic/Pharmacodynamic Modeling NEBI-302 .....	186
4.2.16	Dissolution.....	193
4.2.17	Assay Information Relevant to Drug-Drug Interaction Evaluations.....	198

4.2.18	<i>A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction of Hydrochlorothiazide and Nebivolol HCl in Healthy Volunteers</i> .....	199
4.2.19	<i>A Phase I Open-Label Study Comparing the Interaction of Nebivolol HCl on the Pharmacokinetics of Digoxin in Healthy Volunteers</i> .....	206
4.2.20	<i>A Phase I Open-Label Study Comparing the Interaction of Steady-state Nebivolol HCl on the Pharmacokinetic and Pharmacodynamics of Warfarin Sodium in Healthy Volunteers</i> .....	214
4.2.21	<i>A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction Between Fluoxetine HCl and Nebivolol HCl in Healthy Volunteers</i> .....	222
4.2.22	<i>A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction Between Furosemide and Nebivolol HCl in Healthy Volunteers (NEBI-0213)</i> .....	227
4.2.23	<i>A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction Between Spironolactone and Nebivolol HCl in Healthy Volunteers (NEBI-0214)</i> .....	236
4.2.24	<i>A Phase I Open-Label Multiple-Dose Study of the Effect of Nebivolol HCl on the Pharmacokinetics of Spironolactone in Healthy Volunteers</i> .....	242
4.2.25	<i>A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetic Interaction Between Ramipril and Nebivolol HCl in Healthy Volunteers (Protocol NEBI-0220)</i> .....	247
4.2.26	<i>A Phase I Open-Label Single-Dose Study of the Pharmacokinetic Interaction between Nebivolol HCl and Losartan Potassium in Healthy Volunteers (NEBI-02104)</i> .....	256
4.2.27	<i>A Phase I Open-Label Study of the Effect of Repeated-Dose Activated Charcoal on the Pharmacokinetics of Nebivolol HCl in Healthy Volunteers (#: NEBI-02118)</i> .....	265
4.2.28	<i>An in vitro study on protein binding interactions of rac-nebivolol with other drugs in human plasma</i> 275	
4.3	FILING AND REVIEW FORM .....	279
4.4	SPONSOR'S PROPOSED PACKAGE INSERT .....	281

### List of Tables

Table 1: Summary of Ki values for nebivolol, its enantiomers, proposed metabolites, other known metabolites, and commonly prescribed $\beta$ -blockers .....	29
Table 2: Descriptive statistics obtained for clearance from the posthoc estimates: comparisons of EMs vs. PMs and Caucasians vs. Blacks for d- and l-nebivolol .....	30
Table 3: Comparison of the pharmacokinetic parameters of d-nebivolol after single and multiple 10 mg dose of nebivolol .....	33
Table 4: Comparison of the pharmacokinetic parameters of l-nebivolol after single and multiple 10 mg dose of nebivolol .....	33
Table 5: Comparison of mean (%CV) clearance values estimated in healthy subjects and in patients using NCA or NONMEM.....	34
Table 6: Profiles of Metabolites in Pooled (0-168 hr) Urine (% of Dose).....	39
Table 7: Profiles of Metabolites in Pooled (0-168 hr) Feces (% of Dose).....	40
Table 8: Summary of nebivolol solubility .....	47
Table 9: Nebivolol Tablets Composition .....	48
Table 10: Drug Description.....	68
Table 11: Assay Characteristics for d- and l-Nebivolol.....	68
Table 12: Demographic Data.....	69
Table 13: Mean (%CV) d-Nebivolol PK Parameters .....	70
Table 14: Mean (%CV) l-Nebivolol Parameters .....	70
Table 15: Mean (% CV) dose-normalized pharmacokinetic parameters for d-nebivolol.....	72
Table 16: Mean (% CV) dose-normalized pharmacokinetic parameters for l-nebivolol.....	72
Table 17: Geometric Mean Ratio (%) and 90% CI for the Dose-Normalized Parameters of d-Nebivolol .....	73
Table 18: Geometric Mean Ratio (%) and 90% CI for the Dose-Normalized Parameters of l-Nebivolol .....	73
Table 19: Mean (%CV) d,l-Nebivolol Parameters .....	75
Table 20: Mean (% CV) dose-normalized pharmacokinetic parameters for d,l-nebivolol.....	75
Table 21: Geometric Mean Ratio (%) and 90% CI for the Dose-Normalized Parameters of d,l-Nebivolol .....	76
Table 22: Mean (% CV) pharmacokinetic parameters for nebivolol glucuronides.....	76
Table 23: Mean (% CV) dose-normalized pharmacokinetic parameters for nebivolol glucuronides.....	77
Table 24: Geometric Mean Ratio and 90% CI for PK Parameters of Nebivolol Glucuronides... 78	78
Table 25: Drug Description.....	82
Table 26: Assay Characteristics for d- and l-Nebivolol.....	82
Table 27: Subject Demographics.....	83
Table 28: Mean (%CV) d-Nebivolol PK Parameters .....	84
Table 29: Mean (%CV) l-Nebivolol PK Parameters .....	86
Table 30: Mean (%CV) d,l-Nebivolol PK Parameters .....	88
Table 31: Mean (%CV) Nebivolol Glucuronides PK Parameters .....	89
Table 32: Assay Characteristics for d- and l-Nebivolol.....	93
Table 33: Demographic Data.....	93
Table 34: Mean (CV) d-Nebivolol PK parameters.....	94
Table 35: Mean (CV) l-Nebivolol PK parameters.....	94
Table 36: Mean (CV) d,l-Nebivolol PK parameters.....	94

Table 37: Assay Characteristics for d- and l-Nebivolol.....	98
Table 38: Assay for non-conjugated plus conjugated nebivolol .....	99
Table 39: Demographic Data.....	100
Table 40: Mean (%CV) d-nebivolol PK parameters (single dose, Day 1) .....	100
Table 41: Mean (%CV) d-nebivolol PK parameters (multiple doses, Day 14) .....	101
Table 42: Mean (%CV) l-Nebivolol PK parameters (single dose, Day 1) .....	101
Table 43: Mean (%CV) l-Nebivolol PK parameters (multiple doses, Day 14) .....	101
Table 44: Mean (%CV) d,l-Nebivolol PK parameters (Single Dose, Day 1) .....	102
Table 45: Mean (%CV) d,l-Nebivolol PK parameters (multiple doses, Day 14).....	102
Table 46: Mean (%CV) Nebivolol glucuronide PK parameters (single dose, Day 1) .....	104
Table 47: Mean (%CV) Nebivolol glucuronide PK parameters (multiple doses, Day 14) .....	105
Table 48: Mean ( $\pm$ SD) distribution of d- nebivolol and l- nebivolol in blood of healthy subjects at a concentration of 1ng/mL. ....	110
Table 49: Assay Characteristics for d- and l-Nebivolol.....	112
Table 50: Assay for non-conjugated plus conjugated nebivolol .....	112
Table 51: Demographic Data .....	113
Table 52: parameters of d,l-nebivolol, healthy subjects .....	114
Table 53: Mean (%CV) d-Nebivolol Pharmacokinetic Parameters In Twelve Healthy And Eight Moderate Hepatic Impaired Subjects Following A Single, Oral 5mg (1 x 5mg) Dose Of Nebivolol Hydrochloride Tablets Under Fasting Conditions.....	114
Table 54: Mean (%CV) l-Nebivolol Pharmacokinetic Parameters In Twelve Healthy And Eight Moderate Hepatic Impaired Subjects Following A Single, Oral 5mg (1 x 5mg) Dose Of Nebivolol Hydrochloride Tablets Under Fasting Conditions.....	115
Table 55: Mean (%CV) d,l-Nebivolol Pharmacokinetic Parameters In Twelve Healthy And Eight Moderate Hepatic Impaired Subjects Following A Single, Oral 5mg (1 x 5mg) Dose Of Nebivolol Hydrochloride Tablets Under Fasting Conditions.....	115
Table 56: Mean (%CV) Nebivolol Glucuronides Pharmacokinetic Parameters In Twelve Healthy And Eight Moderate Hepatic Impaired Subjects Following A Single, Oral 5mg (1 x 5mg) Dose Of Nebivolol Hydrochloride Tablets Under Fasting Conditions .....	116
Table 57: Assay Characteristics for d- and l-Nebivolol.....	119
Table 58: Assay for non-conjugated plus conjugated nebivolol .....	119
Table 59: Demographic Data .....	120
Table 60: Mean (CV) d-Nebivolol PK parameters.....	121
Table 61: Mean (CV) l-Nebivolol PK parameters.....	121
Table 62: Mean (CV) d,l-Nebivolol PK parameters.....	122
Table 63: Mean (CV) nebivolol glucuronides parameters.....	122
Table 64: Demographic Data .....	128
Table 65: Individual and mean PK parameters estimated based on total radioactivity in plasma and whole blood after a single oral dose of 15 mg <sup>14</sup> C-nebivolol .....	129
Table 66: Cumulative Percent of Nebivolol Dose Recovered in Urine.....	133
Table 67: Cumulative Percent of Nebivolol Dose Recovered in Feces.....	134
Table 68: Nebivolol metabolites found in plasma, urine and feces.....	137
Table 69: Time Course Metabolite Profile Summary in Plasma from EMs and PMs .....	138
Table 70: Profiles of Metabolites in Pooled (0-168 hr) Urine (% of Dose).....	139
Table 71: Profiles of Metabolites in Pooled (0-168 hr) Feces (% of Dose).....	140
Table 72: Assay Characteristics for d- and l-Nebivolol.....	146

Table 73: Loss of Substrate and Mass Balance for d-Nebivolol.....	147
Table 74: Loss of Substrate and Mass Balance for l-Nebivolol.....	148
Table 75: Effect of Time, Protein and Substrate Concentration (d-Nebivolol).....	149
Table 76: Effect of Time, Protein and Substrate Concentration (l-Nebivolol).....	150
Table 77: Kinetic Constants for R-13 Formation.....	151
Table 78: CYP450 Ki Values.....	158
Table 79: Treatment Schedule.....	159
Table 80: Assay Characteristics for d- and l-Nebivolol.....	160
Table 81: Study drug.....	161
Table 82: Summary of the demographic characteristics by treatment.....	162
Table 83: Comparison of the treatments by QTc interval change from Day 0 to 2 hours post-dose on Day 7.....	164
Table 84: Subjects with Clinically Notable QTc-F Intervals or Increase from Baseline QTc- F Intervals at 2 Hours Post Dose on Day 7.....	168
Table 85: Drug products manufactured Lot#.....	171
Table 86: Nebivolol Assay Characteristics.....	171
Table 87: Assay for non-conjugated plus conjugated nebivolol.....	172
Table 88: Subject' disposition.....	174
Table 89: Pharmacokinetic parameters in healthy subjects.....	175
Table 90: Comparison of the clearance (%CV) estimated using the population and non-compartmental approaches.....	177
Table 91: Demographic Summary for Patients Included in the NONMEM Analysis.....	178
Table 92: Summary of Clinical Laboratory Data by CYP2D6 Genotype for Patients Included in the NONMEM Analysis.....	178
Table 93: Summary of Concomitant Medications by CYP2D6 Genotype for Patients Included in the NONMEM Analysis.....	179
Table 94: PK Parameters of d-nebivolol.....	181
Table 95: PK parameters of l-nebivolol.....	182
Table 96: Demographics of Patients Included in the Pharmacodynamic Analysis.....	188
Table 97: PD Parameter Estimates for Sitting Diastolic Blood Pressure.....	190
Table 98: PD Parameter Estimates for Sitting Heart Rate.....	191
Table 99: Sponsor's proposed dissolution method and specifications.....	194
Table 100: Nebivolol tablets – f2 analysis 5mg dissolution profile compared to 1.25mg dissolution profile.....	194
Table 101: Assay performance Characteristics for Nebivolol.....	201
Table 102: Assay performance Characteristics for hydrochlorothiazide.....	201
Table 103: Mean (%CV) d-Nebivolol Pharmacokinetic Parameters in Fourteen Healthy Male and Female Subjects Following a Daily Oral Dosing of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with Daily Oral Dosing of 25mg Hydrochlorothiazide.....	203
Table 104: Mean (%CV) l-Nebivolol Pharmacokinetic Parameters in Fourteen Healthy Male and Female Subjects Following a Daily Oral Dosing of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with Daily Oral Dosing of 25mg Hydrochlorothiazide.....	204
Table 105: Mean (%CV) Hydrochlorothiazide Pharmacokinetic Parameters in Fourteen Healthy Male and Female Extensive Metabolizers Following a Daily Oral Dosing of 25mg Hydrochlorothiazide for Ten Days Alone or Concomitantly with Daily Oral Dosing of 10mg Nebivolol HCL.....	205

Table 106: L and D-nebivolol Assay Characteristics .....	207
Table 107: Digoxin Assay Characteristics .....	207
Table 108: Mean (%CV) Digoxin Pharmacokinetic Parameters in Fourteen Healthy Male and Female Subjects Following a Daily Oral Dosing of 0.25 mg Digoxin Alone or Concomitantly with Daily Oral Dosing of 10mg Nebivolol HCL.....	209
Table 109: Mean (%CV) <i>d</i> -, and <i>l</i> -Nebivolol Pharmacokinetic Parameters in Twelve Healthy Male and Female Extensive Metabolizers Following a Daily Oral Dosing of 0.25mg Digoxin Alone or Concomitantly with Daily Oral Dosing of 10mg Nebivolol HCL.....	211
Table 110: Mean (%CV) <i>d</i> -, and <i>l</i> -Nebivolol Pharmacokinetic Parameters in Eleven Healthy Male and Female Extensive Metabolizers Following Daily Oral Dosing of 10mg Nebivolol Concomitantly with 0.25mg Digoxin for 10 Days (Subject 1 Excluded) .....	211
Table 111: Assay Characteristics for <i>d</i> - and <i>l</i> -Nebivolol.....	215
Table 112: Assay Characteristics for R- and S- warfarin .....	216
Table 113: Mean (%CV) R-Warfarin Pharmacokinetic Parameters in Twelve Healthy Male and Female Subjects Following a Single, Oral Dose of 10 mg Coumadin® Given Alone or Concomitantly with 10mg Nebivolol HCL Under Fasting Conditions .....	218
Table 114: Mean (%CV) S-Warfarin Pharmacokinetic Parameters in Twelve Healthy Male and Female Subjects Following a Single, Oral Dose of 10mg Coumadin® Given Alone or Concomitantly with 10mg Nebivolol HCL Under Fasting Conditions .....	219
Table 115: Mean (%CV) Prothrombin Time Pharmacodynamic Parameters in Twelve Healthy Male and Female Subjects Following a Single, Oral Dose of 10mg Coumadin® Given Alone or Concomitantly with 10mg Nebivolol HCL Under Fasting Conditions.....	220
Table 116: Assay Characteristics for <i>d</i> - and <i>l</i> -Nebivolol.....	223
Table 117: Assay Characteristics for Fluoxetine and Norfluoxetine.....	223
Table 118: Mean (% CV) <i>d</i> -Nebivolol Pharmacokinetic Parameters in Ten Subjects Following a Single, Oral 10mg (1X10mg) Dose of Nebivolol Hydrochloride Tablets Under Fasting Conditions in the Presence and Absence of Fluoxetine .....	225
Table 119: Mean (%CV) <i>l</i> -Nebivolol Pharmacokinetic Parameters in Ten Subjects Following a Single, Oral 10mg (1X10mg) Dose of Nebivolol Hydrochloride Tablets Under Fasting Conditions in the Presence and Absence of Fluoxetine.....	226
Table 120: Assay Characteristics for <i>d</i> - and <i>l</i> -Nebivolol.....	228
Table 121: Assay Characteristics for furosemide.....	229
Table 122: Mean (%CV) <i>d</i> -Nebivolol Pharmacokinetic Parameters in Twelve Healthy Male and Female Extensive Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Single Oral Dose of 40mg Furosemide .....	230
Table 123: Mean (%CV) <i>d</i> -Nebivolol Pharmacokinetic Parameters in Three Healthy Male and Female Poor Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Single Oral Dose of 40mg Furosemide .....	231
Table 124: Mean (%CV) <i>l</i> -Nebivolol Pharmacokinetic Parameters in Twelve Healthy Male and Female Extensive Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Single Oral Dose of 40mg Furosemide .....	233
Table 125: Mean (%CV) <i>l</i> -Nebivolol Pharmacokinetic Parameters in Three Healthy Male and Female Poor Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Single Oral Dose of 40mg Furosemide .....	233

Table 126: Mean (%CV) Furosemide Pharmacokinetic Parameters in Fifteen Healthy Male and Female Subjects Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Single Oral Dose of 40mg Furosemide.....	234
Table 127: Assay Characteristics for d- and l-Nebivolol.....	237
Table 128: Mean (%CV) d-Nebivolol Pharmacokinetic Parameters in Eleven Healthy Male and Female Extensive Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Daily Oral Dose of 25mg Spironolactone.....	239
Table 129: Mean (%CV) d-Nebivolol Pharmacokinetic Parameters in Four Healthy Male and Female Poor Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Daily Oral Dose of 25mg Spironolactone.....	239
Table 130: Mean (%CV) l-Nebivolol Pharmacokinetic Parameters in Eleven Healthy Male and Female Extensive Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Daily Oral Dose of 25mg Spironolactone.....	240
Table 131: Mean (%CV) l-Nebivolol Pharmacokinetic Parameters in Four Healthy Male and Female Poor Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Daily Oral Dose of 25mg Spironolactone.....	241
Table 132: Spironolactone Assay Characteristics .....	243
Table 133: Mean (%CV) Spironolactone Pharmacokinetic Parameters in Thirty-five Healthy Male and Female Volunteers Following a Daily Oral Dose of 25mg Spironolactone for Ten Days Alone or Concomitantly with a Daily Oral Dose of 10mg Nebivolol HCL.....	244
Table 134: Mean (%CV) Canrenone Pharmacokinetic Parameters in Thirty-five Healthy Male and Female Volunteers Following a Daily Oral Dose of 25mg Spironolactone for Ten Days Alone or Concomitantly with a Daily Oral Dose of 25mg Nebivolol HCL.....	245
Table 135: Mean (%CV) 7 $\alpha$ -Thiomethyl Spironolactone Pharmacokinetic Parameters in Thirty-five Healthy Male and Female Subjects Following a Daily Oral Dose of 25mg Spironolactone for Ten Days Alone or Concomitantly with a Daily Oral Dose of 10mg Nebivolol HCL.....	245
Table 136: Assay Characteristics for d- and l-Nebivolol.....	249
Table 137: Assay Characteristics for ramipril/ramiprilat .....	249
Table 138: Mean (%CV) d-Nebivolol Pharmacokinetic Parameters in Twelve Healthy Male and Female Extensive Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Daily Oral Dose of 5mg Ramipril .....	251
Table 139: Mean (%CV) d-Nebivolol Pharmacokinetic Parameters in Three Healthy Male and Female Poor Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Daily Oral Dose of 5mg Ramipril .....	251
Table 140: Mean (%CV) l-Nebivolol Pharmacokinetic Parameters in Twelve Healthy Male and Female Extensive Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Daily Oral Dose of 5mg Ramipril .....	252
Table 141: Mean (%CV) l-Nebivolol Pharmacokinetic Parameters in Three Healthy Male and Female Poor Metabolizers Following a Daily Oral Dose of 10mg Nebivolol HCL for Ten Days Alone or Concomitantly with a Daily Oral Dose of 5mg Ramipril .....	253
Table 142: Mean (%CV) Ramipril Pharmacokinetic Parameters in Fifteen Healthy Male and Female Subjects Following a Daily Oral Dose of 5mg Ramipril for Ten Days Alone or Concomitantly with a Daily Oral Dose of 10mg Nebivolol HCL .....	254
Table 143: Mean (%CV) Ramiprilat PK Parameters in 15 Healthy Subjects Following a 5 mg Ramipril QD for Ten Days Alone or with 10mg Nebivolol HCL QD.....	255

Table 144: losartan and EXP-3174 Assay Characteristics.....	257
Table 145: l- and d-nebivolol Assay Characteristics.....	258
Table 146: Mean (%CV) d-Nebivolol PK Parameters in Extensive Metabolizers.....	260
Table 147: Mean (% CV) d-Nebivolol Pharmacokinetic Parameters in Poor Metabolizers Following a Single Oral Dose of 10mg Nebivolol HCL Alone or Concomitantly with a Single Oral Dose of 50mg Losartan Potassium.....	260
Table 148: Mean (%CV) l-Nebivolol Pharmacokinetic Parameters in Extensive Metabolizers Following a Single Oral Dose of 10mg Nebivolol HCL Alone or Concomitantly with a Single Oral Dose of 50mg Losartan Potassium.....	261
Table 149: Mean (%CV) l-Nebivolol Pharmacokinetic Parameters in Poor Metabolizers Following a Single Oral Dose of 10mg Nebivolol HCL Alone or Concomitantly with a Single Oral Dose of 50mg Losartan Potassium.....	262
Table 150: Mean (%CV) Losartan Pharmacokinetic Parameters in All Subjects Following a Single Oral Dose of 50mg Losartan Potassium Alone or Concomitantly with a Single Oral Dose of 10mg Nebivolol HCL.....	263
Table 151: Mean (%CV) EXP-3174 Pharmacokinetic Parameters in All Subjects Following a Single Oral Dose of 50mg Losartan Potassium Alone or Concomitantly with a Single Oral Dose of 10mg Nebivolol HCL.....	263
Table 152: Assay Characteristics for d- and l-Nebivolol.....	267
Table 153: Assay Characteristics for total nebivolol.....	267
Table 154: d-nebivolol PK measures in the presence and absence of charcoal.....	269
Table 155: d-nebivolol PK measures in the presence and absence of charcoal.....	270
Table 156: l-nebivolol PK measures in the presence and absence of charcoal in EMs.....	271
Table 157: l-nebivolol PK measures in the presence and absence of charcoal in PMs.....	271
Table 158: Nebivolol-GUD PK measures in the presence and absence of charcoal in EMs.....	272
Table 159: Nebivolol-GUD PK measures in the presence and absence of charcoal in PMs.....	273
Table 160: Influence of other drugs on <i>in vitro</i> plasma protein binding of <i>rac</i> -nebivolol (per Applicant).....	276
Table 161: Influence of other drugs on <i>in vitro</i> plasma protein binding of <i>rac</i> -nebivolol (per Applicant).....	277

## List of Figures

---

Figure 1: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male EM Subjects.....	18
Figure 2: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male PM Subjects.....	19
Figure 3: Schematic presentation of the clinical pharmacology program .....	26
Figure 4: Diastolic blood pressure vs. sum of d- and l-nebivolol plasma concentrations. Circles, observed values, lines, population predicted values (upper curve for the peak and lower curve for the trough plasma concentrations). Upper panel, EMs, lower panel, PMs. ....	28
Figure 5: Clearance vs. race in PM subjects: d-Nebivolol, left panel, l-nebivolol, right panel ....	30
Figure 6: Change in QTcF vs. Plasma Nebivolol Concentrations.....	32
Figure 7: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male EM Subjects.....	37
Figure 8: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male PM Subjects.....	38
Figure 9: Clearance of d-Nebivolol (left) and l-nebivolol (right) vs. creatinine clearance in EM patients. Lines are the results of linear regression. ....	42
Figure 10: Clearance of d-nebivolol in PM subjects .....	43
Figure 11: Clearance of l-nebivolol in PM subjects .....	43
Figure 12: Dissolution profiles for various clinical lots for 900mL dissolution volumes .....	49
Figure 13: Mean d-nebivolol plasma concentrations vs. time for EMs (left panel) and PMs (right panel).....	71
Figure 14: d-Nebivolol Plasma concentrations vs. time. 0-EMs, 1-PMs. Doses: 2.5 mg (1), 5mg (2), 10mg (3), and 20mg (4) .....	74
Figure 15: l-Nebivolol Plasma concentrations vs. time. 0-EMs, 1-PMs. Doses: 2.5 mg (1), 5mg (2), 10mg (3), and 20mg (4) .....	74
Figure 16: Nebivolol glucuronides plasma concentrations vs. time. 0-EMs, 1-PMs. Doses: 2.5 mg (1), 5mg (2), 10mg (3), and 20mg (4) .....	79
Figure 17: Mean Plasma d-Nebivolol Concentrations vs. Time in EM (upper panel) and PM (lower panel) subjects.....	85
Figure 18: Mean Plasma l-Nebivolol Concentrations vs. Time in EM (upper panel) and PM (lower panel) subjects.....	87
Figure 19: Mean Plasma d,l-Nebivolol Concentrations vs. Time in EM (left panel) and PM (right panel) subjects.....	88
Figure 20: Mean Plasma Nebivolol Glucuronide Concentrations vs. Time in EM (upper panel) and PM (lower panel) subjects.....	90
Figure 21: Mean Plasma concentrations of d-nebivolol vs. time. Left panel, EM, right panel, PM .....	95
Figure 22: Mean Plasma concentrations of l-nebivolol vs. time. Left panel, EM, right panel, PM .....	95
Figure 23: Mean plasma concentrations of d,l-nebivolol vs. time. Left panel, EM, right panel, PM .....	95
Figure 24: Mean plasma concentrations of d-nebivolol vs. time. Upper panel, EM, low panel, PM .....	103

Figure 25: Mean plasma concentrations of l-nebivolol vs. time. Upper Panel, EM, left panel, PM	104
Figure 26: Mean plasma concentrations of nebivolol glucuronide vs. time. Upper panel, EM, low panel, PM.	106
Figure 27: Mean Plasma concentrations of d-nebivolol vs. time.	123
Figure 28: Mean Plasma concentrations of l-nebivolol vs. time.	123
Figure 29: Mean Plasma concentrations of d,l-nebivolol vs. time	124
Figure 30: Mean Plasma concentrations of nebivolol glucuronides vs. time.	124
Figure 31: Mean Concentration of Radioactivity in Whole Blood for EM and PM Subjects following Administration of a Single 15mg Dose of 100 $\mu$ Ci of $^{14}\text{C}$ - Nebivolol HCL.	128
Figure 32: Mean Concentration of Radioactivity in Plasma for EM and PM Subjects following Administration of a Single 15mg Dose of 100 $\mu$ Ci of $^{14}\text{C}$ Nebivolol HCL.	129
Figure 33: Nebivolol ng-equivalents per mL of urine and feces.	130
Figure 34: Mean Concentrations of Total Radioactivity in Plasma and Whole Blood for a Period of 0.5–24 h Following a Single Oral Dose of $^{14}\text{C}$ -Nebivolol to EM and PM subjects.	132
Figure 35: Mean Concentrations of Total Radioactivity (TR) in Urine and Feces After a Single Oral Dose of $^{14}\text{C}$ -Nebivolol to EM and PM subjects.	134
Figure 36: Comparison of Pooled Plasma Methanol Extracts from Poor and Extensive Metabolizers	135
Figure 37: Comparison of Pooled Urine Methanol Extracts from Poor and Extensive Metabolizers	135
Figure 38: Comparison of Pooled Feces Methanol Extracts from Poor and Extensive Metabolizers	136
Figure 39: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male EM Subjects.	141
Figure 40: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male PM Subjects	142
Figure 41: Lineweaver-Burk plot	151
Figure 42: Metabolism- independent inhibition of CYP1A2 and CYP2C8 by nebivolol	154
Figure 43: Metabolism- independent inhibition of CYP 2A6 and CYP2B6 by nebivolol	154
Figure 44: Metabolism- independent inhibition of CYP2C9 and CYP2C19 by nebivolol	154
Figure 45: Metabolism- independent inhibition of CYP2D6 and CYP4A9/11 by nebivolol	155
Figure 46: Metabolism- independent inhibition of CYP3A4/5 (testosterone 6 $\beta$ -hydroxylase, left panel) and (midazolam 1'-hydroxylase, right panel) by nebivolol.	155
Figure 47: Metabolism- dependent reversible inhibition of human P450 enzymes by nebivolol	156
Figure 48: Metabolism- dependent irreversible inhibition of human P450 enzymes by nebivolol	157
Figure 49: Observed nebivolol plasma concentrations, left panel- EMs, right panel – PMs. Upper panel – Day 1, middle panel – Day 4, lower panel - Day 7.	163
Figure 50: Least Squares (LS) Mean Change from Baseline in QTc- P Intervals on Day 7.	165
Figure 51: Change in QTcF vs. Plasma Nebivolol Concentrations.	165
Figure 52: The individual QTcF values vs. d,l-nebivolol plasma concentrations for males (left panels) and females (right panels) on Day 1.	166
Figure 53: The individual QTcF values vs. d,l-nebivolol plasma concentrations for males (left panels) and females (right panels) on Day 7	166

Figure 54: The individual QTcF values vs. d,l-nebivolol plasma concentrations for males (left panels) and females (right panels) on Day 4 .....	167
Figure 55: Changes in QTcF values vs. time post dose on Day 7. The curve is Loess smoothing line.....	167
Figure 56: Model diagnostics for d-nebivolol (upper panel, l-nebivolol (middle panel) and nebivolol glucuronides (lower panel).....	176
Figure 57: Plasma concentrations vs. time.....	180
Figure 58: Diagnostics plots for d-nebivolol.....	181
Figure 59: Diagnostics plots for l-nebivolol .....	182
Figure 60: d-Nebivolol Clearance vs. Race EM subjects .....	183
Figure 61: d-Nebivolol Clearance vs. Race, PM subjects.....	183
Figure 62: Clearance of l-nebivolol in EM subjects.....	184
Figure 63: Clearance of l-nebivolol in PM subjects .....	184
Figure 64: Individual predicted vs. observed (left) and IRES vs. observed (right) DBP .....	189
Figure 65: Population predicted vs. observed (left) and WRES vs. observed (right) DBP .....	189
Figure 66: Population predicted vs. observed (left) and WRES vs. observed HR.....	190
Figure 67: Nebivolol dissolution profiles .....	193
Figure 68: Plasma concentration-time profile of <i>d</i> -nebivolol +/- hydrochlorothiazide.....	202
Figure 69: Plasma concentration-time profile of <i>l</i> -nebivolol +/- hydrochlorothiazide.....	203
Figure 70: Plasma concentration-time profile of hydrochlorothiazide +/- <i>l</i> -nebivolol.....	204
Figure 71: Mean Plasma digoxin concentration-time profile in absence (n = 14) and presence (n = 13) .....	208
Figure 72: Mean Plasma d-nebivolol concentration-time profile in presence of digoxin (n = 11) .....	210
Figure 73: Mean Plasma l-nebivolol concentration-time profile in presence of digoxin (n = 11) .....	210
Figure 74: Mean R-warfarin plasma concentration-time profile.....	218
Figure 75: Mean S-warfarin plasma concentration-time profile .....	219
Figure 76: Warfarin prothrombin time in the absence and presence of nebivolol .....	220
Figure 77: INR vs. time profile for warfarin in the presence and absence of nebivolol.....	221
Figure 78: d-nebivolol plasma concentration time-profile in the absence and presence of fluoxetine.....	224
Figure 79: l-nebivolol plasma concentration time-profile in the absence and presence of fluoxetine.....	225
Figure 80: Plasma concentration-time profile of d-nebivolol in EMs and PMs .....	230
Figure 81: Plasma concentration-time profile of l-nebivolol in EMs (upper panel) and PMs (lower panel).....	232
Figure 82: Furosemide Plasma concentration-time profile in all subjects.....	234
Figure 83: Plasma Concentration time profile for <i>d</i> -nebivolol in EM and PM.....	238
Figure 84: Plasma Concentration time profile for l-nebivolol in EM and PM.....	240
Figure 85: Plasma Concentration-time Profiles for Spironolactone, Canrenone, and 7 $\alpha$ -Thiomethyl Spironolactone in Healthy Subjects (A- spironolactone alone and B- spironolactone + nebivolol).....	244
Figure 86: Concentration versus time profiles for <i>d</i> -nebivolol in EM and PM .....	250
Figure 87: Mean concentration versus time profiles for l-nebivolol in EM and PM .....	252

Figure 88: Ramipril Plasma Concentration-Time Profile in presence and absence of Nebivolol .....	253
Figure 89: Ramiprilat Plasma Concentration-Time Profile in presence and absence of Nebivolol .....	254
Figure 90: Plasma concentration-time profiles for <i>d</i> -neбиволol in the presence and absence of losartan .....	259
Figure 91: mean concentration versus time profiles for <i>l</i> -neбиволol in EMs and PMs .....	261
Figure 92: Losartan and EXP-3174 Plasma Concentration-Time Profiles in the presence and absence of neбиволol .....	262
Figure 93: <i>d</i> -neбиволol Plasma Concentration-Time Profiles in Extensive (EMs) and Poor Metabolizers (PMs) with and without coadministration with charcoal (per applicant).....	269
Figure 94: Plasma concentration-time profiles for <i>l</i> -neбиволol in EMs and PMs.....	270
Figure 95: Nebivolol-glucuronide plasma concentration-time profiles in EMs and PMs .....	272

## 1 EXECUTIVE SUMMARY

### 1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-742 and finds the clinical pharmacology and biopharmaceutics sections acceptable provided the labeling comments are adequately addressed. The requested biowaiver for the 2.5 mg dosage strength of the nebivolol tablet is granted.

The following dissolution method and specifications are recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	— , in 15 minutes

### 1.2 COMMENTS:

Issues not addressed by the sponsor include:

1. The pharmacokinetics of the active metabolites of nebivolol was not assessed. This led to the inability to explain why the striking difference in pharmacokinetics of the parent drug in extensive and poor metabolizers of CYP2D6 did not show any differences in the drug effect.
2. The relationship between pharmacokinetics and pharmacodynamics of nebivolol was not established. The reasons include poor study design and inability to measure all pharmacologically active moieties.
3. The sponsor is requested to evaluate the PK/PD relationship in African-American hypertensive patients.

\_\_\_\_\_  
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Clinical Pharmacology Reviewer

Date \_\_\_\_\_

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CPB Briefing was held on January 26, 2005

Attendees: Drs. K. Hicks, J. Hunt, A. Karkowsky, R. Kumi, S. Lemtouni, P. Marroum, M. Mehul, E. Mishina, A. Selen, N. Stockbridge.

cc list: NDA 21-742, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

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### 1.3 Summary of OCBP Findings

#### 1.3.1 Background

Bertek Pharmaceuticals Inc. is seeking approval of nebivolol immediate release tablets 2.5, 5, and 10 mg for the treatment of hypertension.

Nebivolol is a selective  $\beta_1$ -adrenergic receptor antagonist that is also believed to increase nitric oxide concentrations within vascular endothelial cells. In addition to these properties, nebivolol is also postulated to have antioxidant and anti-proliferative properties. Some of the metabolites of nebivolol (hydroxy-nebivolols and nebivolol glucuronides) have shown similar pharmacologic activity in vitro as nebivolol itself.

#### 1.3.2 Current Submission

Item 6 of NDA 21-742 contains 90 study reports including population PK and PK-PD analyses using the combined database of several studies. This review focused on studies involving the clinical pharmacology (19), in vitro metabolism and protein binding studies (4), a QT study, a population PK and PK/PD study, and a biopharmaceutics (tablet dissolution) study. The remaining studies were not reviewed because they did not provide additional information. Dr. Kumi focused on the in vivo drug-drug interaction studies. Dr. Mishina reviewed the pharmacometrics data analysis performed by the sponsor and the rest of the studies, summarized the findings of both reviewers in the QBR, the Executive Summary and the Recommendations for the Labeling.

#### PK

##### Healthy Subjects

Nebivolol is a weak base with a pKa of 8.5 and is slightly soluble in water and highly lipophilic. Nebivolol contains four chiral centers which could result in its composition of 16 different stereoisomers. The active drug is a racemic mixture of two stereoisomers, d-nebivolol and l-nebivolol (SRRR- nebivolol and RSSS- nebivolol). These stereoisomers differ in pharmacologic properties. D-Nebivolol is responsible for the  $\beta$ -blocking effect, and the l-isomer increases nitric oxide in the endothelial cells. In addition, the sponsor claimed that if administered alone, d-nebivolol has less  $\beta$ -blocking activity compared to the administration of nebivolol as a racemic mixture.

Nebivolol undergoes polymorphic metabolism involving cytochrome P450 2D6 (CYP2D6), a drug metabolizing enzyme that is deficient in about 7% of Caucasians, 2% of African Americans, and 2% of Asians (poor metabolizers, PM). The pharmacokinetics and metabolic disposition of d- and l-nebivolol are significantly affected by the subject's CYP2D6 genotype. When the racemic nebivolol is administered, the pharmacokinetics of d- and l-nebivolol is quite different. In the EM population, following oral administration under steady-state conditions, the apparent mean elimination half-life and clearance of d- and l-nebivolol are 13 and 17 hours, and 960 and 500 L/hr, respectively. In PMs, both d- and l-nebivolol are sustained in plasma longer. The half-life and clearance of d-nebivolol are 22 hours and 50 L/hr respectively. The half-life of l-nebivolol was not calculated appropriately (over 70 hours) and the clearance is about 9 L/hr.

The exposure (AUCI) to the l-isomer is about 2-fold larger for the EMs, and 2-5 fold larger for the PMs than the exposure to the d-isomer. Nebivolol does not accumulate in plasma of EMs when administered QD. The fluctuations of d- and l-nebivolol around  $C_{ss}$  were very large, over 460% in EMs and 40-100% in PMs.

### Absorption

Peak concentrations of d- and l-nebivolol reached at 1.5-2 and 4 hours post-dosing in extensive and in poor metabolizers respectively. The absolute bioavailability of nebivolol is not known. The relative bioavailability of nebivolol tablets compared to an oral solution was approximately 87% for extensive metabolizers and 111% for poor metabolizers. Food has no impact on the bioavailability of nebivolol.

### Distribution

The apparent plasma protein binding of d- and l-nebivolol averaged 98.13% and 97.85% respectively measured at room temperature over the clinically relevant concentration range.

The main binding protein is human serum albumin (HSA). The binding to  $\alpha_1$ -acid glycoprotein is 74.14% for d- nebivolol and 71.53% for l-nebivolol. The blood to plasma concentration ratio of d- and l-nebivolol averaged 1.11 and 1.28, respectively. In healthy subjects, the mean volume of distribution of d-nebivolol is about 16000 L (EM) and 1300 L (PM), and for l-nebivolol it is 11000 L (EM) and 950 L (PM). The sparse data available from the hypertensive patients did not allow to calculate the volume of distribution.

### Metabolism

In vitro (human microsomes) nebivolol is metabolized primarily by CYP2D6 isoenzyme and to a lesser extent by CYP3A4.

#### *Healthy subjects*

In vivo, nebivolol is metabolized primarily by direct glucuronidation and hydroxylation at either the alicyclic (4 or 4' position) or aromatic (5/5' or 7/7' vs. 8/8' positions) ring. In plasma, most of the metabolites detected were glucuronides of unchanged drug in addition to oxidative N-dealkylated acid. Nebivolol glucuronides (G-UD) comprised a large amount of the EM plasma profile followed by glucuronides G-1, G-3, G-6 – G-9, and G-11 and non-conjugated metabolites A-3, A-10, and unchanged nebivolol. In PM plasma G-UD was the largest component, followed by A-10, and G-8 and unchanged nebivolol.

Due to the stereo complexity of the parent molecule and difficulties in the synthesis of stereo and structural specific reference materials, the sponsor did not identify the definitive structures of the stereo-specific hydroxyl and glucuronide metabolites. The chiral inversion between d- or l-nebivolol has not been seen in animals and in man.

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EM Male Subjects\*

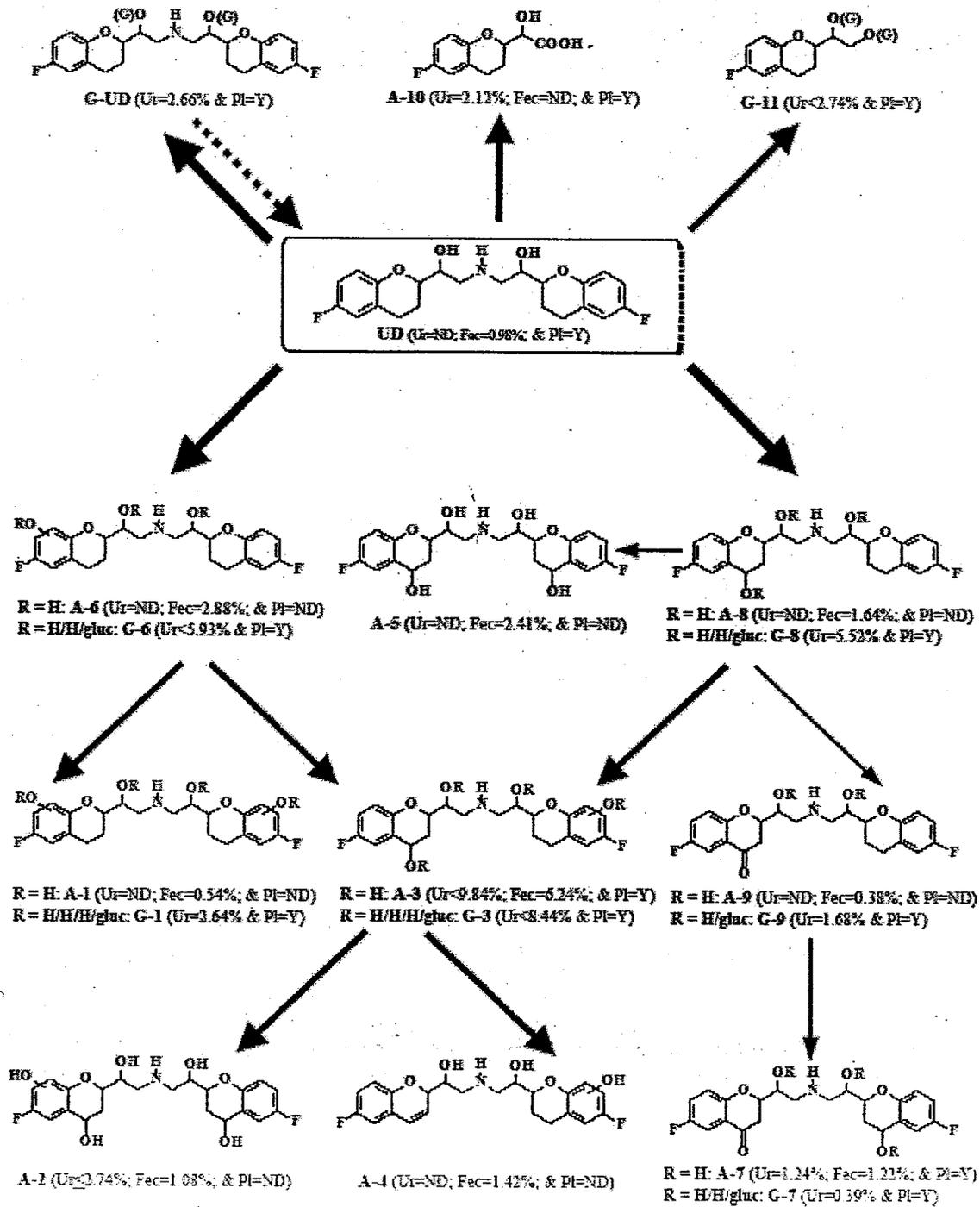
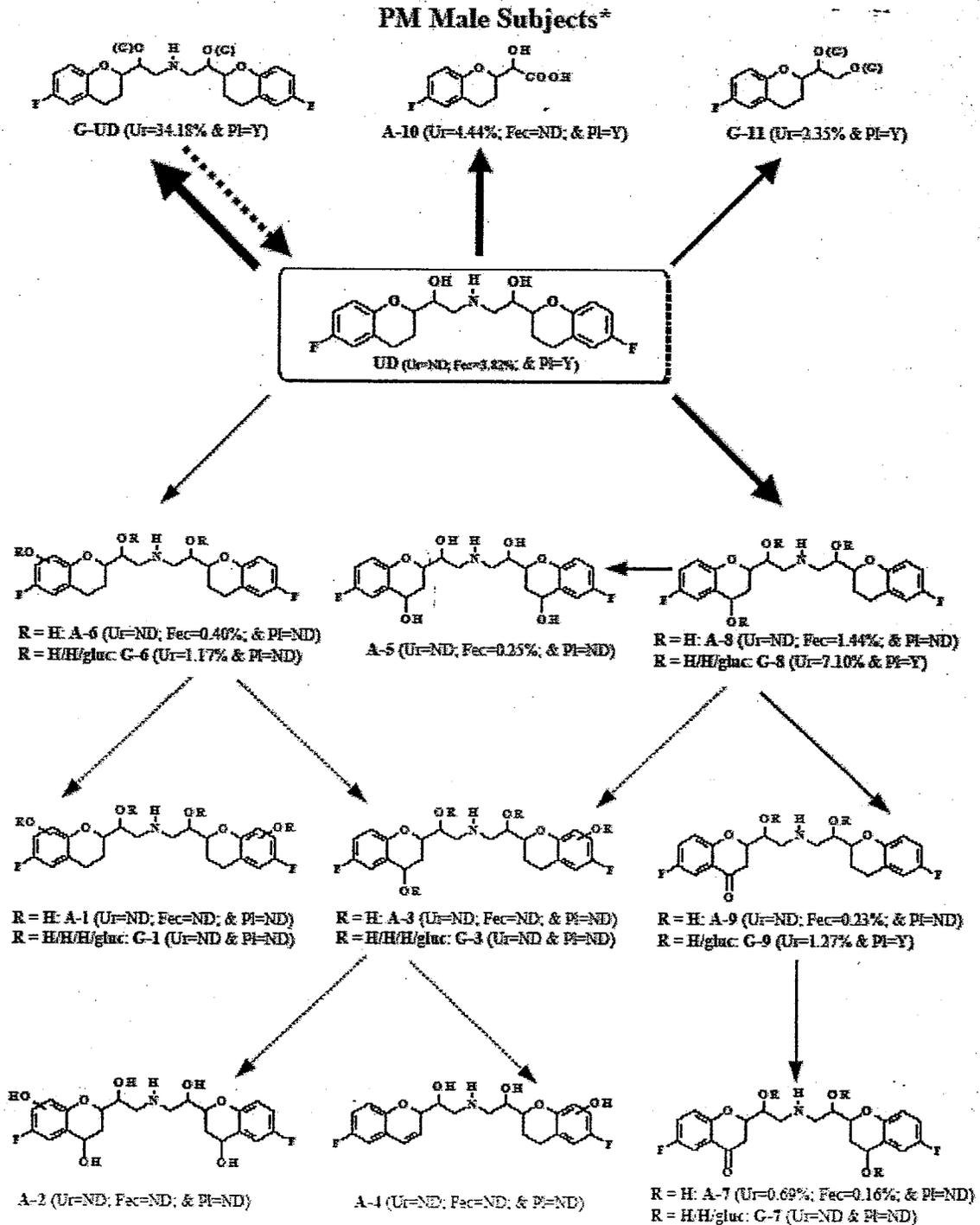


Figure 1: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male EM Subjects



**Figure 2: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male PM Subjects**

**Excretion**

In urine of EM subjects, 38.4% and of the nebivolol dose was recovered as glucuronide conjugates of unchanged drug or hydroxylated and N-dealkylated metabolites. In PM's urine 66.5% of the administered dose was recovered, out of which 34.2% were the glucuronides of unchanged nebivolol. In feces 43.6% (EM) and 13.1% (PM) of the nebivolol dose recovered with more unchanged drug in PM than EM subjects.

**Renal impairment**

There is no difference in the mean unbound nebivolol in plasma in renally impaired subjects compared to the healthy volunteer's data. In subjects with moderately and severely impaired renal function the clearance of *d*-nebivolol decreased by 30% and 55% compared to the healthy subjects. The clearance of *l*-nebivolol is decreased by 34% for patients with severe renal impairment. No formal studies have been conducted in patients receiving dialysis.

**Hepatic impairment**

In moderately hepatic impaired subjects, the unbound fraction of nebivolol in plasma is increased as compared to the healthy subjects (1.90 vs. 2.45%). Compared to healthy subjects, the exposure to *d*- and *l*-nebivolol (AUCI) in patients with moderate hepatic impairment increased 10- and 5-fold, half-life increased 2.5 and 1.6 times and the apparent clearance decreased by 86 and 75%. The low 2.5 mg dose is recommended as a starting dose for these patients.

The pharmacokinetic of nebivolol in severely impaired patients have not been studied and nebivolol is contraindicated to them.

**PK/PD drug-drug interaction information**

Apart from fluoxetine, a CYP2D6 inhibitor, no clinically relevant PK/PD interactions were observed between *l*-nebivolol or *d*-nebivolol (10 mg QD) and comedications (given at therapeutic doses) used in hypertension therapy. Fluoxetine increased nebivolol (CYP2D6 substrate) exposure: approximately 3-fold increase in C<sub>max</sub> and ~ 8-fold increase in AUC of *d*-nebivolol and approximately 2-fold increase in C<sub>max</sub> and ~ 5-fold increase in AUC of *l*-nebivolol. Nebivolol did not significantly alter (increases or decreases ≤ 14 %) the AUC or C<sub>max</sub> of digoxin, losartan, hydrochlorothiazide, warfarin (R and S), furosemide or ramipril/ramiprilat. Repeated administration (4, 8, 12, 16, 22, 28, 36 and 48 hours after nebivolol administration) of activated charcoal (Actidose-Aqua<sup>®</sup>) with nebivolol (single dose) did not lead to a drug-drug interaction. However, based on the findings in poor metabolizers (increased nebivolol apparent oral clearance) and historical data with other beta-blockers (such as nadolol, propranolol, and sotalol), coadministration of nebivolol and charcoal should be avoided.

Pharmacodynamic (PD) interactions were not typically evaluated in the drug interaction studies; however, no clinically significant PD changes were observed in the studies where PD was evaluated.

Nebivolol does not cause significant displacement in the plasma protein binding of diazepam, digoxin, diphenylhydantoin, hydrochlorothiazide, imipramine, or warfarin at their therapeutic concentrations. Similarly, the changes in nebivolol plasma protein binding are not clinically significant (< 10 % increase in nebivolol free fraction) when nebivolol is incubated with digoxin,

diphenylhydantoin, hydrochlorothiazide, indomethacin, propranolol, sulfamethazine, tolbutamide, warfarin, imipramine, diazepam or enalapril.

**Patients**

Due to poor study design the pharmacokinetic profiles of the parent drug and active metabolites of nebivolol in patients were not characterized.

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### Pharmacogenetics

Despite the drastic difference in the nebivolol pharmacokinetic disposition between the extensive and poor metabolizers of CYP2D6, the pharmacodynamics was not affected by the genetic polymorphism. Dose adjustment was not needed for the poor metabolizers. The pharmacologic contribution of various metabolites of nebivolol to the overall clinical activity either directly and/or via possible back conversion from their respective glucuronide metabolites might be important but it was not accounted for in this NDA.

### Exposure-Response Relationships

The sponsor attempted to describe the effect of d- and l-nebivolol on the decrease of diastolic blood pressure and heart rate in hypertensive patients. The Emax model proposed by the sponsor estimated an unreasonably low EC50 value for the effect nebivolol on diastolic blood pressure (0.068 ng/mL). This value is 220 fold higher than in vitro affinity of nebivolol to  $\beta_1$ -adrenoceptor in human myocardium (Ki 5-15 ng/mL). Moreover, the average d-nebivolol plasma concentrations measured in Study NEBI-302 was about 6 ng/mL, which was the same order of magnitude as the Ki value and the effect of lowering blood pressure with nebivolol was achieved.

The same comments as above for DBP are applicable for the heart rate response model (estimated by the sponsor EC50 of 0.0017 ng/mL). The EC50 values estimated by the sponsor do not reflect the physiologic parameters for  $\beta$ -adrenoceptor activity of nebivolol; moreover, the data obtained by the sponsor were not sufficient to evaluate the time course of effect.

The PK/PD population models proposed by the sponsor were deemed unacceptable.

### Factors influencing the drug effect

Although the sponsor did not find any of the demographic covariates except for the genotype important in the models, an increase of clearance of d- and l-nebivolol was found if the patients were African American and poor metabolizers.

### Effect of nebivolol on QT and QTc interval

Nebivolol prolongs the QT interval but does not prolong the corrected QTc interval due to the decrease in heart rate which is common for  $\beta$ -blockers.

After dosing 40 mg/day for 7 days, only twenty subjects out of 71 had elevation of QTcF more than 30 msec on all days of the study, and the individual QTcF values were less than 455 msec for males and less than 460 msec for females.

### Biopharmaceutics

The following dissolution method and specifications are recommended:

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	in 15 minutes

The requested biowaiver for the 2.5 mg dosage strength of the nebivolol tablet is granted based on comparability of the dissolution profiles in 3 media.

**Issues not addressed by the sponsor include:**

1. The pharmacokinetics of the active metabolites of nebivolol were not assessed. This led to the inability to explain why the striking difference in exposure to the parent drug in extensive and poor metabolizers of CYP2D6 did not show any differences in the drug effect.
2. The relationship between pharmacokinetics and pharmacodynamics of nebivolol was not established. The reasons include poor study design and inability to measure all pharmacologically active moieties.
3. The sponsor is requested to evaluate the PK/PD relationship in African-American hypertensive patients.

**Conclusions and Recommendations for the Labeling**

Since nebivolol stereoisomers have different pharmacokinetic properties, the CLINICAL PHARMACOLOGY Section is rewritten to include the finding for both entities.

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## 2 QUESTION BASED REVIEW

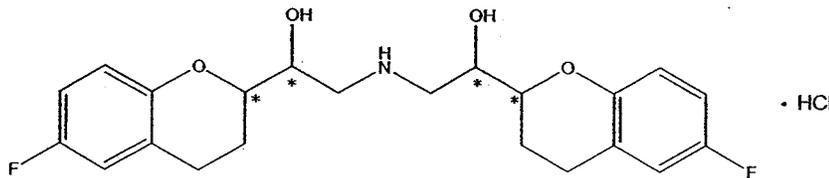
### 2.1 General Attributes

#### History of Nebivolol Development and Current Marketing Status

Nebivolol Hydrochloride (HCL) is currently marketed by Menarini International Operations of Luxembourg as Nebilet Tablets; 5mg are approved in over 30 countries in Europe, Central America, and South America for the treatment of hypertension. The product is an immediate release tablet that was originally developed and marketed by Janssen Pharmaceutica. Nebivolol was first marketed in the Netherlands and Germany in January 1997. The sponsor is seeking the approval of nebivolol hydrochloride in the United States as an oral agent for the treatment of hypertension.

#### Highlights of chemistry and physical- chemical properties of the drug substance and product

The chemical name for nebivolol is  $(\pm)[2R^*[R^*[R^*(S^*)]]]-\alpha,\alpha'-[iminobis(methylene)] bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]$  hydrochloride. Nebivolol is a racemate composed of d-nebivolol and l-nebivolol with the stereochemical designations of [SRRR]-nebivolol and [RSSS] nebivolol, respectively. Nebivolol's molecular formula is  $(C_{22}H_{25}F_2NO_4 \cdot HCL)$ , molecular weight is 441.90 kD, with the following structural formula:



\* stereogenic centers

Nebivolol is a weak base with a pKa of 8.5 and is slightly soluble in water (~ 1mg/mL, pH 5.5) but exhibits lower solubility in 0.1N HCL (0.066mg/mL pH 1.0, 37 ° C). Nebivolol is highly lipophilic expressed by a partition coefficient of 10715 (log P = 4.03) between n-octanol and an aqueous buffer solution of pH 11.8. Nebivolol contains four asymmetric carbons (C2, C11, C2' and C11'). Theoretically, the four chiral centers of nebivolol could result in nebivolol being composed of 16 different stereoisomers. The active drug is composed of only two stereoisomers, d- nebivolol and l- nebivolol (SRRR- nebivolol and RSSS- nebivolol). The tablets for oral administration contain nebivolol hydrochloride equivalent to 2.5 mg, 5 mg, and 10 mg of nebivolol.

#### *What are the proposed mechanisms of action and therapeutic indication?*

Nebivolol hydrochloride is a selective  $\beta_1$ -adrenergic receptor antagonist. The sponsor also found that it increases nitric oxide concentrations within vascular endothelial cells. In addition to these properties, nebivolol also has antioxidant and anti-proliferative properties. Some of metabolites

of nebivolol (hydroxy-nebivolols and nebivolol glucuronides) have shown similar pharmacologic activity in vitro as nebivolol itself.

Nebivolol is proposed for use in the management of \_\_\_\_\_ hypertension as monotherapy or in combination with other antihypertensive agents.

**What are the proposed dosages and route of administration?**

The recommended starting dose is 5 mg once daily, with or without food as monotherapy or in combination with other antihypertensive agents. The clinical effects of doses exceeding 40 mg as monotherapy and 20 mg in combination have not been studied.

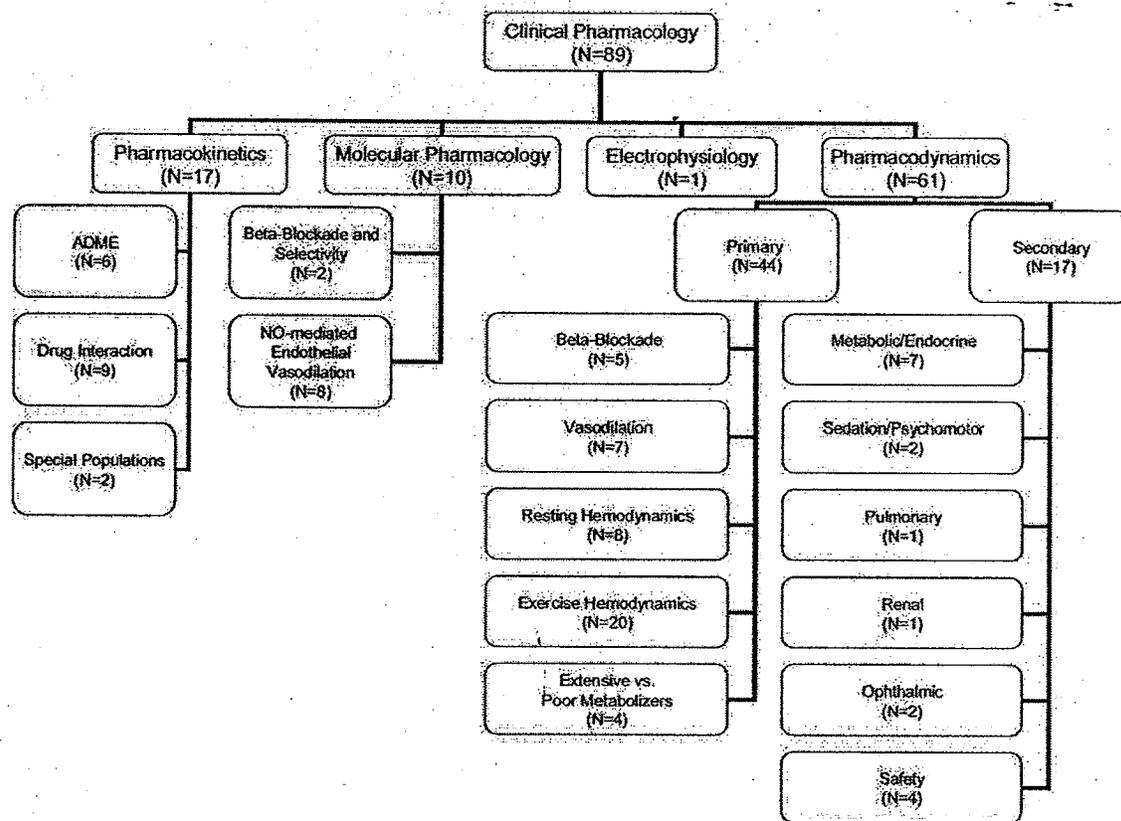
## 2.2 General Clinical Pharmacology

*What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

The sponsor's biopharmaceutics/pharmacokinetics program was designed to obtain basic information on the absorption and metabolism of nebivolol, its pharmacokinetic and pharmacodynamic behavior, the influence of polymorphic metabolism, and the effect various disease states may have on the pharmacokinetic profile of nebivolol. The program includes 16 Phase I studies utilizing 260 volunteers, and a population pharmacokinetic analysis from a Phase III study in over 800 hypertensive patients. Metabolite identification and profiling was also investigated in conjunction with an in vivo <sup>14</sup>C mass balance study. Several circulating metabolites of nebivolol have been identified in the plasma of both poor and extensive metabolizers which likely possess significant pharmacologic activity in vivo, including the major group of metabolites, glucuronides. In addition, the program also addressed the drug interaction potential of nebivolol via several in vivo studies utilizing specific markers of various isoenzymes, along with agents likely to be co-administered in the intended patient population. Schematically the total clinical pharmacology program is shown below (Figure 3).

The clinical pharmacology data included in this application consists of 17 completed pharmacokinetic studies conducted in healthy volunteers, 10 in-vitro mechanism of action studies, an electrophysiology study conducted in healthy volunteers and 61 in-vivo pharmacodynamic studies.

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**Figure 3: Schematic presentation of the clinical pharmacology program**

*Was there a reasonable basis for selecting the response endpoints and were they measured properly to assess efficacy and safety in the clinical pharmacology studies?*

Nebivolol hydrochloride is a selective  $\beta_1$ -adrenergic receptor antagonist that also increases nitric oxide concentrations within vascular endothelial cells.

The primary response endpoint measured in clinical pharmacology and clinical studies (NEB302, NEB305) was the lowering of the sitting diastolic blood pressure at trough at the staff end of treatment compared to baseline. The potential of nebivolol to prolong the QT interval duration was assessed in the separate clinical pharmacology study (NEB122).

The primary efficacy and safety endpoints were measured properly.

*Were the correct moieties identified and properly measured to assess clinical pharmacology?*

Not entirely.

The sponsor was able to assay in plasma, urine and feces d-nebivolol, l-nebivolol and the total concentration of the nebivolol glucuronides.

The pharmacokinetics of d- and l-nebivolol was assessed separately after single and multiple doses, in special populations, and in the pharmacodynamic studies. It was shown that the pharmacokinetic properties of these two substances are quite different. Nevertheless, in the Package Insert the sponsor referred to the pharmacokinetic parameters of the and of so called d,l-

nebivolol, which is not a separate moiety but a sum of d-nebivolol and l-nebivolol plasma concentrations at each sampling point. Although several of the hydroxy metabolites of nebivolol have similar  $\beta$ -blocking effects as the parent drug, none of them was measured in the pharmacokinetic studies. This led the sponsor to the wrong conclusions regarding the exposure-response relationship of nebivolol. For example, no explanation was provided for why a 40 fold difference in exposure to the parent drug between extensive and poor metabolizers of CYP2D6 did not result in differences in the efficacy and safety of nebivolol.

The concentration of the mixture of nebivolol glucuronides was determined by the subtraction of the total nebivolol content obtained after enzymatic glucuronidation of the plasma samples. The sponsor estimated the pharmacokinetic parameters of the mixture of glucuronides, as it is a single molecular entity which is not a valid approach since each of them could have distinct pharmacokinetic properties. The AUC and half-life for the mixture of nebivolol glucuronides was underestimated and the clearance overestimated due to incomplete plasma sampling. Some of the nebivolol glucuronides have pharmacologic activity but the sponsor had never assayed them separately except for the mass-balance study in 6 volunteers.

#### *Assay Validation*

The assay validation reports were provided for each of the studies. The results provided for the assay validation of d-, l-nebivolol and nebivolol glucuronides in plasma using high performance liquid chromatography with tandem mass spectrometric detection were acceptable. The assay validation for the parent drug and metabolites by radio-HPLC in mass-balance study was also acceptable.

#### **Nebivolol Exposure-response (efficacy and safety)**

##### *Were the relationship between efficacy endpoints and safety endpoints and drug plasma concentration described?*

Yes.

The sponsor performed a population PK/PD data analysis based on the data obtained from part of the patients involved in the pivotal clinical study NEB302; however, the approach as well as the model adopted by the sponsor was deemed unacceptable.

The sponsor attempted to evaluate the relationship between the plasma concentrations of the sum of d- and l-nebivolol and sitting diastolic blood pressure changes (efficacy endpoint) and between the plasma concentrations of d,l-nebivolol and heart rate (safety endpoint). An Emax model was proposed by the sponsor for both relationships.

Figure 4 shows the population prediction for the diastolic blood pressure vs. d,l-nebivolol plasma concentrations. The predictions are very poor. Moreover, the model diagnostics plots indicate that the population predictions for the diastolic blood pressure and heart rate do not correlate with the observed values (see NEB302 review in Appendix).

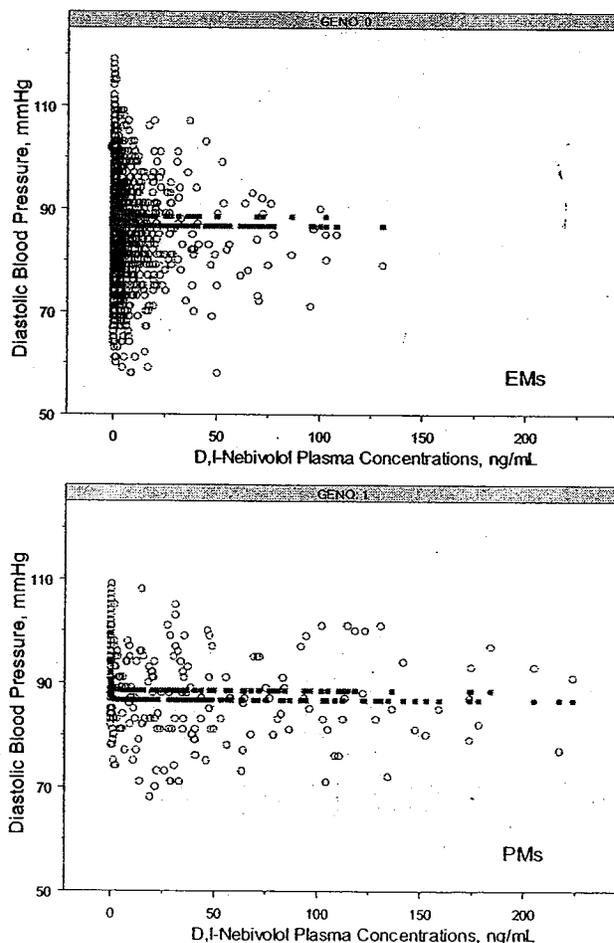
The model developed by the sponsor estimated an unreasonably low EC50 values for both the lowering of the diastolic blood pressure (0.068 ng/mL) and lowering of the heart rate (0.0017 ng/mL). It is well recognized that for the Emax saturable model, the estimation of EC50 (50% of the drug concentration responsible for the maximal effect) should correlate with the receptor activity measured by  $K_i$ . The most comprehensive assessment of  $K_i$  of nebivolol in human myocardium is described in Maack et al 2001. In this paper the authors estimate the  $K_i$  of the  $\beta_1$ -adrenoceptor as about 7-8 mol/L which reflects a concentration at the effect site of 5-15

ng/mL. The effect site is the heart; therefore, d-nebivolol (the isomer with the preferential  $\beta_1$ -adrenoceptor activity) plasma concentrations would be the closest approximation of the drug concentration which drives this effect.

The sponsor's estimation of the EC50 for the sitting diastolic blood pressure (0.068 ng/mL) is 220 fold higher than  $K_i$ . Moreover, the average d-nebivolol plasma concentrations measured in Study NEBI-302 was about 6 ng/mL, this value was the same order of magnitude as the  $K_i$  value. The EC50 values estimated by the sponsor do not reflect the physiologic parameters ( $K_i$ ) for  $\beta$ -adrenoceptor activity of nebivolol.

The same comments as above for DBP are applicable for the heart rate response model.

Although the sponsor attempted to describe the exposure-response relationship, the estimation of the parameters for these relationships (diastolic blood pressure vs. sum of d- and l-nebivolol and heart rate vs. sum of d- and l-nebivolol) were not physiologically plausible, and therefore, the models were not acceptable.



**Figure 4: Diastolic blood pressure vs. sum of d- and l-nebivolol plasma concentrations. Circles, observed values, lines, population predicted values (upper curve for the peak and lower curve for the trough plasma concentrations). Upper panel, EMs, lower panel, PMs.**

***What factors influence the drug effect?***

Although all demographic covariates were tested, the sponsor did not find any of them significant. The pharmacokinetics of d- and l-nebivolol in extensive and poor metabolizers were strikingly different but the model describing the relationship between the sum of d- and l-nebivolol and DBP predicted the same effect in EMs and PMs. This fact probably could be explained by the effect of other metabolites which occur in EMs and have similar to the parent drug affinity to the  $\beta$ -receptors as the parent drug.

Many of the proposed metabolites of nebivolol, including the major metabolites nebivolol glucuronides, have demonstrated pharmacologic activity in vitro similar in nature and magnitude to nebivolol itself, Table 1.

**Table 1: Summary of Ki values for nebivolol, its enantiomers, proposed metabolites, other known metabolites, and commonly prescribed  $\beta$ -blockers**

Compound	$\beta_1$ (nM)	$\beta_2$ (nM)	$\beta_1/\beta_2$ selectivity
d,l-Nebivolol	0.7	225	320
d-Nebivolol	0.401	101	251
4-Hydroxy Nebivolol	0.681 <sup>a</sup>	101	148
8-Hydroxy Nebivolol	4.52	306	68
Nebivolol Glucuronide(s)	10.5	580	55
5-Hydroxy Nebivolol	0.972	50.9	52
4-Hydroxy-8-Phenol Nebivolol	19.8	397	20
4-Hydroxy-5-Phenol Nebivolol	5.65	69	12
l-Nebivolol	715	>10 <sup>4</sup>	-
Betaxolol	6.19	576	93
Metoprolol	43	3186	67.8
Bucindolol	2.35	2.35	1.0
Carvedilol	3.84	3.84	1.0
Propranolol	3.63	3.63	1.0

Table 1 lists the Ki values estimated in vitro for nebivolol, its metabolites and other  $\beta$ -blockers

The most important differences in drug effect were expected in African American patients. The post-hoc estimates of clearance obtained by the sponsor were analyzed by race (Table 2).

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Table 2: Descriptive statistics obtained for clearance from the posthoc estimates: comparisons of EMs vs. PMs and Caucasians vs. Blacks for d- and l-nebivolol

	EM		PM*		
	d-nebivolol	White	Black	White	Black
Mean		716.3	590.9	61.4	118.9
Standard Error		4.1	9.0	2.1	12.4
Median		698.5	583.6	42.0	109.9
Standard Deviation		378.0	361.5	53.5	74.5
Minimum		24.9	39.0	17.1	44.4
Maximum		2741.0	1980.3	262.1	211.5
<i>l-nebivolol</i>					
Mean		454.6	401.4	27.0	78.7
Standard Error		2.3	6.7	1.7	2.5
Median		453.3	382.8	8.2	85.9
Standard Deviation		215.3	266.2	44.5	14.9
Minimum		7.2	24.2	4.0	53.3
Maximum		1628.8	2519.8	180.3	89.4

In EM subjects, there was no apparent change in clearance for any of the studied races. However, the median clearance values for the PM subjects were 2-3 times larger for the Blacks both for d- and l-nebivolol, Figure 5. It is difficult if not impossible to quantify the effect of race in this study because the signal may be diffused: Blacks were represented by only 18% of the analyzed population and there were only 49 PMs included in this study.

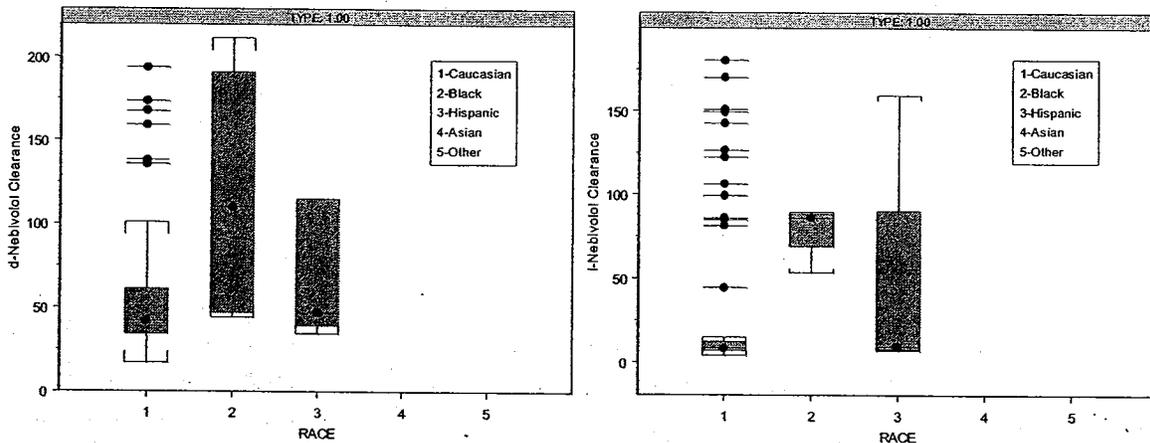


Figure 5: Clearance vs. race in PM subjects: d-Nebivolol, left panel, l-nebivolol, right panel

Since there was a very small number of black poor metabolizers in the studied group (N=2), these results should be interpreted with caution. The Agency recommended to the sponsor to study the effect of nebivolol in blacks in a separate study.

*Was the time course of effect studied?*

No.

The data set analyzed included the data which were not sufficient to evaluate the time course of drug effect. Although the number of samples (3-4 per subject) was sufficient to use population modeling approach, the sampling occurred only at the peak and trough plasma concentrations and there was no information about the drug effect and plasma concentrations in between of these points.

***Were the models proposed by the sponsor acceptable?***

No.

Apparently, the pharmacokinetic plasma sampling and effect measurements for this study were not properly designed. The Population PK Guidance for the industry recommends having 3-4 plasma samples per patients covering the full plasma concentration vs. time profile. The time course of the effect was not assessed by the sponsor. Moreover, the assumption that the effect of the drug correlates with the sum of d- and l-nebivolol plasma concentrations is not valid. The  $\beta$ -blocking effect of l-nebivolol is not significant. In the mean time, some (4- and 8-hydroxy) metabolites of d-nebivolol have similar pharmacologic activity as the parent drug. Unfortunately, their plasma concentrations were not measured in the clinical studies. It is possible that some or all of these factors led to the difficulties in correlating the effects of nebivolol and its plasma concentrations.

The attempt to describe the data with a linear PK/PD model by this reviewer did not lead to a better model fit.

**Does nebivolol prolong the QT or QTc interval?**

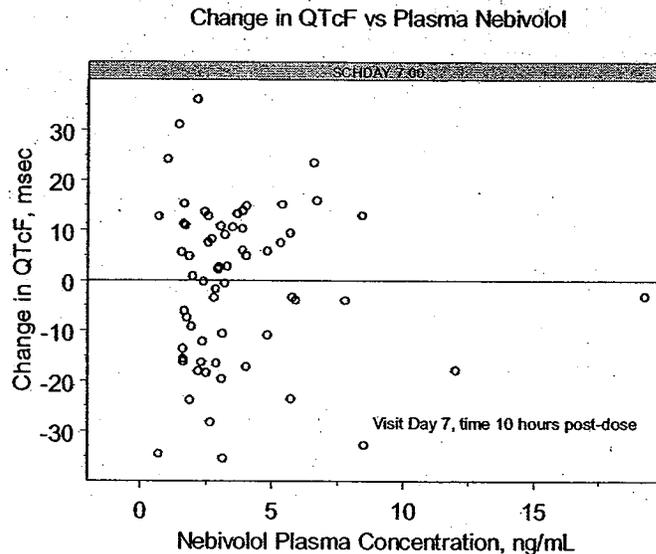
Nebivolol prolongs the QT interval but does not prolong the corrected QTc interval due to the decrease in heart rate which is common for  $\beta$ -blockers.

The effects of nebivolol on the electrocardiographic intervals of normal healthy volunteers were evaluated at the highest doses of drug (20 and 40 mg, for 7 days). The subjects were stratified by sex and randomized in a 1: 1: 1: 1 ratio to one of four treatment groups: nebivolol, atenolol (active-control), moxifloxacin (positive-control), or placebo. Each of the nebivolol and the atenolol groups included 3 PMs. The QT intervals were corrected for variations in HR using a population correction factor, Bazett's and Fridericia's formulas, the latter was preferred at low heart rates.

The data submitted by the sponsor included only the sum of d- and l-nebivolol plasma concentrations. The plasma nebivolol profiles for Days 1, 4, and 7 were similar to the profiles described in the pharmacokinetic studies (NEB126 and NEB127). The comparisons of the QTc interval changes are shown in Table 83. The administration of moxifloxacin increased the QTc interval calculated with any correction method, with a 6 msec change detectable in this study. The sponsor compared nebivolol versus placebo at 2 hours after dosing on Day 7 (peak effect), the mean difference in QTc interval (95% CI) was 1.14 msec (- 4.09 , 6.38) using the population correction factor and 0.68 msec (- 4.57 , 5.93) using Fridericia's formula. The sponsor admitted that the upper bound of the 95% confidence interval was slightly higher than 6 msec for the population corrected data, and concluded that the difference between nebivolol and placebo treatments were not statistically significant (based on the small mean differences).

The treatment with nebivolol and atenolol (active control) showed similar results, with mean reductions in QTc of approximately 5 msec for both treatments at the time of peak effect.

The relationship between all QTcF changes vs. nebivolol plasma concentration obtained from the subjects on Day 7 at 10 hours post-dose are shown in Figure 6 below.



**Figure 6: Change in QTcF vs. Plasma Nebivolol Concentrations**

No trend was observed in this plot. Therefore, no correlation was observed between QTcF and nebivolol plasma concentrations.

After repeated doses of nebivolol over 7 days at the highest possible dose of 40 mg/day, the individual QTcF values were less than 455 msec for males and less than 460 msec for females. From the 71 subjects who had participated in the nebivolol group, twenty subjects on all days and nine subjects on Day 7 had an increase of QTcF over 30 msec. For the PM subjects (n=3) who received nebivolol, none had a change in QTcF above 20 msec.

Therefore, nebivolol does not prolong the QTc interval when administered chronically at the highest studied clinical dose of 40 mg daily.

**Is the dose and dosing regimen selected by the sponsor acceptable?**

Yes.

The proposed dosage regimen is acceptable because sufficient efficacy and safety were shown in the pivotal clinical trials using the proposed regimen (See Medical Review). The antihypertensive efficacy of nebivolol in oral, once-daily doses ranging from 1.25 mg to 40 mg, has been demonstrated in three randomized, double-blind, placebo-controlled, monotherapy trials conducted in the US and Europe. The sponsor proposed to individualize the dose of nebivolol to the needs of the patient. The recommended starting dose is 5 mg once daily, with or without food as monotherapy or in combination with other antihypertensive agents. Once daily regimen will provide sufficient nebivolol plasma concentration to lower and maintain the sitting systolic/diastolic blood pressure from -12.4 to -7.1/-11.3 to -8.0 mmHg.

**What undesirable effects of nebivolol are dose limiting?**

Bradycardia is a dose limiting effect of nebivolol. In the clinical pharmacology part of Study NEB302 from 750 patients receiving nebivolol, forty had a heart rate less than or equal to 50 bpm, and only 2 patients had bradycardia after nebivolol doses below 5 mg.

**Do pharmacokinetic parameters change with time?**

No.

The sponsor compared the pharmacokinetic parameters of the sum of d- and l-nebivolol estimated after single and multiple daily 10 mg doses of nebivolol. The 90% CIs confidence intervals for the ratio of single dose and steady state PK parameters were estimated. Although all CIs were skewed, the difference was found only for CPEAK and half-life estimated in PM subjects. The steady state half-life was 28% larger compared to single dose. The CPEAK values were over 3-fold higher under steady state conditions in comparison with the single dose value. Although the sponsor explains this increase by a low number of PM subjects (N=6), it could be also attributed to the non-linear kinetics of nebivolol.

Since d- and l-nebivolol have different pharmacologic and pharmacokinetic properties, their parameters after single and multiple doses were compared by this reviewer. In EMs, the parameters of d- and l-nebivolol did not change significantly (90% CIs were in the range of 80 to 125%), Table 3.

**Table 3: Comparison of the pharmacokinetic parameters of d-nebivolol after single and multiple 10 mg dose of nebivolol**

Parameter	Extensive Metabolizers (EMs) (n=16)	EMs Least Squares Mean Ratio (%) <sup>a</sup>	EMs 90% Confidence Interval (%) <sup>a</sup>	Poor Metabolizers (PMs) (n=6)	PMs Least Squares Mean Ratio (%) <sup>a</sup>	PMs 90% Confidence Interval (%) <sup>a</sup>
AUCTAU (ng·hr/mL)	7.512 (109.1)	98.9	87.8 - 112	104.9 (18.23)	87.5	80.4 - 95.2
CPEAK (ng/mL)	1.204 (46.86)	101	90.0 - 114	6.538 (14.81)	355	131 - 183
KEL (hr <sup>-1</sup> )	0.057 (29.31)	101	89.3 - 112	0.053 (25.90)	99.5	83.7 - 113
HALF (hr)	12.92 (25.89)	96.3	84.7 - 108	22.53 (24.82)	105	87.3 - 123
TPEAK (hr)	1.250 (46.19)	102	84.1 - 121	3.833 (30.50)	95.7	61.5 - 130

In PMs for d-nebivolol there was no difference between single dose and steady state parameters except CPEAK which increased by 55%. The mean AUClast values were more than 80% of the mean AUCI values for d-nebivolol. The fluctuations of d- and l-nebivolol around C<sub>ss</sub> were very large, over 460% in EMs and 40-100% in PMs.

**Table 4: Comparison of the pharmacokinetic parameters of l-nebivolol after single and multiple 10 mg dose of nebivolol**

Parameter	Extensive Metabolizers (EMs) (n=16)	EMs Least Squares Mean Ratio (%) <sup>a</sup>	EMs 90% Confidence Interval (%) <sup>a</sup>	Poor Metabolizers (PMs) (n=6)	PMs Least Squares Mean Ratio (%) <sup>a</sup>	PMs 90% Confidence Interval (%) <sup>a</sup>
AUCTAU (ng·hr/mL)	42.22 (67.73)	97.3	91.9 - 103	528.3 (21.44)	114	105 - 125
CPEAK (ng/mL)	2.251 (37.58)	104	91.4 - 118	25.83 (23.51)	475	423 - 534
KEL (hr <sup>-1</sup> )	0.044 (20.84)	101	92.2 - 110	0.011 (40.41)	89.3	63.3 - 115
HALF (hr)	16.69 (26.45)	101	90.6 - 111	73.37 (38.32)	126	90.1 - 162
TPEAK (hr)	1.250 (46.19)	111	84.7 - 137	5.667 (89.75)	131	44.7 - 218

In PMs, the estimation of the half-life of l-nebivolol as 73 hours is not acceptable since plasma samples were collected only up to 72 hours not covering at least 3 half-lives. The mean AUClast values were about 54% of the mean AUCI values for l-nebivolol pointing out that the parameters

estimated for l-nebivolol, particularly, the accumulation ratio value may be unreliable. Therefore, only CPEAK (increase by 355%) and TPEAK (increase by 31%) could be compared for PMs, Table 4.

Since only d-nebivolol has  $\beta$ -adrenoceptor properties, and the changes in its parameters were not significant except for only CPEAK, it is not expected that the difference in l-nebivolol parameters at steady state be of clinical significance.

The pharmacokinetic profile of nebivolol glucuronides was not completely characterized and therefore any comparison of the pharmacokinetic parameters is meaningless. The only parameters which could be compared for glucuronides are CPEAK and TPEAK. After repeated administration of nebivolol, CPEAK values in EMs were not changed, while in PMs CPEAK values increased by 53%. The fluctuations of nebivolol glucuronides plasma concentrations around  $C_{ss}$  values were very large (400%, EMs and 140%, PMs).

#### **Are the pharmacokinetics of nebivolol in healthy subjects and in hypertensive patient different?**

A formal comparison of the nebivolol pharmacokinetics in healthy subjects and in patients was not performed. When the sponsor modeled the population PK in study NEB302, they assumed that there is no influence of disease on the pharmacokinetics of nebivolol. The pharmacokinetic parameters of nebivolol were estimated based on rich data sets from studies NEB126 and NEB127 in healthy subjects. In these studies the limitation of the assay for the low doses of drug and failure to obtain plasma samples at least up to 3 half-lives led to poor characterization of the nebivolol pharmacokinetics. The parameters estimated in these studies by the non-compartmental method were used by the sponsor as a reference to accept the population model estimation. In order to estimate the clearance and volume of distribution of the central compartment for the sparse data set in the patients, the sponsor fixed the majority of parameters estimated for the healthy subjects. The clearance values estimated for d- and l-nebivolol are compared in Table 5. The clearance in the patient population was reduced for d-nebivolol by 20% in EMs and 55% in PMs. For l-nebivolol, no change was observed in EMs and the clearance increased 2.5 times in PMs. Considering the variability in parameters, the differences between healthy subjects and patients are not statistically significant.

**Table 5: Comparison of mean (%CV) clearance values estimated in healthy subjects and in patients using NCA or NONMEM**

CL/F (L/hr)	EM			PM		
	Healthy		Patients	Healthy		Patients
	NCA	NONMEM	NONMEM	NCA	NONMEM	NONMEM
d-Nebivolol	1041(49)	822(53)	635(3)	39(24)	31(53)	49(13)
l-Nebivolol	494(46)	416(41)	413(3)	9(23)	7(40)	18(24)

\*NCA- noncompartmental method

\*\*NONMEM – population method

#### **What are the characteristics of drug absorption?**

After a single oral administration of nebivolol in solution, the drug was rapidly absorbed with CPEAK reached at 2 and 4 hours post-dosing in extensive and in poor metabolizers respectively. The absolute bioavailability of nebivolol was not reported. The relative bioavailability of

neбиволol tablets compared to an oral solution was approximately 87% for extensive metabolizers and 111% for poor metabolizers; therefore, polymorphic metabolism did not significantly influence the absorption of neбиволol. After a high fat meal, CPEAK and the extent of absorption (AUCI) were not significantly affected by food in both EMs and PMs. The time to peak plasma concentration was delayed by about 1 hour in extensive metabolizers, and was unchanged in poor metabolizers.

#### **What are the characteristics of drug distribution?**

Protein binding and red cell partitioning have not been determined in patients with the target disease.

#### *Healthy Volunteers*

The plasma protein binding of d- and l- neбиволol averaged 98.13% and 97.85% respectively measured at room temperature over the clinically relevant concentration range. The protein binding of one enantiomer was not influenced by the presence of the other. Changes in pH influenced the binding of both enantiomers, at higher pH the binding of both d- and l- neбиволol was increased. In the pH range of 7.0 to 7.7, the binding of d- neбиволol increased from 96.17% to 98.51% and that of l- neбиволol from 95.36% to 98.46%. The investigation of the binding to purified human plasma proteins showed that the enantiomers were predominately bound to human serum albumin (HSA). The binding to HSA at a normal physiological concentration of 4.3% was 99.29% for d- neбиволol and 98.91% for l- neбиволol. The binding to purified  $\alpha$ 1-acid glycoprotein at a normal physiological concentration of 0.07% was 74.14% for d- neбиволol and 71.53% for l- neбиволol.

The in vitro binding of  $^3\text{H}$ -d,l- neбиволol to human plasma proteins was not significantly changed (97.63 to 97.82% at 1 ng/mL) when tested in the presence of high concentrations of various drugs. Additionally d, l- neбиволol at concentrations of 25 ng/mL did not alter the binding of various marker compounds when tested at their normal therapeutic plasma concentrations.

The blood to plasma concentration ratio of d- and l- neбиволol averaged 1.11 and 1.28, respectively. Overall, the plasma protein binding and the distribution of neбиволol enantiomers in blood is similar with only minor differences in the stereospecific partitioning of l- neбиволol into red blood cells.

The volume of distribution of the central compartment of d- neбиволol was about 16000 L (EM) and 1300 L (PM), and for l- neбиволol it was 11000 L (EM) and 950 L (PM).

#### *Hypertensive patients*

The sparse data available from patients did not allow to calculate the volume of distribution using the noncompartmental method. According to the results of the population PK data analysis, the Vd of d- neбиволol was about 3700 L for EMs and 1800 L for PMs, and for l- neбиволol it was 3000 L for EMs and 870 L for PMs.

#### *Subjects with hepatic impairment*

In moderately hepatic impaired subjects, the unbound fraction of neбиволol in plasma was increased as compared to healthy subjects. The least squares mean for the percentage of unbound neбиволol in a healthy individual in plasma was 1.90%, while for a moderate hepatic impaired subject, the percent of unbound neбиволol in plasma was 2.45%. This corresponds to a

statistically significant ( $p < 0.05$ ) increase in the percent of unbound nebivolol circulating in the plasma in a moderately hepatic impaired individual relative to a healthy subject.

These results may indicate the need to decrease the initial dose of nebivolol when administering nebivolol to patient with moderate hepatic impairment.

#### *Subjects with renal impairment*

For renally impaired subjects, the mean unbound nebivolol in plasma was 2.12% (mild), 2.11% (moderate), and 2.02% (severe). None of these values were statistically different from the healthy volunteer's data.

#### **Metabolism**

In vitro studies with human microsomes confirmed that nebivolol is metabolized primarily by CYP2D6 isoenzyme and to a lesser extent CYP3A4. Utilizing human hepatocytes both d- and l-nebivolol demonstrated glucuronidation of nebivolol, oxidative N-dealkylation as well as alicyclic and aromatic hydroxylation at the benzopyran moiety.

#### *Healthy subjects*

The mass-balance study of nebivolol in 3 EM and 3 PM subjects satisfactorily described its metabolic pathways (Figure 7 and Figure 8). In patients, the formation of the metabolites was not studied and only the sum of glucuronides was quantified in plasma.

In vivo, nebivolol is metabolized primarily by direct glucuronidation and hydroxylation at either the alicyclic or aromatic ring. Alicyclic oxidation occurs at either the 4 or 4' position, resulting in alcohol or keto derivatives while hydroxylation in the aromatic rings is thought to predominate at the 5/5' or 7/7' vs. 8/8' positions to yield phenolic metabolites. Hydroxylation results in mono-, di-, and tri-hydroxylated metabolites which are further metabolized by conjugation via glucuronidation. N-dealkylation results in hydroxy acid and dihydroxylated cleavage products were also identified. Due to the stereo complexity of the parent molecule and difficulties in the synthesis of stereo and structural specific reference materials, the sponsor did not identify the definitive structures of the stereo-specific hydroxyl and glucuronide metabolites. The chiral inversion between d- or l-nebivolol has not been seen in animals and in man.

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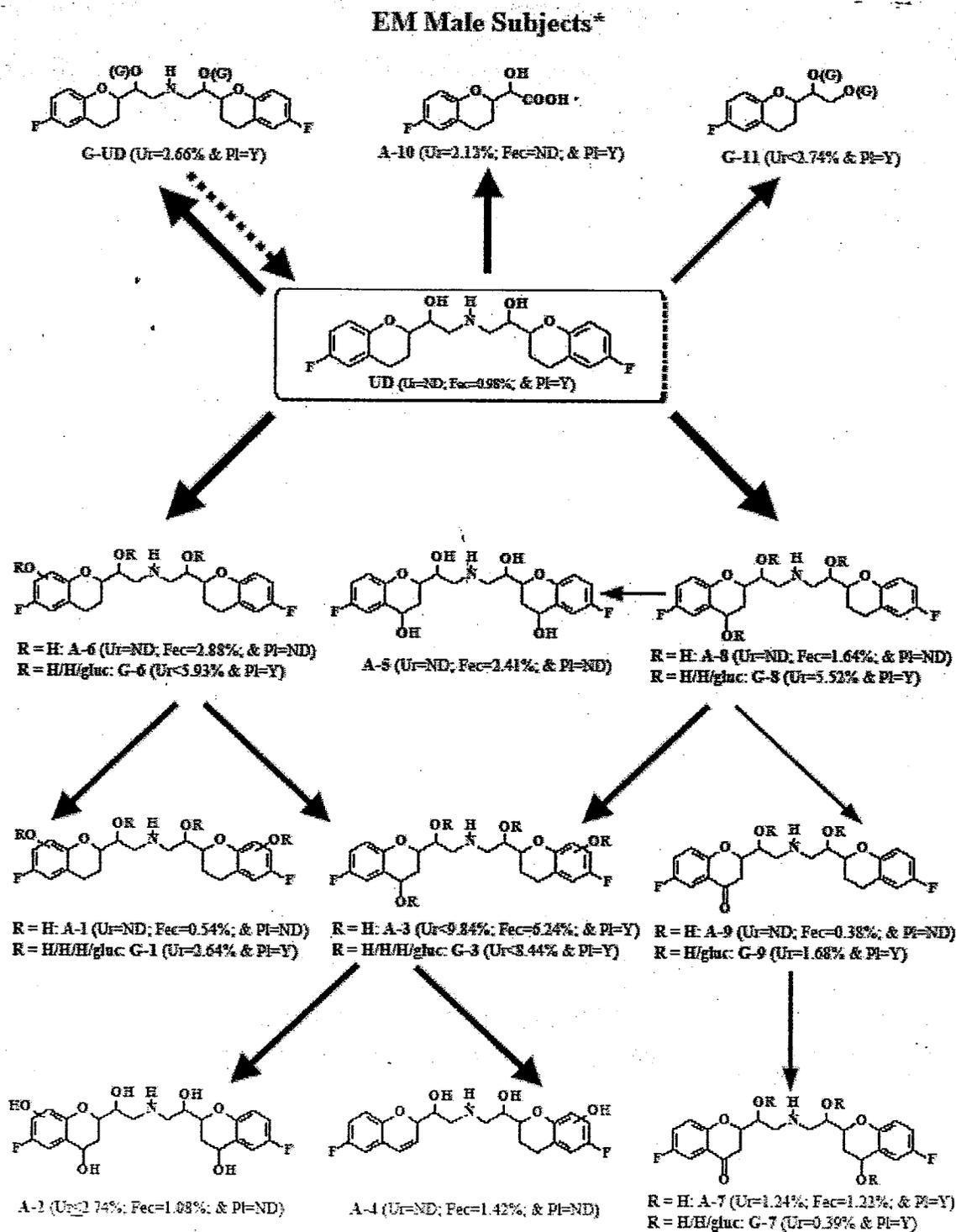


Figure 7: Proposed Metabolic Pathways of Nebivolol Following a Single Oral Dose in Male EM Subjects

in addition to oxidative N-dealkylated acid. Nebivolol glucuronides (G-UD) comprised a large amount of the EM plasma profile (maximum of 52.9 ng/mL at 2 hours). The plasma of EM subjects also contained glucuronides G-1, G-3, G-6 – G-9, and G-11 and non-conjugated metabolites A-3, A-10, and unchanged nebivolol. In PM plasma G-UD was the largest component (173.0 ng/mL at 4 hours), followed by A-10, and G-8 and unchanged nebivolol.

### Excretion

In urine of the EM and PM subjects, 38.4% and 66.5% of the nebivolol dose were recovered. In urine, the major products were conjugated metabolites, N-dealkylated oxidative and hydroxylated conjugates, and small amount of unconjugated metabolites. In EM's urine glucuronide conjugates of unchanged drug or hydroxylated and N-dealkylated metabolites were found. In PM's urine 34.2% of the administered dose were glucuronides of unchanged nebivolol. Minor amounts of conjugates of monohydroxy-nebivolol and non-conjugated metabolites were also present (Table 6).

**Table 6: Profiles of Metabolites in Pooled (0-168 hr) Urine (% of Dose)**

% Dose in Pooled Urine:		EM (Subjects 1-3)		PM (Subjects 4-6)	
		36.82%		57.08%	
Region	Met. Code	%HPLC	%Dose	%HPLC	%Dose
1	G-1	7.18%	2.64%	ND	NA
2	A-10	5.75%	2.12%	7.78%	4.44%
3	G-11 & A-2	7.45%	2.74%	4.11%	2.35% (G-11 only)
4	G-3	12.31%	4.53%	ND	NA
5	A-3 & G-3	10.61%	3.91%	ND	NA
6	G-6 & A-3	16.11%	5.93%	2.05%	1.17% (G-6 only)
7	G-7	1.06%	0.39%	ND	NA
8	G-8	13.67%	5.03%	8.68%	4.95%
9	G-9	4.56%	1.68%	2.22%	1.27%
10	G-8	1.33%	0.49%	3.77%	2.15%
11	A-7	3.36%	1.24%	1.21%	0.69%
12	G-UD	7.23%	2.66%	59.88%	34.18%
Subtotal:		90.62%	33.40%	89.70%	51.20%
Unknown:		9.38%	3.42%	10.30%	5.88%

The fraction of the nebivolol dose recovered in feces of EM and PM subjects was 43.6% and 13.1%, respectively. All metabolites in feces consist of non-conjugated, hydroxylated, or oxidative (i.e., keto) metabolites with transformations occurring on the aliphatic rings and/or aromatic rings. Levels of unchanged drug were much higher in PM than EM subjects. The EM fecal extract contained nine groups of non-conjugated metabolites and unchanged drug. The PM fecal extract contained five minor groups of metabolites and unchanged drug, Table 7.

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**Table 7: Profiles of Metabolites in Pooled (0-168 hr) Feces (% of Dose)**

		EM (Subjects 1-3)		PM (Subjects 4-6)	
% Dose in Pooled Feces:		41.75%		8.34%	
		% Distribution	% Dose	% Distribution	% Dose
Methanol Extracts		53.43%	22.31%	89.61%	7.47%
Region	Met. Code	%HPLC	%Dose	%HPLC	%Dose
1	A-1	2.43%	0.54%	ND	NA
2	A-2	4.84%	1.08%	ND	NA
3	A-3	27.98%	6.24%	ND	NA
4	A-4	6.35%	1.42%	ND	NA
5	A-5	10.78%	2.41%	3.29%	0.25%
6	A-6	12.92%	2.88%	5.34%	0.40%
7	A-7	5.45%	1.22%	2.08%	0.16%
8	A-8+A-6	7.33%	1.64%	19.28%	1.44% (A-8 only)
9	A-9	1.72%	0.38%	3.09%	0.23%
10	UD	4.38%	0.98%	51.12%	3.82%
Subtotal:		84.18%	18.79%	84.20%	6.30%
Unknown:		15.82%	3.52%	15.80%	1.17%
PES		46.57%	19.44%	10.39%	0.87%

**Does nebivolol inhibit any of the cytochrome P450 isozymes?**

No. Nebivolol does not inhibit either CYP2D6 pathway or other isozymes that include CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4/5, and CYP4A9/11 (in vitro study). Therefore, nebivolol would not be expected to inhibit the metabolism of concomitantly administered drugs that are metabolized by these enzymes.

**Was the pharmacokinetics of nebivolol linear in the proposed dose range?**

Yes for some of the analyzed entities.

The design of the dose proportionality study did not allow to describe l-nebivolol pharmacokinetics in PMs because the plasma samples were not obtained long enough to cover at least 3 half-lives of the drug. For the same reason, the pharmacokinetic of the nebivolol glucuronides were not properly characterized. The assay sensitivity did not allow to measure the d-nebivolol plasma concentrations after the lower doses of 2.5 and 5 mg to estimate the terminal half life.

Conclusions about dose proportionality were made based on the parameters calculated for the sum of d- and l-nebivolol. Noteworthy, d-nebivolol eliminated from blood faster than the l-isomer, therefore, at later times only the l-isomer was measured in plasma.

The pharmacokinetics of d- and l-nebivolol in healthy EM subjects after single doses of nebivolol were described properly for the doses of 5, 10 and 20 mg but not for the low 2.5 mg dose. The estimation of l-nebivolol half-life in EMs as 24 hour is not reliable particularly for the lower doses of 2.5 and 5 mg, where the drug was detected in plasma up to 36 and 48 hours respectively.

In PMs, the results are acceptable for d-nebivolol but not for l-nebivolol. The estimation of half-lives of the l-isomer as 74 hours might not be accurate since the last plasma sample was obtained at 72 hours and the ratio of AUClast/AUC $\infty$  for l-nebivolol was below 80%.

In PMs, d-nebivolol pharmacokinetics was linear in the dose range from 2.5 to 20 mg. In EMs, CPEAK changes across dose were linear but AUCL and AUCI increased more than dose proportionally with an increase by 100% from 2.5 mg to 20 mg dose. Since the pharmacokinetic profiles for the low doses were not completely characterized conclusions about linearity could not be made.

After the administration of racemic nebivolol, the exposure estimated as AUCL and AUCI of the l-isomer was about 2-fold larger for the EMs, and 2-5 fold larger for the PMs than the d-isomer.

### 2.3 Intrinsic Factors

**What is the inter- and intra-subject variability of the PK parameters in volunteers and patients, and what are the major causes of variability?**

Nebivolol is a highly variable drug. The inter-individual variability of the pharmacokinetic parameters estimated for d- and l-nebivolol from the population PK data analysis in healthy volunteers ranged from 40% (clearance) to 160% (Ka). Inter-occasion variability was estimated in the range of 13 to 130%.

**What intrinsic factors influence exposure?**

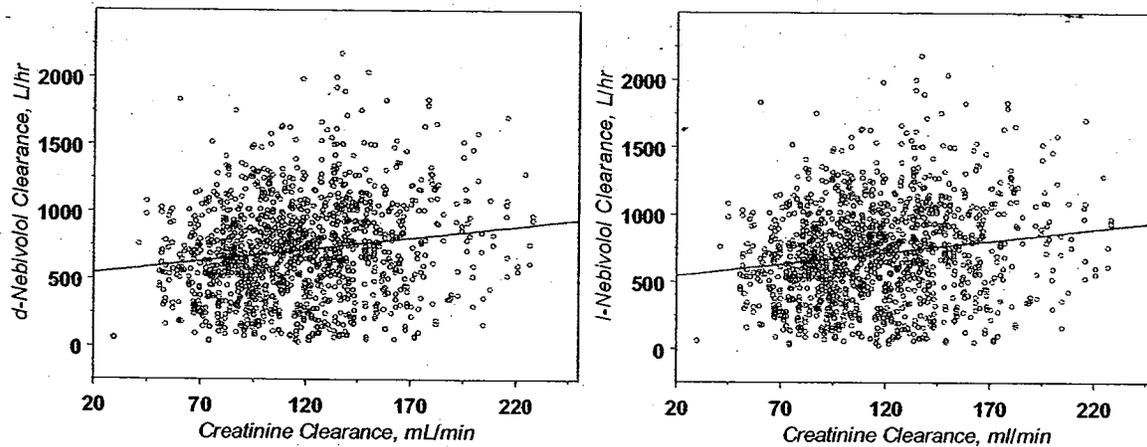
#### *Healthy subjects*

Although age, gender, race, weight, dose level, genetic polymorphism, kidney dysfunction, diabetic status, and concomitant medications were evaluated as covariates in the model, only genotype was included as a significant covariate in the population PK model for healthy subjects. For the extensive metabolizers the clearance values were 26-fold (d-nebivolol) and 56-fold (l-nebivolol) higher than the clearance values calculated for the poor metabolizers.

#### *Patients*

All parameters of the population model (except for clearance and volume of distribution of the central compartment) were fixed to the values obtained in healthy subjects. The effect of covariates (gender, race, age, smoking status, diabetic status, nebivolol dose level, creatinine clearance, body weight and concomitant medications) was tested only for oral clearance. Although some patients had hepatic abnormalities, the covariates related to the hepatic function were not tested. Only creatinine clearance had a significant influence on clearance. The clearance values of d- and l-nebivolol in EM patients decreased slightly with decreased creatinine clearance. The estimates of CL/F in EM patients vs. creatinine clearance values are illustrated in Figure 9 for d- nebivolol and l- nebivolol, respectively. There were only 49 PMs in this study with the distribution of clearance values being very skewed; therefore, the conclusions about the effect of the covariates on clearance of the PM subjects could not be made.

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**Figure 9: Clearance of d-Nebivolol (left) and l-nebivolol (right) vs. creatinine clearance in EM patients. Lines are the results of linear regression.**

Previous studies indicated that d- and l- nebivolol are mainly eliminated by metabolism. In EM subjects, only 38% of the nebivolol dose was recovered in urine. It is not expected that the change in renal function will affect their total body clearance. Although the total urine recovery was 67% in PMs, the insufficient amount of data does not allow to make a conclusion on the influence of the renal function on the clearance values.

#### **What is the impact of any differences in exposure on efficacy or safety responses?**

The relationship between effect and nebivolol plasma concentrations could not be established based on the data obtained by the sponsor. The impact of the active metabolites to the effect was not assessed. The time course of the effect was not properly studied.

#### **Elderly**

Age appears not to be a clinically relevant covariate for d- and l-nebivolol pharmacokinetics.

#### **Pediatric Patients**

No studies were conducted in pediatric subjects.

#### **CYP 2D6 Poor Metabolizer Phenotype**

The extensive metabolizers of CYP2D6 produce the active metabolites of nebivolol which are equipotent to the parent drug; therefore, the dose adjustment for nebivolol according to CYP2D6 phenotype appears not to be necessary.

#### **Gender**

Gender did not have any effect on the d- and l-nebivolol pharmacokinetics.

#### **Race**

The most important changes could be in the African-American group of patients. The reviewer compared the clearance values estimated for different races using the box plots. In EM subjects, there is no apparent change in clearance for any of the studied races. However, the median

clearance values for the PM subjects were 2-3 times larger for the Blacks both for d- and l-nebivolol (Figure 10, Figure 11).

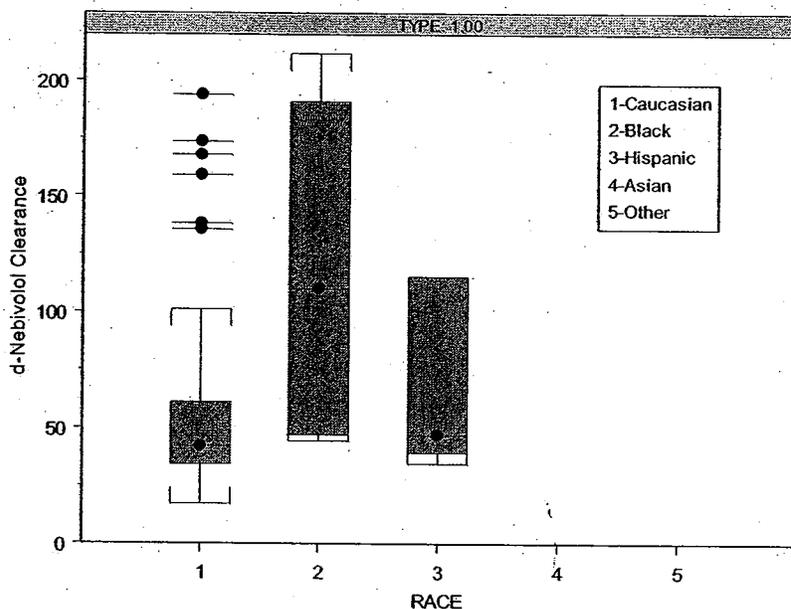


Figure 10: Clearance of d-nebivolol in PM subjects

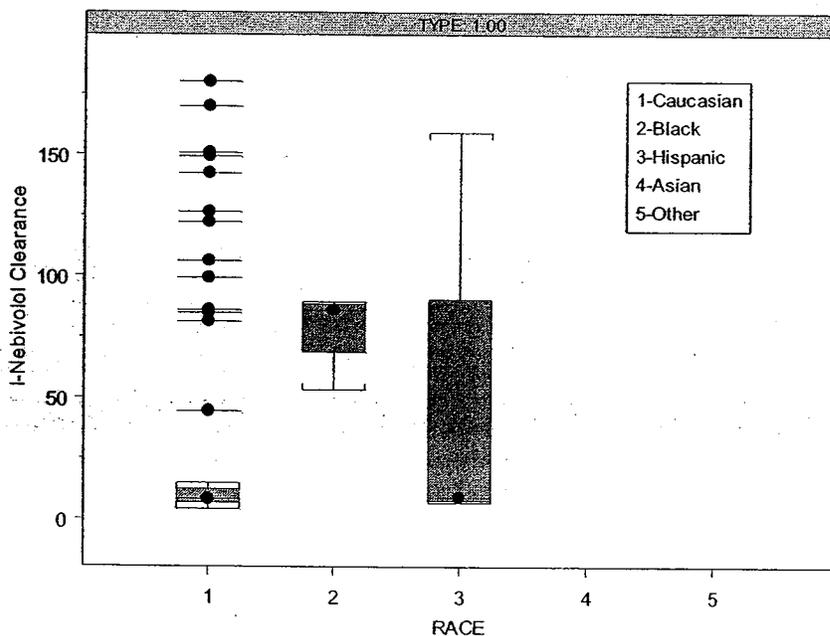


Figure 11: Clearance of l-nebivolol in PM subjects

It is difficult if not impossible to quantify the effect of race in this study because the signal may

be diffused: Blacks were represented by only 18% of the analyzed population and there was a total of 49 PMs in this study. An additional study is needed to evaluate the effect of race as a covariate on the pharmacokinetics and the pharmacodynamics of nebivolol.

#### **Renal impairment**

The sponsor adequately characterized the pharmacokinetic of each of d-, l-nebivolol and nebivolol glucuronides in the EM subjects with mild, moderate and severe renal impairment. The sponsor assumed that since nebivolol is a racemic mixture, the parameters should be calculated for the sum of plasma concentration of d- and l-nebivolol. Since l-nebivolol was detectable in plasma longer than the d-isomer, the last plasma measurements reflect only the l-isomer and estimation of the parameters of this mixture is not feasible and therefore, any obtained estimates would not be deemed reliable.

If compared to the values calculated for the healthy subjects in studies NEBI126 and NEBI127, the decrease in clearance of d-nebivolol was 30% in patients with moderately impaired renal function and 55% in patients with severely impaired renal function. The decrease in clearance of l-nebivolol was 34% for patients with severe renal impairment. In the Package Insert the sponsor proposed to use an initial low dose of nebivolol (2.5 mg) with followed by dose titration for patients with severe renal impairment. Nebivolol should be used with caution in patients receiving dialysis, since no formal studies have been conducted in this population. These recommendations are acceptable.

#### **Hepatic impairment**

Compared to healthy subjects, the exposure to d- and l-nebivolol (AUCI) in patients with moderate hepatic impairment increased 10- and 5-fold, half-life increased 2.5 and 1.6 times and the apparent clearance decreased by 86 and 75%. The exposure to nebivolol glucuronides (AUCI) in patients with moderate hepatic impairment increased 13-fold, half-life increased 4.4 times and the apparent clearance decreased by 52%. The comparison of nebivolol glucuronides parameters should be interpreted with caution because the parameters reflect the behavior of the mixture of many compounds whose pharmacokinetic characterization was not complete for the healthy subjects at low nebivolol dose of 5 mg due to assay limitation.

The pharmacokinetic of nebivolol in severely impaired patients have not been studied.

Increasing the dose in hepatically impaired patients should be performed with caution. No formal studies have been performed in patients with severe hepatic impairment; therefore, nebivolol should be contraindicated for these patients.

#### **What pharmacogenetics information is there in the application and is it important or not?**

The effect of genetic polymorphism on the pharmacokinetics of nebivolol is clear. However, the drastic differences in nebivolol PK between EMs and PMs did not lead to changes in pharmacodynamics. It seems appropriate that the genotype was tested in the PK and the PK/PD model but there will be no impact on dose selection, safety, or efficacy of drug based on the phenotype of the patient.

In the general US population only approximately 7% of Caucasians, 2% of African Americans or Asians exhibit the genotype for CYP2D6 deficiency. Despite the pharmacokinetic disposition difference, the clinical efficacy studies have not noted any marked differences in the activity and adverse effects of nebivolol in these two population subgroups. The pharmacologic contribution of various metabolites of nebivolol to the overall clinical activity either directly and/or via a

possible back conversion from their respective glucuronide metabolites account for the pharmacokinetic/metabolic differences noted between the two population subgroups.

## 2.4 Extrinsic Factors

### *What extrinsic factors influence nebivolol exposure and/or response?*

The effects of smoking and concomitant medications were evaluated by the sponsor in the PK/PD model. None of the tested covariates was found to be significant but since the model is not accepted by the Agency, the conclusions on the effect of these covariates could not be accepted.

### Drug-drug interactions

#### *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

*In vitro* metabolism information indicates that nebivolol is primarily a CYP2D6 substrate and subject to oxidative metabolism. CYP3A4 also plays a minor role in nebivolol metabolism. Consequently, CYP2D6 inhibitors or inducers may alter nebivolol exposure (pharmacokinetics). *In vitro* data also indicate that nebivolol is subject to glucuronidation. Several nebivolol metabolites have been observed; the occurrence of metabolites appears to be stereoselective and the metabolites are hydroxylated and glucuronidated products of the respective enantiomers. Since nebivolol does not inhibit either CYP2D6 pathway or other isozymes that include CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11, nebivolol would not be expected to inhibit the metabolism of concomitantly administered drugs that are metabolized by these enzymes. The induction potential of nebivolol was not evaluated.

#### *Does nebivolol undergo plasma protein binding displacement interactions with commonly prescribed medications?*

*In vitro*, nebivolol does not cause significant displacement in the plasma protein binding of diazepam, digoxin, diphenylhydantoin, hydrochlorothiazide, imipramine, or warfarin at their therapeutic concentrations. Similarly, the changes in nebivolol plasma protein binding are not clinically significant (< 10 % increase in nebivolol free fraction) when nebivolol is incubated with digoxin, diphenylhydantoin, hydrochlorothiazide, indomethacin, propranolol, sulfamethazine, tolbutamide, warfarin, imipramine, diazepam or enalapril.

#### *Is nebivolol a substrate and/or an inhibitor of P-glycoprotein transport processes?*

The potential role of PGP and other transporters on nebivolol PK was not evaluated in this NDA.

#### *In vivo studies with medications that are likely\* to be administered for treatment of hypertension*

In several clinical PK/PD studies, orally administered nebivolol did not show any clinically relevant interactions with some of the drugs commonly used in hypertension therapy. The major class of antihypertensives that the applicant did not evaluate was calcium channel blockers. Generally, nebivolol did not significantly alter (increases or decreases  $\leq 14$  %) the AUC or C<sub>max</sub> of the coadministered drugs. The only clinically significant drug-drug interaction was observed with a model CYP2D6 inhibitor, fluoxetine. Relative to nebivolol alone, fluoxetine increased nebivolol exposure:

1) Approximately 3-fold increase in C<sub>max</sub> and ~ 8-fold increase in AUC of d-nebivolol  
 2) Approximately 2-fold increase in C<sub>max</sub> and ~ 5-fold increase in AUC of l-nebivolol  
 Based on *in vitro* information, nebivolol is metabolized to some degree by CYP3A4, thus; ideally, the effect of CYP3A4 inhibition and induction should have been evaluated. Based on a literature report, cimetidine, a non-specific CYP inhibitor, caused ~ 20 % increase in nebivolol (both enantiomers) AUC and C<sub>max</sub>. Drug-drug interaction studies were conducted with the following drugs:

1. Diuretic	hydrochlorothiazide (Study 0128)- multiple dose
2. Cardiac Glycoside	digoxin (Study 0174)- multiple dose
3. Anticoagulant	warfarin (Study 0181)- single dose
4. Antidepressant	fluoxetine* (Study 0184)- single dose
5. Diuretic	furosemide (Study 0213)- multiple dose
6. Diuretic	spironolactone (Study 0214)- multiple dose
7. ACE inhibitor	ramipril (Study 0220)- multiple dose
8. Angiotensin Receptor Blocker	losartan (Study 02104)- single dose
9. H <sub>2</sub> Receptor Antagonists	cimetidine and ranitidine (Kamali <i>et al</i> , 1997)- single dose

\* fluoxetine was used as a model inhibitor, not typically used in hypertension therapy

The drug interaction studies were conducted in healthy volunteers, who were either extensive or poor metabolizers.

In Study 02118, activated charcoal (Actidose-Aqua<sup>®</sup>) was administered repeatedly (4, 8, 12, 16, 22, 28, 36 and 48 hours after nebivolol administration) with nebivolol to determine if nebivolol undergoes enterohepatic recycling (EHR). The information obtained from the study was insufficient to 1) determine the extent or significance of EHR and 2) determine if a drug-drug interaction would occur if charcoal and nebivolol were administered at the same time. Based on the findings in poor metabolizers (increased nebivolol apparent oral clearance) and historical data with other beta-blockers, where charcoal was administered simultaneously with the beta-blocker, coadministration of nebivolol and charcoal should be avoided.

#### ***Overview of Drug-Drug Interaction Labeling Recommendations***

As shown in the preceding sections, there is a low potential for nebivolol to undergo drug-drug interactions with comedications that are likely to be prescribed in hypertension. Cautionary language should be included to capture the potential for increased nebivolol exposure in the presence of a CYP2D6 inhibitor, such as fluoxetine. In general, the applicant's proposed labeling is acceptable. For most studies, the applicant describes the study and presents the study findings. Please see Detailed Labeling Recommendations for OCPB labeling revisions.

## **2.5 General Biopharmaceutics**

### ***What are the solubility characteristics of nebivolol?***

Nebivolol hydrochloride is slightly soluble in water at approximately 1mg/mL. The solubility in gastric fluid and diluted hydrochloric acid solutions is lower than that in water. In addition, nebivolol hydrochloride is very hydrophobic with a contact angle of approximately 80°.

The solubility of nebivolol HCL drug substance was assessed in 0.1N HCL (pH 1), 0.01N HCL (pH 2), acetate buffer (pH 4), and phosphate buffer (pH 6). Nebivolol HCL is much more soluble at pH 2 and pH 4 than at pH 1 or pH 6 at 37 ° C (Table 8).

**Table 8: Summary of nebivolol solubility**

Dissolution Medium	Solubility @ 37°C (mg/mL)
pH 1	↘
pH 2	
pH 4	
pH 6	

*Was an adequate link established between the clinical and to be marketed formulations of nebivolol?*

Yes.

The 5mg, 10mg and 20mg to-be-marketed formulations deviate from the clinical formulations only in the addition of colorants to the tablets for identification purposes (SUPAC- IR level I change). The 5mg, 10mg and 20mg market formulations are proportionally similar to one another, as the change

falls within the SUPAC-IR level II range of  $\pm 10\%$

The quantitative composition of the clinical formulations for nebivolol tablets is expressed in the following table on a mg per tablet and % w/ w basis in Table 9.

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**Table 9: Nebivolol Tablets Composition**

Compound	2.5mg		5mg		10mg	
	mg/tab	%	mg/tab	%	mg/tab	%
Nebivolol Hydrochloride <sup>BP</sup>	2.72		5.45		10.9	
Hypromellose USP						
Polysorbate 80, NF						
Lactose Monohydrate, NF						
Pregelatinized Starch, NF						
Croscarmellose Sodium, NF						
Microcrystalline Cellulose, NF						
Colloidal Silicon Dioxide, NF						
Magnesium Stearate/Sodium Lauryl Sulfate						
<b>Total Theoretical Wt.</b>	<b>230.0</b>	<b>100</b>	<b>230.0</b>	<b>100</b>	<b>230.0</b>	<b>100</b>

2.725mg, 5.45mg, 10.9mg of nebivolol hydrochloride are equivalent to 2.5mg, 5mg, 10mg of nebivolol base, respectively.

Based on submitted data on the composition and comparable dissolution performance of the 2.5mg strength the sponsor requested a bio waiver. The composition of the 2.5mg strength tablets are proportionately similar and the dissolution profiles of the 2.5mg tablets in 4 media, water and buffers of pH 1, 2, 4, and 6 are sufficiently similar as evidenced by the results of the f2 test. Based on the demonstrated compositional and dissolution similarity of the 2.5mg tablets an in vivo bioavailability waiver is granted.

***Was there an impact of food on the bioavailability of nebivolol?***

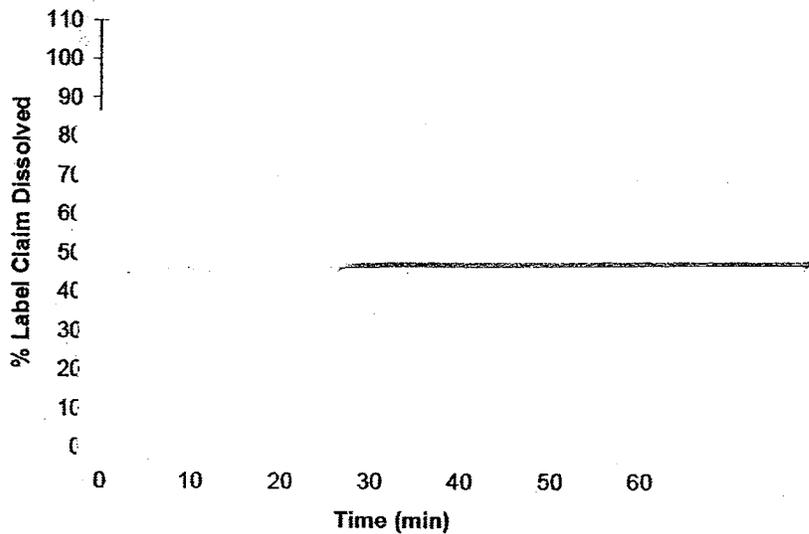
No.

Food did not affect either the extent or the rate of unchanged nebivolol.

***How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?***

Dissolution testing for initial stability testing of clinical lots of Nebivolol Tablets was performed at time points of 15, 30, 45, and 60 minutes as specified in the current dissolution procedure, Figure 12.

**Nebivolol Tablets: Clinical Lots in 900 mL 0.01 N HCl,  
Paddles @ 50 rpm**



**Figure 12: Dissolution profiles for various clinical lots for 900mL dissolution volumes**

*Are the sponsor proposed dissolution medium and specifications acceptable?*

Yes, with revision.

The sponsor proposed the dissolution specification as \_\_\_\_\_ in 60 minutes. From the submitted dissolution data it is obvious that the drug dissolves on average \_\_\_\_\_ in 15 minutes for the proposed tablet strength of 2.5, 5, and 10 mg.

Condition	FDA Recommendation
Dissolution Medium	0.01N HCL
Paddle Speed	50 rpm
USP Apparatus II	
Volume	900 mL
Specifications	_____ in 15 minutes

**2.6 Analytical section**

*How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

The sponsor developed and validated two bioanalytical assays for the individual d- nebivolol and l- nebivolol enantiomers and total nebivolol (conjugated + non- conjugated) in human plasma. An HPLC with tandem mass spectrometric method was used for the determination of d- and l- nebivolol in human plasma. Three standard curve ranges were validated and used to assay the appropriate samples from all of the studies. The selection of standard curve range was based upon dosing parameters and the metabolic status of the individual subjects.

An HPLC with mass spectrometric detection for the determination of total nebivolol (conjugated and non-conjugated) in human plasma has been developed in order to determine the extent of glucuronidation of the parent nebivolol compound. This assay is designed to liberate nebivolol from nebivolol glucuronides through enzyme hydrolysis, with subsequent analysis for nebivolol.

***Which metabolites have been selected for analysis and why?***

The 4- and 8-hydroxy metabolites of nebivolol have the similar in vitro  $\beta$ -blocking activity as d-nebivolol. None of them were quantified in plasma and their pharmacokinetic properties are unknown. Multiple metabolites of nebivolol formed glucuronides in vivo. Some of the glucuronides have pharmacologic activity. Only the sum of nebivolol glucuronides was measured in the clinical pharmacology studies.

Therefore, the impact of the active metabolites on the pharmacodynamic effect could not be assessed. This is a major deficiency in this application.

***Were the validation characteristics of the assay acceptable?***

Yes.

Both assays have their validation reports, see individual study reviews.

***What is the overall conclusion regarding NDA 21-742?***

Overall the clinical pharmacology and biopharmaceutics section is acceptable.

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           Trade Secret / Confidential

  X   Draft Labeling

           Deliberative Process

## 4.2 Individual Study Reviews

### 4.2.1 Single Dose, Dose-Proportionality Pharmacokinetic Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status (NEBI- 0126)

**DRUG STUDIED:** Nebivolol HCL Tablets, 2.5mg, 5mg, 10mg, and 20mg  
Mylan Pharmaceuticals Inc.  
2.5mg Lot # R1H1180  
5mg Lot # R1H1181  
10mg Lot # R1H1182  
20mg Lot # R1J1650

**INVESTIGATOR(S) AND STUDY SITE:** Thomas S. Clark, M. D., M. S.

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#### **OBJECTIVES:**

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

The single dose pharmacokinetics and dose proportionality of nebivolol absorption, among both extensive and PMs, was assessed by statistical comparisons of various pharmacokinetic parameters derived from the plasma concentration- time curves of d-nebivolol, l-nebivolol, and d, l-nebivolol.

#### **STUDY DESIGN:**

This was a randomized, single dose, dose proportionality, four periods, pharmacokinetic study to investigate the single dose pharmacokinetics of nebivolol in healthy, adult volunteers characterized according to their metabolizing status. Sixteen healthy, non- smoking, male and female adult volunteers, 8 extensive metabolizers (EMs) and 8 poor metabolizers (PMs) between the ages of 20 and 50 entered into this study.

The randomization scheme for this study was as follows:

##### Extensive Metabolizers [EM]

ABCD – Subject s 4 and 6

BDAC – Subject s 1 and 7

CADB – Subject s 2 and 8

DCBA – Subject s 3 and 5

##### Poor Metabolizers [PM]

ABCD – Subject's 11 and 13

BDAC – Subject's 12 and 16

CADB – Subject's 10 and 14

DCBA – Subject's 9 and 15

After an overnight fast (at least 10 hours) each subject received a single, oral dose of nebivolol according to the randomization scheme (2.5mg, 5mg, 10mg, or a 20mg tablet). Subjects received

a standard meal and snack 13.5 hours and 10.5 hours prior to dosing and 4 hours and 10 hours after dosing. Subjects consumed 240mL of ambient temperature water 1.25 hours prior to dosing and 1 hour after dosing. Water was not permitted from 1 hour prior to dosing until 1 hour after dosing, but was allowed at all other times. Lead II ECGs were measured prior to dose administration, and at 4, 8, 12, 24 and 48 hours after drug administration with the PR and QT intervals promptly evaluated. All subjects were monitored throughout confinement for adverse reactions to the study formulations and/or procedures. Serial blood samples, 10mL, were collected within 45 minutes prior to dosing and at the following times relative to dosing: 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 10, 24, 36, 48, and 72 hours. The treatments, formulations, lot numbers and manufacturing date are shown in Table 10.

**Table 10: Drug Description**

Treatment	Dose	Lot #'s	Manufacturing Date
A	2.5mg (1 x 2.5mg) nebivolol HCl tablet	R1H1180	April 14, 2000
B	5mg (1 x 5mg) nebivolol HCl tablet	R1H1181	April 17, 2000
C	10mg (1 x 10mg) nebivolol HCl tablet	R1H1182	April 17, 2000
D	20mg (1 x 20mg) nebivolol HCl tablet	R1J1650	June 14, 2001

**ASSAY:**

The assay utilized two different standard curve ranges, one for EMs 2.5, 5, and 10mg dose in EMs and the 2.5mg dose in PMs, Table 11. Another standard curve was utilized for the 20mg dose in EMs and the 5mg, 10mg and 20mg dose in PMs. The method for the analysis of d-nebivolol and l-nebivolol in human plasma (heparin) was performed using high performance liquid chromatography with tandem mass spectrometric detection. Chromatograms were shown.

**Table 11: Assay Characteristics for d- and l-Nebivolol**

Parameter	Measure	Reviewer Comment
	Assay for Extensive Metabolizers (Curve I)	
Linearity	0.02ng/mL to 1.5ng/mL	Satisfactory
Precision (CV %)	d-nebivolol $\leq 8.57\%$	l-nebivolol $\leq 7.03\%$
Accuracy	d-nebivolol	l-nebivolol
Between day	between -5.00% and 10.00%	between -7.88% and 7.78%
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory
	Assay for Poor Metabolizers (Curve II)	
Linearity	linear from 0.2ng/mL to 15ng/mL	Satisfactory
Precision (CV %)	d-nebivolol $\leq 4.67\%$	l-nebivolol $\leq 5.47\%$
Accuracy	d-nebivolol	l-nebivolol
Between day	between -5.28% and 17.0%	between -6.92% and 4.83%
LLOQ	0.2ng/mL	Satisfactory
Specificity		Satisfactory

**RESULTS**

Fifteen volunteers completed the clinical phase of this study. Subject # 7 was discontinued prior to dosing Period 4 due to an adverse experience, Table 12.

**Table 12: Demographic Data**

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

Mean (% CV) pharmacokinetic parameters for d-, l-, and d,l-nebivolol are shown in Tables 4-6. Mean (% CV) dose-normalized pharmacokinetic parameters for d-, l-, and d,l-nebivolol are shown in Tables 7-9, respectively. The pharmacokinetic parameters for linearity testing for d-nebivolol, and l-nebivolol are presented in Table 13, Table 14.

Mean d-, l-, and d,l-nebivolol CPEAK, AUCL and AUCI values increased with the ascending dose levels, while TPEAK values were similar among the increasing doses and ranged in EMs from 1.1 to 1.8 hours for d-nebivolol, and 0.9 to 1.6 hours for l-nebivolol. In PMs, the mean TPEAK values ranged from 3.7 to 4.3 hours for d-nebivolol, and 6.7 to 8.3 hours for l-nebivolol. The mean CPEAK was increased approximately 4 to 5- fold, and 3 to 4- fold in PMs as compared to EMs for d-nebivolol, and l-nebivolol, respectively. Mean t<sub>1/2</sub> increased roughly 2 to 5- fold, and 3 to 5- fold in PMs as compared to EM subjects for d-nebivolol, and l-nebivolol. The increase in AUCL in PMs relative to EMs was by 16 to 35- fold, and 27 to 35- fold, for d- and l-nebivolol. The mean apparent clearance of d-, and l-nebivolol was on average 36 and 55- fold larger, respectively, in EMs compared to PMs. The mean t<sub>1/2</sub> values for d-, and l-nebivolol for EMs were 9, and 19 hours, respectively. For PMs, the mean t<sub>1/2</sub> values were 23, and 73 hours, respectively. Although the pharmacokinetic parameters differ dramatically between the extensive and PM groups, the sponsor reported that the incidents of adverse events did not increase.

In comparing the pharmacokinetic parameters between the d- and l- enantiomers of nebivolol, the EMs and PMs have several things in common. The AUCL and AUCI are consistently larger for l-nebivolol relative to d-nebivolol (2- fold for EMs and 2 to 5- fold greater in PMs). CPEAK was approximately 2 fold higher for EMs, but only between 10 and 57% higher in PMs for l-nebivolol as compared to d-nebivolol. T<sub>1/2</sub> for l-nebivolol was 2 to 3- fold longer for all subjects relative to d-nebivolol. The apparent clearance of l-nebivolol was 2 to 4 times smaller for all

subjects as compared to d-nebivolol. The similar stereoselectivity in the pharmacokinetics was previously described for another substrate of CYP2D6, fluoxetine.

**Table 13: Mean (%CV) d-Nebivolol PK Parameters**

Treatment (Dose of nebivolol) [# of subjects]	Parameter – [EM Group; 6 males and 2 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr <sup>-1</sup> )	HALF (hr)	Cl/F <sup>3</sup> (L/hr)	Vd/F <sup>5</sup> (L)
A: (2.5mg) [n= 8]	0.765 (75.63)	0.970 (80.62)	0.208 (40.08)	1.125 (31.43)	0.240 (63.61)	5.068 (90.48)	1969 (56.62)	8833 (17.01)
B: (5mg) [n= 8]	1.988 (81.82)	2.349 (73.69)	0.437 (37.72)	1.500 (50.40)	0.105 (55.70)	8.925 (54.99)	1568 (58.19)	15858 (47.79)
C: (10mg) [n= 7]	5.164 (63.45)	5.765 (59.47)	0.988 (44.20)	1.429 (37.42)	0.063 (15.24)	11.17 (14.46)	1059 (40.92)	17012 (45.63)
D: (20mg) [n= 8]	13.67 (76.24)	14.25 (72.92)	1.605 (50.10)	1.750 (26.45)	0.060 (17.22)	11.82 (15.83)	1038 (55.67)	17387 (59.57)
Treatment (Dose of nebivolol) [# of subjects]	Parameter – [PM Group; 4 males and 3 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr <sup>-1</sup> )	HALF (hr)	Cl/F <sup>3</sup> (L/hr)	Vd/F <sup>5</sup> (L)
A: (2.5mg) [n= 7]	26.43 (24.42)	31.86 (23.59)	0.898 (26.08)	3.857 (37.95)	0.031 (16.06)	23.02 (18.26)	41.38 (25.98)	1340 (18.89)
B: (5mg) [n= 7]	59.29 (26.03)	72.15 (19.68)	2.116 (16.78)	3.714 (43.17)	0.029 (17.41)	24.86 (18.16)	35.77 (18.87)	1279 (26.79)
C: (10mg) [n= 7]	112.8 (20.15)	127.4 (21.67)	3.801 (18.46)	4.286 (37.42)	0.031 (10.89)	22.73 (10.97)	40.79 (20.62)	1330 (21.56)
D: (20mg) [n= 7]	225.2 (20.86)	263.1 (19.27)	8.265 (22.65)	3.714 (29.96)	0.031 (27.76)	23.25 (22.27)	39.22 (18.72)	1305 (27.91)

**Table 14: Mean (%CV) l-Nebivolol Parameters**

Treatment (Dose of nebivolol) [# of subjects]	Parameter – [EM Group; 6 males and 2 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr <sup>-1</sup> )	HALF (hr)	Cl/F <sup>3</sup> (L/hr)	Vd/F <sup>5</sup> (L)
A: (2.5mg) [n= 8]	1.543 (35.48)	2.494 (25.69)	0.392 (30.25)	0.875 (26.45)	0.042 (97.40)	24.09 (43.09)	541.2 (34.82)	17201 (41.96)
B: (5mg) [n= 8]	4.222 (35.10)	4.998 (30.65)	0.876 (39.23)	1.500 (50.40)	0.035 (15.76)	20.17 (15.28)	542.5 (30.21)	16230 (42.04)
C: (10mg) [n= 7]	9.726 (31.91)	10.60 (28.83)	1.959 (41.91)	1.357 (46.18)	0.045 (21.46)	16.11 (21.87)	506.6 (29.09)	12124 (48.05)
D: (20mg) [n= 8]	22.79 (42.60)	23.77 (41.17)	3.043 (39.04)	1.625 (31.85)	0.045 (16.58)	15.85 (17.55)	477.8 (35.19)	11039 (46.56)
Treatment (Dose of nebivolol) [# of subjects]	Parameter – [PM Group; 4 males and 3 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr <sup>-1</sup> )	HALF (hr)	Cl/F <sup>3</sup> (L/hr)	Vd/F <sup>5</sup> (L)
A: (2.5mg) [n= 7]	53.96 (32.61)	126.8 (34.51)	1.022 (23.80)	8.286 (88.34)	0.010 (19.54)	73.21 (18.30)	10.86 (33.12)	1100 (21.79)
B: (5mg) [n= 7]	132.1 (22.10)	275.0 (17.47)	2.623 (19.11)	8.286 (88.34)	0.011 (35.56)	72.61 (42.81)	9.362 (19.61)	932.1 (30.14)
C: (10mg) [n= 7]	273.1 (19.11)	545.1 (27.68)	5.493 (18.95)	7.714 (93.99)	0.010 (20.86)	70.13 (19.40)	9.696 (23.32)	958.9 (21.79)
D: (20mg) [n= 7]	611.8 (26.42)	1319 (24.00)	12.98 (17.86)	6.714 (114.6)	0.011 (33.67)	75.83 (49.96)	7.901 (20.45)	811.2 (27.86)

In order to assess linearity over the studied dosage range, the sponsor compared the dose normalized parameters (CPEAK, AUCL, and AUCI), Figure 13, Table 16. In the PMs, nebivolol PK was linear after the dose range between 2.5 to 20 mg. In the EMs, CPEAK was linear across all doses but AUCL increased approximately 2 fold when the 2.5 mg dose was compared to the 20 mg dose. The increase in AUCI values between the lowest and highest dose was from 20% (l-nebivolol) to 84% (d-nebivolol). The sponsor attributed this change to improper characterization of the plasma concentration curve for the EMs at the lower dosage strengths due to assay limitations. According to the data on file, this is possible, however, only with regards to the 2.5 mg dose. The sponsor could compare the AUC over the same time interval (24 hours). An example of mean plasma concentrations vs. time plot for d-nebivolol is shown in the Figure 1 below.

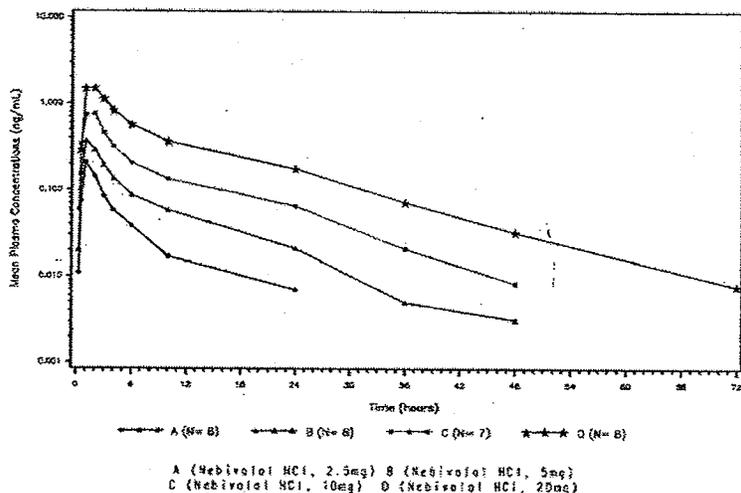


Figure 13,

Figure 13: Mean d-nebivolol plasma concentrations vs. time for EMs (left panel) and PMs (right panel).

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**Table 15: Mean (% CV) dose-normalized pharmacokinetic parameters for d-nebivolol**

Parameter*	Treatment – EM GROUP (6 males and 2 females)			
	A=2.5mg [n= 8]	B=5mg [n= 8]	C=10mg [n= 7]	D=20mg [n= 8]
nCPEAK	0.166 (40.08)	0.175 (37.72)	0.198 (44.20)	0.160 (50.10)
nAUCL	0.612 (75.63)	0.795 (81.82)	1.033 (63.45)	1.367 (76.24)
nAUCI	0.776 (80.62)	0.939 (73.69)	1.153 (59.47)	1.425 (72.92)
Parameter*	Treatment – PM GROUP (4 males and 3 females)			
	A=2.5mg [n= 7]	B=5mg [n= 7]	C=10mg [n= 7]	D=20mg [n= 7]
nCPEAK	0.718 (26.08)	0.847 (16.78)	0.760 (18.46)	0.826 (22.65)
nAUCL	21.15 (24.42)	23.72 (26.03)	22.56 (20.13)	22.53 (20.86)
nAUCI	25.49 (23.59)	28.86 (19.68)	25.48 (21.67)	26.31 (19.27)

\* Normalized based upon the amount of *d*-nebivolol administered for each treatment. Since nebivolol is a racemic mixture of *d*-nebivolol and *l*-nebivolol, the amount of *d*-nebivolol administered for each treatment would be equivalent to ½ the dose of nebivolol.

**Table 16: Mean (% CV) dose-normalized pharmacokinetic parameters for l-nebivolol**

Parameter*	Treatment – EM GROUP (6 males and 2 females)			
	A=2.5mg [n= 8]	B=5mg [n= 8]	C=10mg [n= 7]	D=20mg [n= 8]
nCPEAK	0.314 (30.25)	0.350 (39.23)	0.392 (41.91)	0.504 (39.04)
nAUCL	1.234 (35.48)	1.689 (35.10)	1.945 (31.91)	2.279 (42.60)
nAUCI	1.995 (25.69)	1.999 (30.65)	2.120 (28.83)	2.377 (41.17)
Parameter*	Treatment – PM GROUP (4 males and 3 females)			
	A=2.5mg [n= 7]	B=5mg [n= 7]	C=10mg [n= 7]	D=20mg [n= 7]
nCPEAK	0.818 (23.80)	1.049 (19.11)	1.099 (18.95)	1.298 (17.86)
nAUCL	43.17 (32.61)	52.86 (22.10)	54.62 (19.11)	61.18 (26.42)
nAUCI	101.4 (34.51)	110.0 (17.47)	109.0 (27.68)	131.9 (24.00)

\* Normalized based upon the amount of *l*-nebivolol administered for each treatment. Since nebivolol is a racemic mixture of *d*-nebivolol and *l*-nebivolol, the amount of *l*-nebivolol administered for each treatment would be equivalent to ½ the dose of nebivolol.

The analysis of variance performed on the dose-normalized parameters are shown in Table 17 and Table 18. The results confirm dose linearity for the PM subjects. For the EM group, the increase of CPEAK, AUCL, and AUCI were not linear with the increasing dose. The changes were not dose proportional when the parameters were compared for the lower doses (treatments A and B), and since the pharmacokinetic profiles for the small doses were not completely characterized the conclusions about non-linearity may be not valid.

**Table 17: Geometric Mean Ratio (%) and 90% CI for the Dose-Normalized Parameters of d-Nebivolol**

Parameter	Treatment <sup>a</sup> – EM GROUP (6 males and 2 females)					
	GMR B vs A 5.0mg vs 2.5mg	90 % Confidence Intervals	GMR C vs B 10mg vs 5.0mg	90 % Confidence Intervals	GMR D vs C 20mg vs 10mg	90 % Confidence Intervals
lnnCPEAK	103	81 – 131	122	95 – 156	73	57 – 94
lnnAUCL	127	101 – 159	162	127 – 206	106	84 – 135
lnnAUCI	125	99 – 157	151	119 – 193	100	78 – 127
Parameter	Treatment <sup>a</sup> – PM GROUP (4 males and 3 females)					
	GMR B vs A 5.0mg vs 2.5mg	90 % Confidence Intervals	GMR C vs B 10mg vs 5.0mg	90 % Confidence Intervals	GMR D vs C 20mg vs 10mg	90 % Confidence Intervals
lnnCPEAK	119	110 – 129	90	83 – 97	107	99 – 116
lnnAUCL	113	101 – 125	96	87 – 107	99	89 – 110
lnnAUCI	114	106 – 122	88	82 – 94	103	96 – 111

<sup>a</sup> Treatment A = 2.5mg nebivolol; B = 5.0mg nebivolol; C = 10mg nebivolol; D = 20mg nebivolol

**Table 18: Geometric Mean Ratio (%) and 90% CI for the Dose-Normalized Parameters of l-Nebivolol**

Parameter	Treatment <sup>a</sup> – EM GROUP (6 males and 2 females)					
	GMR B vs A 5.0mg vs 2.5mg	90 % Confidence Intervals	GMR C vs B 10mg vs 5.0mg	90 % Confidence Intervals	GMR D vs C 20mg vs 10mg	90 % Confidence Intervals
lnnCPEAK	108	88 - 132	121	98 - 150	72	58 - 90
lnnAUCL	136	120 - 155	124	108 - 142	107	94 - 123
lnnAUCI	108	93 - 126	112	96 - 131	103	89 - 120
Parameter	Treatment <sup>a</sup> – PM GROUP (4 males and 3 females)					
	GMR B vs A 5.0mg vs 2.5mg	90 % Confidence Intervals	GMR C vs B 10mg vs 5.0mg	90 % Confidence Intervals	GMR D vs C 20mg vs 10mg	90 % Confidence Intervals
lnnCPEAK	127	116 – 140	106	96 – 117	118	103 – 130
lnnAUCL	126	109 – 147	107	92 – 124	109	94 – 126
lnnAUCI	104	86 – 126	99	83 – 118	125	105 – 149

<sup>a</sup> Treatment A = 2.5mg nebivolol; B = 5.0mg nebivolol; C = 10mg nebivolol; D = 20mg nebivolol

The trellis plots of the individual plasma concentrations for d-, and l-nebivolol are shown in Figure 14 and Figure 15.

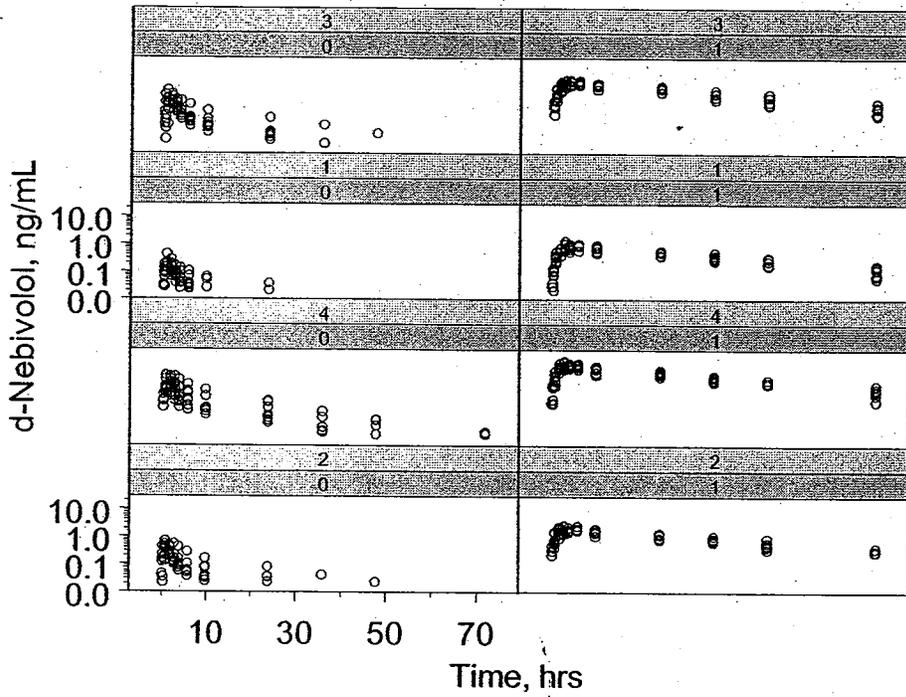


Figure 14: d-Nebivolol Plasma concentrations vs. time. 0-EMs, 1-PMs. Doses: 2.5 mg (1), 5mg (2), 10mg (3), and 20mg (4)

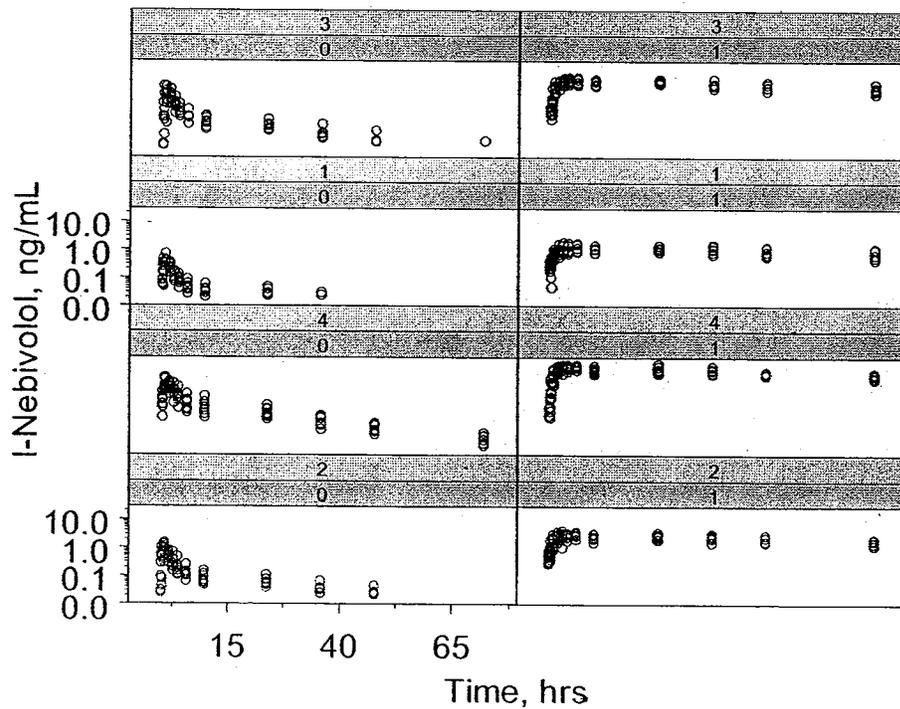


Figure 15: l-Nebivolol Plasma concentrations vs. time. 0-EMs, 1-PMs. Doses: 2.5 mg (1), 5mg (2), 10mg (3), and 20mg (4)

Since nebivolol is administered as a racemic mixture of d- and l-isomers, the pharmacokinetic parameters were calculated for the combined measurements of both isomers Table 19.

**Table 19: Mean (%CV) d,l-Nebivolol Parameters**

Treatment (Dose of nebivolol) [# of subjects]	Parameter – [EM Group; 6 males and 2 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr <sup>-1</sup> )	HALF (hr)	Cl/F <sup>a</sup> (L/hr)	Vd/F <sup>a</sup> (L)
A: (2.5mg) [n= 8]	2.402 (48.78)	3.501 (40.55)	0.393 (33.83)	0.875 (26.45)	0.099 (81.50)	9.640 (45.17)	834.0 (48.70)	9803 (34.18)
B: (5mg) [n= 8]	6.384 (46.57)	7.036 (46.09)	1.313 (37.54)	1.500 (50.40)	0.047 (15.19)	15.05 (14.59)	831.4 (39.28)	18316 (46.05)
C: (10mg) [n= 7]	15.15 (41.81)	15.81 (40.04)	2.923 (40.15)	1.429 (37.42)	0.059 (14.51)	12.07 (14.82)	709.0 (33.96)	12606 (46.19)
D: (20mg) [n= 8]	36.70 (54.28)	37.68 (53.80)	4.643 (42.07)	1.625 (31.85)	0.053 (17.02)	13.41 (15.81)	657.4 (44.07)	12549 (47.52)
Treatment (Dose of nebivolol) [# of subjects]	Parameter – [PM Group; 4 males and 3 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr <sup>-1</sup> )	HALF (hr)	Cl/F <sup>a</sup> (L/hr)	Vd/F <sup>a</sup> (L)
A: (2.5mg) [n= 7]	80.39 (28.80)	148.0 (29.13)	1.844 (23.50)	5.571 (37.56)	0.013 (21.84)	55.37 (27.12)	18.22 (30.09)	1390 (18.36)
B: (5mg) [n= 7]	192.79 (21.28)	299.9 (20.44)	4.676 (18.58)	5.143 (28.46)	0.018 (23.12)	41.00 (20.26)	17.26 (20.20)	993.3 (14.39)
C: (10mg) [n= 7]	385.9 (18.29)	613.5 (24.06)	9.213 (18.70)	4.429 (34.14)	0.014 (21.74)	50.15 (18.89)	17.05 (21.86)	1206 (19.16)
D: (20mg) [n= 7]	837.1 (23.10)	1428 (13.07)	20.94 (17.67)	4.429 (34.14)	0.014 (25.61)	54.17 (27.17)	14.23 (14.52)	1103 (25.60)

Dose-normalized parameters for the mixture of both isomers are shown in Table 14.

**Table 20: Mean (% CV) dose-normalized pharmacokinetic parameters for d,l-nebivolol**

Parameter <sup>a</sup>	Treatment – EM GROUP (6 males and 2 females)			
	A=2.5mg [n= 8]	B=5mg [n= 8]	C=10mg [n= 7]	D=20mg [n= 8]
nCPEAK	0.238 (33.83)	0.263 (37.54)	0.292 (40.15)	0.232 (42.07)
nAUCL	0.961 (48.78)	1.277 (46.57)	1.515 (41.81)	1.835 (54.28)
nAUCI	1.400 (40.55)	1.407 (46.09)	1.581 (40.04)	1.884 (53.80)
Parameter <sup>a</sup>	Treatment – PM GROUP (4 males and 3 females)			
	A=2.5mg [n= 7]	B=5mg [n= 7]	C=10mg [n= 7]	D=20mg [n= 7]
nCPEAK	0.737 (23.50)	0.935 (18.58)	0.921 (18.70)	1.047 (17.67)
nAUCL	32.16 (28.80)	38.56 (21.28)	38.59 (18.29)	41.85 (23.10)
nAUCI	59.21 (29.13)	59.97 (20.44)	61.35 (24.06)	71.42 (13.07)

<sup>a</sup> Normalized based upon the amount of nebivolol administered

Based on the Table 11, the sponsor concluded that in PMs, CPEAK, AUCL and AUCI values for d,l-nebivolol were dose proportional. However, for the EMs, the changes were not dose-proportional, particularly, when the lower doses were used for comparison (Table 21).

**Table 21: Geometric Mean Ratio (%) and 90% CI for the Dose-Normalized Parameters of d,l-Nebivolol**

Parameter	Treatment – EM GROUP					
	d-nebivolol		l-nebivolol		d,l- nebivolol	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
CPEAK	0.984	87 – 110	0.996	89 – 110	0.996	89 – 110
AUCL	1.401	130 – 151	1.284	122 – 135	1.305	123 – 138
AUCI	1.329	122 – 144	1.110	105 – 118	1.230	115 – 131
Parameter	Treatment – PM GROUP					
	d-nebivolol		l-nebivolol		d,l- nebivolol	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
CPEAK	1.044	100 – 109	1.211	117 – 126	1.151	111 – 119
AUCL	1.026	98 – 108	1.178	114 – 125	1.130	107 – 119
AUCI	0.996	95 – 104	1.119	103 – 120	1.097	103 – 116

\*Utilized the mixed procedure power model, as noted by the equation  $\log Y = \log a + b \log X$ . Each subject has his/her own intercept ( $\log a$ ) where the variable b (slope) is fixed. The test is performed to see if b is equal to 1. If the slope (b) is equal to one then there is a linear relationship between the variables tested.

**Table 22: Mean (% CV) pharmacokinetic parameters for nebivolol glucuronides**

Treatment (Dose of nebivolol) [# of subjects]	Parameter – [EM Group; 6 males and 2 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr <sup>-1</sup> )	HALF (hr)	Cl/F <sup>0.5</sup> (L/hr)	Vd/F <sup>0.5</sup> (L)
A: (2.5mg) [n= 8]	42.45 (38.07)	52.81 (32.44)	8.973 (33.57)	2.250 (20.57)	0.2349 (13.05)	2.998 (14.27)	52.02 (33.61)	223.3 (32.67)
B: (5mg) [n= 8]	106.8 (43.95)	119.4 (38.50)	20.01 (32.31)	2.250 (39.40)	0.2226 (17.19)	3.217 (21.68)	46.29 (29.28)	209.0 (26.24)
C: (10mg) [n= 7]	252.2 (40.50)	264.8 (37.95)	40.04 (29.02)	2.286 (21.35)	0.1940 (38.35)	4.045 (35.84)	42.38 (36.41)	226.6 (24.62)
D: (20mg) [n= 8]	643.7 (26.15)	653.7 (25.75)	91.30 (28.00)	2.500 (21.38)	0.1341 (21.11)	5.356 (18.93)	32.46 (25.87)	246.7 (28.10)
Treatment (Dose of nebivolol) [# of subjects]	Parameter – [PM Group; 4 males and 3 females]							
	AUCL (ng x hr/mL)	AUCI (ng x hr/mL)	CPEAK (ng/mL)	TPEAK (hr)	KEL (hr <sup>-1</sup> )	HALF (hr)	Cl/F <sup>0.5</sup> (L/hr)	Vd/F <sup>0.5</sup> (L)
A: (2.5mg) [n= 7]	569.4 (31.79)	678.2 (27.52)	34.89 (27.19)	4.000 (0.000)	0.0269 (41.44)	29.11 (34.03)	3.960 (30.16)	164.0 (37.57)
B: (5mg) [n= 7]	1217 (24.88)	1416 (19.16)	70.57 (30.18)	3.857 (9.799)	0.0250 (25.11)	29.50 (29.49)	3.649 (19.89)	158.8 (45.55)
C: (10mg) [n= 7]	2426 (23.38)	2725 (21.00)	157.6 (18.00)	3.714 (13.14)	0.0301 (39.51)	25.46 (29.61)	3.809 (20.48)	142.8 (40.44)
D: (20mg) [n= 7]	5133 (30.10)	6285 (27.56)	328.7 (20.64)	4.000 (0.000)	0.0269 (33.94)	32.16 (72.24)	3.389 (26.43)	145.5 (49.23)

The sponsor concluded that for the EM subjects, the mean nebivolol glucuronides values were approximately 16-fold higher for both CPEAK and AUCI, while for the PM subjects the CPEAK values were roughly 17- fold higher and AUCI values were 4.5- fold larger for nebivolol glucuronides as compared to d, l-nebivolol. The mean half-lives of both the PM and EM subjects for nebivolol glucuronides were shorter than the parent compound (d, l-nebivolol) half-lives for the respective treatment groups, Table 22.

The results from the ANOVA analysis of the dose-normalized natural log transformed pharmacokinetic parameters for CPEAK, AUCL, and AUCI support linearity in the PM group for nebivolol glucuronides across all dosage strengths investigated. In the EM group, normalized CPEAK displayed linearity, while normalized AUCL and normalized AUCI values increased more than proportional with dose.

**Table 23: Mean (% CV) dose-normalized pharmacokinetic parameters for nebivolol glucuronides**

Parameter	Treatment – EM GROUP (6 males and 2 females)			
	A=2.5mg [n= 8**]	B=5mg [n= 8]	C=10mg [n= 7]	D=20mg [n= 8]
nCPEAK	3.589 (33.57)	4.002 (32.31)	4.004 (29.02)	4.565 (28.00)
nAUCL	16.98 (38.07)	21.37 (42.95)	25.22 (40.50)	32.19 (26.15)
nAUCI	21.13 (32.44)	23.88 (38.50)	26.48 (37.95)	32.69 (25.75)
Parameter	Treatment – PM GROUP (4 males and 3 females)			
	A=2.5mg [n= 7]	B=5mg [n= 7]	C=10mg [n= 7]	D=20mg [n= 7]
nCPEAK	13.96 (27.19)	14.11 (30.18)	15.76 (18.00)	16.44 (20.64)
nAUCL	227.7 (31.79)	243.5 (24.88)	242.6 (23.38)	256.7 (30.10)
nAUCI	271.3 (27.52)	283.2 (19.16)	272.5 (21.00)	314.3 (27.56)

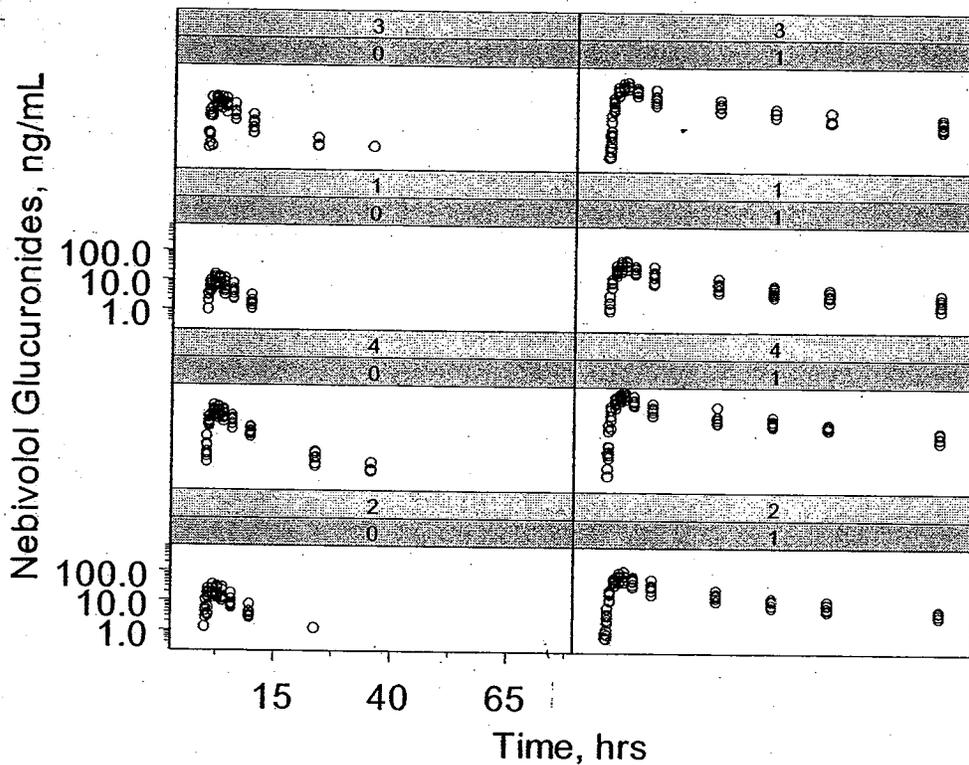
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**Table 24: Geometric Mean Ratio and 90% CI for PK Parameters of Nebivolol Glucuronides**

Parameter	Treatment - EM GROUP (6 males and 2 females)					
	GMR B vs A 5.0mg vs 2.5mg	90 % Confidence Intervals	GMR C vs B 10mg vs 5.0mg	90 % Confidence Intervals	GMR D vs C 20mg vs 10mg	90 % Confidence Intervals
lnnCPEAK	112	99 - 126	108	95 - 122	107	94 - 121
lnnAUCL	126	104 - 152	124	102 - 152	126	103 - 154
lnnAUCI	116	96 - 140	115	96 - 139	122	101 - 147
Parameter	Treatment - PM GROUP (4 males and 3 females)					
	GMR B vs A 5.0mg vs 2.5mg	90 % Confidence Intervals	GMR C vs B 10mg vs 5.0mg	90 % Confidence Intervals	GMR D vs C 20mg vs 10mg	90 % Confidence Intervals
lnnCPEAK	101	91 - 112	112	101 - 125	106	95 - 118
lnnAUCL	110	99 - 123	100	90 - 111	104	94 - 116
lnnAUCI	108	96 - 121	96	85 - 108	115	102 - 129

The trellis plot for the nebivolol glucuronides plasma concentrations vs. time for all treatments in EM, and PM subjects is shown in Figure 16.

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**Figure 16: Nebivolol glucuronides plasma concentrations vs. time. 0-EMs, 1-PMs. Doses: 2.5 mg (1), 5mg (2), 10mg (3), and 20mg (4)**

**COMMENTS:**

1. The sponsor properly characterized in this study the pharmacokinetics of d- and l-nebivolol in healthy subjects (EMs and PMs) after single doses of nebivolol (5, 10 and 20 mg). However, the pharmacokinetics of all analytes after the low 2.5 dose was not properly described due to the assay limitations and  $k_{el}$ , AUC, clearance and half-life were not estimated correctly. The study design and assay limitations did not allow for the proper characterization of the pharmacokinetic of the nebivolol glucuronides.
2. This study showed that d- and l-isomers of nebivolol have different pharmacokinetic characteristics and pharmacologic activity. It is unclear why the kinetics of the mixture of two substances (d,l-nebivolol) was presented as it was one substance.
3. After oral administration, both d- and l-nebivolol metabolize to several hydroxyl derivatives, therefore in the body nebivolol glucuronides are represented by a complex mixture of several substances from which some components have pharmacologic activity. The method of the assay used by the sponsor did not allow to separate them, therefore, the pharmacokinetics of these metabolites was not characterized and their impact on the overall nebivolol activity is unclear.
4. For PMs, the estimation of half-life of the l-isomer as 74 hours might not be accurate since the last plasma sample was obtained at 72 hours and the ratio of  $AUC_{last}/AUC_{\infty}$  for l-nebivolol was below 80%.

5. The estimation of l-nebivolol half-life in EMs as 24 hour is not reliable particularly for the lower doses of 2.5 and 5 mg, where the drug was detected in plasma up to 36 and 48 hours respectively.
6. After the administration of racemic nebivolol, exposure estimated as AUCL and AUCI of the l-isomer was about 2-fold larger for the EMs, and 2-5 fold larger for the PMs than the d-isomer. In PMs, nebivolol PK (all analytes) was linear in the dose range from 2.5 to 20 mg. In EMs, CPEAK changes across the dose were linear but AUCL and AUCI increased less than dose proportionally. The analysis of variance performed on dose-normalized parameters confirm the dose linearity for the PM subjects. For the EM group, the increase of CPEAK, AUCL, and AUCI were not linear with increasing doses. The changes were not dose proportional when the parameters were compared with the lower doses (treatments A and B), and since the pharmacokinetic profiles for these doses were not completely characterized the conclusions about non-linearity may be not valid.
7. The sponsor has calculated mean half-lives of nebivolol glucuronides for both the PM and EM subjects shorter than the sum of parent compounds (so called d,l-nebivolol) half-lives. This is an unusual finding. Most likely, the sponsor failed to measure the plasma concentrations of the nebivolol glucuronides for EMs (not enough assay sensitivity) and for PMs, the plasma concentrations of nebivolol glucuronides were not measured long enough to characterize the terminal phase of elimination. The sponsor recognized that in the report, however, the results of data analysis are presented in the report. All nebivolol glucuronides parameters except for the CPEAK calculated in this study cannot be considered as plausible.

#### **CONCLUSIONS:**

In both EMs and PMs, the exposures (AUCL and AUCI) were consistently larger for l-nebivolol relative to d-nebivolol (2- fold for EMs and 2 to 5- fold greater in PMs). The C<sub>max</sub> value was approximately 2 fold higher for EMs, but only between 10 and 57% higher in PMs for l-nebivolol as compared to d-nebivolol. T<sub>1/2</sub> for l-nebivolol was 2 to 3- fold longer for all subjects relative to d-nebivolol. The apparent clearance of l-nebivolol was 2 to 4 times smaller for all subjects as compared to d-nebivolol.

In the PMs, nebivolol PK was linear for the dose range between 2.5 to 20 mg. In the EMs, C<sub>max</sub> was linear across all doses but AUCL increased approximately 2 fold when the 2.5 mg dose was compared to the 20 mg dose. The increase in AUCI values between the lowest and highest dose was from 20% (l-nebivolol) to 84% (d-nebivolol). The sponsor attributed this change to improper characterization of the plasma concentration curve for the EMs at the lower dosage strengths due to assay limitations. According to the data on file, this is possible, however, only with regards to the 2.5 mg dose.

For the EM and PM subjects, the mean C<sub>max</sub> values of nebivolol glucuronides were about 16-fold higher when compared to the C<sub>max</sub> values of d,l-nebivolol. The calculated mean half-lives of nebivolol glucuronides for both the PM and EM subjects were shorter than the same values for the parent compounds. The failure to measure the plasma glucuronide concentrations long enough led the sponsor to unacceptable characterization of the plasma concentration vs. time profile and the conclusions about the comparison of the exposure to the nebivolol glucuronides could not be made.

#### 4.2.2 Single-Dose, Relative Bioavailability and Food Effect Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status (NEBI- 0127)

**DRUG STUDIED:** Nebivolol Tablets, 10mg Nebivolol  
Oral Solution, 40mL (0.25mg/mL)  
Mylan Pharmaceuticals Inc.

**INVESTIGATORS:** Thomas S. Clark, M. D., M. S.

**STUDY SITE:**

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#### **OBJECTIVES:**

To determine the relative bioavailability of nebivolol tablets compared to nebivolol oral solution under fasting conditions, and

To compare the rate and extent of absorption of nebivolol tablets under fed and fasting conditions in healthy, adult volunteers characterized according to their metabolizing status.

The single- dose pharmacokinetics of nebivolol absorption, among both extensive and poor metabolizers, was assessed by statistical comparisons of various pharmacokinetic parameters derived from the plasma concentration- time curves of d-nebivolol, l-nebivolol, and d, l-nebivolol.

#### **STUDY DESIGN:**

This was a single-center, randomized three-way crossover, single-dose, open-label pharmacokinetic study. After a supervised overnight fast (at least 10 hours), each subject received a single, oral dose of nebivolol as either a single, oral 10mg tablet (Treatment A) or 40mL (0.25mg/mL) of oral solution (Treatment C) under fasting conditions, or a single, oral 10mg tablet (Treatment B) under fed conditions.

Subjects received a standard meal and snack 13.5 hours and 10.5 hours, respectively, prior to dosing and 4 hours and 10 hours after dosing. Subjects receiving Treatment B (10mg tablet under fed conditions) received a standard high fat breakfast 30 minutes prior to dosing. Breakfast for Treatment B consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz. of hashed brown potatoes, and 8 ounces of whole milk. In addition, all subjects consumed 240mL of ambient temperature water 1.25 hours prior to dosing and 1 hour after dosing.

Serial blood samples, 10mL, were collected within 45 minutes prior to dosing and at the following times relative to dosing: 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 14, 24, 36, 48, and 72 hours.

Nineteen subjects were entered into the study, and eighteen subjects completed this study. There were 12 EM and 6 PM subjects.

The treatments, formulations, lot numbers and manufacturing date are shown in Table 25.

**Table 25: Drug Description**

Treatment	Dose	Lot #'s	Manufacturing Date
A	10mg nebivolol tablet (fasting conditions)	R1H1182	4/17/2000
B	10mg nebivolol tablet (fed conditions)	R1H1182	4/17/2000
C*	40mL (0.25mg/mL) nebivolol oral solution (fasting conditions)	Gr. A Per 1 – R1J2736 Gr. A Per 2 – R1J2737 Gr. A Per 3 – R1J2738 Gr. D Per 2 – R1J3326 Gr. C Per 2 – R1J3349 Gr. C Per 3 – R1J3350	9/13/2001 9/27/2001 10/11/2001 11/08/2001 11/12/2001 11/26/2001

Note: \* A new oral solution was manufactured within 48 hours of dosing when required by the randomization schedule to ensure appropriate potency levels of nebivolol.

**ASSAY:**

The assay utilized two different standard curve ranges, one for EMs and another for PMs. The method for the analysis of d-nebivolol and l-nebivolol in human plasma (heparin) was performed using high performance liquid chromatography with tandem mass spectrometric detection.

**Table 26: Assay Characteristics for d- and l-Nebivolol**

Parameter	Measure	Reviewer Comment
	Assay for Extensive Metabolizers (Curve I)	
Linearity	0.02ng/mL to 1.5ng/mL	Satisfactory
Precision (CV %)	d-nebivolol $\leq$ 9.12% l-nebivolol $\leq$ 6.59%	Satisfactory
Accuracy Between day	d-nebivolol between -5.66% and 3.81% l-nebivolol between -3.65% and 4.16%	Satisfactory
LLOQ	0.02ng/mL	Satisfactory
Specificity		Satisfactory
	Assay for Poor Metabolizers (Curve II)	
Linearity	linear from 0.2ng/mL to 15ng/mL	Satisfactory
Precision (CV %)	d-nebivolol $\leq$ 4.91% l-nebivolol $\leq$ 4.8%	Satisfactory
Accuracy Between day	d-nebivolol between -4.40% and 11.7% l-nebivolol between -3.67% and 9.67%	Satisfactory
LLOQ	0.2ng/mL	Satisfactory
Specificity		Satisfactory

Chromatograms were shown.

**RESULTS:**

Table 27 provides the demographic data on the subjects participated in the study.

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**Table 27: Subject Demographics**

Subject Number	Age	Sex	Genotype (alleles)	Race	Height (in)	Frame Size	Entry Weight (lbs)	Exit Weight (lbs)
1	32	M	EM (*1/*1)	W	68.25	L	187	186
2	22	M	EM (*1/*1)	W	71.50	L	165	163
3	20	M	EM (*1/*1)	W	73.00	L	155	156
4	29	M	EM (*1/*1)	W	68.00	L	173	172
5	52	M	EM (*1/*1)	W	70.00	M	150	151
6	29	M	EM (*1/*1)	W	73.00	L	184	181
7	42	M	EM (*1/*5)	W	71.50	L	215	218
8	22	M	EM (*1/*4)	W	66.50	M	152	156
9	42	F	EM (*1/*1)	W	64.50	L	157	158
10	18	F	EM (*1/*1)	W	67.50	S	131	135
11	52	F	EM (*1/*4)	W	63.00	L	147	147
12	33	F	EM (*1/*1)	W	68.00	L	164	166
13	35	F	PM (*4/*4)	W	67.00	M	142	143
14	28	M	PM (*4/*4)	W	72.50	L	181	184
15	20	M	PM (*4/*4)	W	68.00	M	163	163
16	24	F	PM (*4/*6)	W	65.50	M	146	142
17	36	F	PM (*4/*5)	W	64.25	L	146	143
18	34	M	PM (*4/*4)	W	77.00	L	220	225
19	24	M	PM (*5/*4)	W	69.75	M	165	166

Table 28-Table 31 provide the summary PK parameters for d-nebivolol, l-nebivolol and d, l-nebivolol and nebivolol glucuronide in EM and PM subjects. Figures below display the plasma concentrations profiles for d-nebivolol, l-nebivolol and d, l-nebivolol and nebivolol glucuronide in EM and PM subjects for each treatment.

Within each group, EMs and PMs, the mean d-nebivolol, l-nebivolol and d, l-nebivolol CPEAK, AUCL and AUCI values were similar between treatments. Between dosage form comparisons revealed that the relative bioavailability with respect to AUCI for the nebivolol tablets relative to the oral solution (used as the reference) both administered under fasting conditions was approximately 87% for extensive metabolizers and roughly 111% for poor metabolizers (calculated for d,l-nebivolol). In poor metabolizers, food does not affect the rate or extent of nebivolol absorption with all least square mean fed to fasting ratios comparing the 10mg tablet for LnAUCL, LnAUCI, and LnCPEAK for d-, l-, and d, l-nebivolol falling within 80% to 125%. In extensive metabolizers, the least square mean fed to fasting ratios for LnAUCL, LnAUCI, and LnCPEAK for the racemic mixture (d, l-nebivolol) also fell within the 90% confidence limits of 80% to 125%. For d-nebivolol, the least square mean fed to fasting ratios (%) comparing the 10mg tablet for LnAUCL, LnAUCI, LnCPEAK are 142%, 139%, and 98%, respectively, and for l-nebivolol, the least square mean fed to fasting ratios for LnAUCL, LnAUCI, and LnCPEAK were 94%, 97%, and 75%, respectively.

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**Table 28: Mean (%CV) d-Nebivolol PK Parameters**

PROTOCOL NUMBER NEBI-0127							
EM GROUP N=12	Treatment A 10mg tablet - fasting	Treatment B 10mg tablet - fed	Treatment C 10mg solution -fasting	Least Square Mean Ratio*(%)		90% Confidence Interval*(%)	
				B/A	A/C	B/A	A/C
AUCL (ng x hr/mL)	6.599 (89.50)	8.405 (60.86)	7.898 (93.81)	142	81.9	120 - 169	69.0 - 97.4
AUCI (ng x hr/mL)	7.127 (82.30)	9.048 (57.40)	8.423 (87.35)	139	83.5	119 - 162	71.7 - 97.2
CPEAK (ng/mL)	1.149 (51.54)	1.218 (57.72)	1.371 (76.19)	97.6	88.4	78.9 - 121	71.5 - 109
TPEAK (hr)	1.417 (47.19)	2.417 (59.73)	1.083 (43.27)				
KEL (hr <sup>-1</sup> )	0.066 (16.10)	0.068 (12.24)	0.063 (19.08)				
HALF (hr)	10.77 (17.02)	10.28 (11.53)	11.37 (18.69)				
Cl/F <sup>s</sup> (L/hr)	1041 (49.10)	725.4 (50.33)	849.1 (44.75)				
Vd/F <sup>s</sup> (L)	16062 (54.94)	10373 (44.21)	13898 (49.13)				
PM GROUP N=6 <sup>s</sup>	Treatment A 10mg tablet - fasting	Treatment B 10mg tablet - fed	Treatment C 10mg solution - fasting	Least Square Mean Ratio*(%)		90% Confidence Interval*(%)	
				B/A	A/C	B/A	A/C
AUCL (ng x hr/mL)	115.4 (23.31)	143.1 (34.18)	114.14 (23.82)	124	101	121 - 127	98.2 - 103
AUCI (ng x hr/mL)	135.3 (24.27)	168.1 (27.26)	131.3 (24.37)	124	103	118 - 130	98.3 - 108
CPEAK (ng/mL)	4.321 (29.62)	5.143 (24.14)	3.606 (25.16)	120	119	97.5 - 149	96.2 - 147
TPEAK (hr)	3.833 (38.40)	4.000 (44.72)	3.667 (41.06)				
KEL (hr <sup>-1</sup> )	0.028 (12.82)	0.028 (16.02)	0.030 (11.90)				
HALF (hr)	25.28 (13.56)	25.41 (15.72)	23.20 (11.08)				
Cl/F <sup>s</sup> (L/hr)	38.77 (23.61)	31.44 (24.06)	39.98 (23.41)				
Vd/F <sup>s</sup> (L)	1399 (22.80)	1141 (25.65)	1328 (23.12)				

\*Used Log Transformed Parameters

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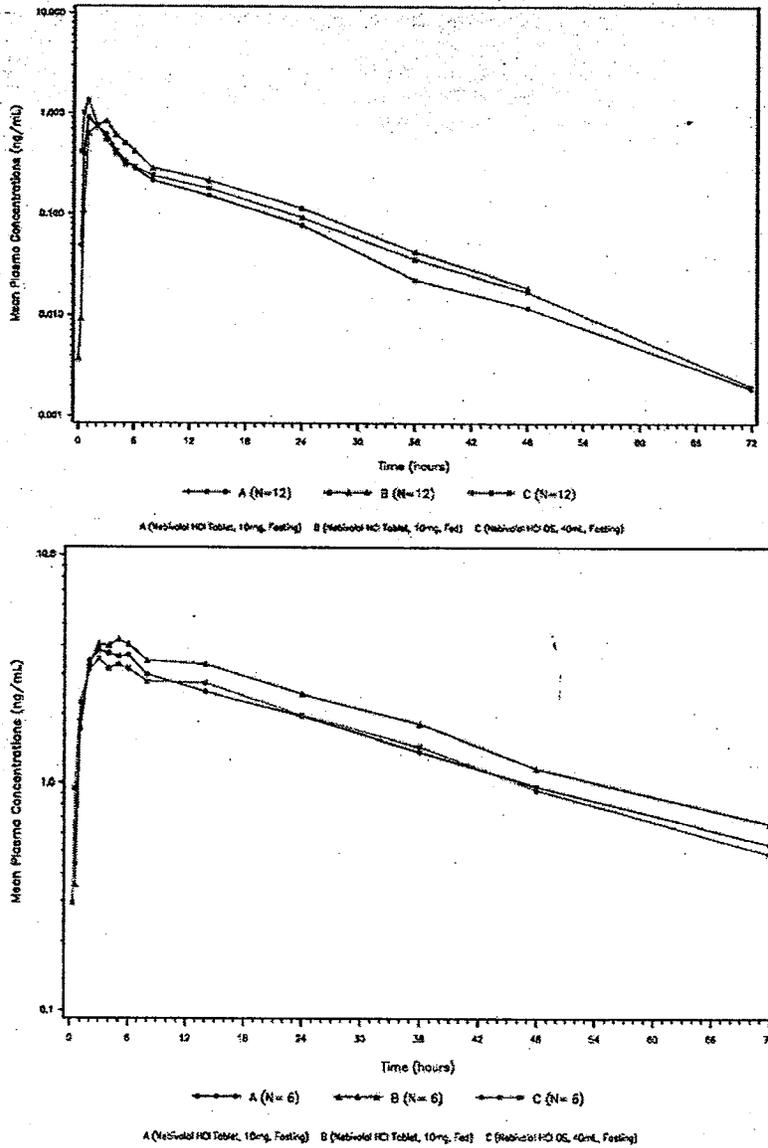


Figure 17: Mean Plasma d-Nebivolol Concentrations vs. Time in EM (upper panel) and PM (lower panel) subjects

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