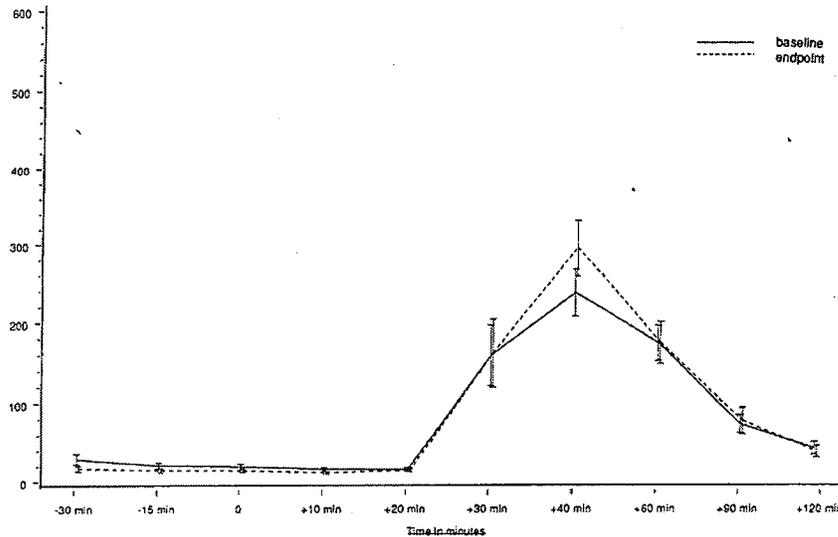


A plot of ACTH levels in response to insulin provocation is shown below.

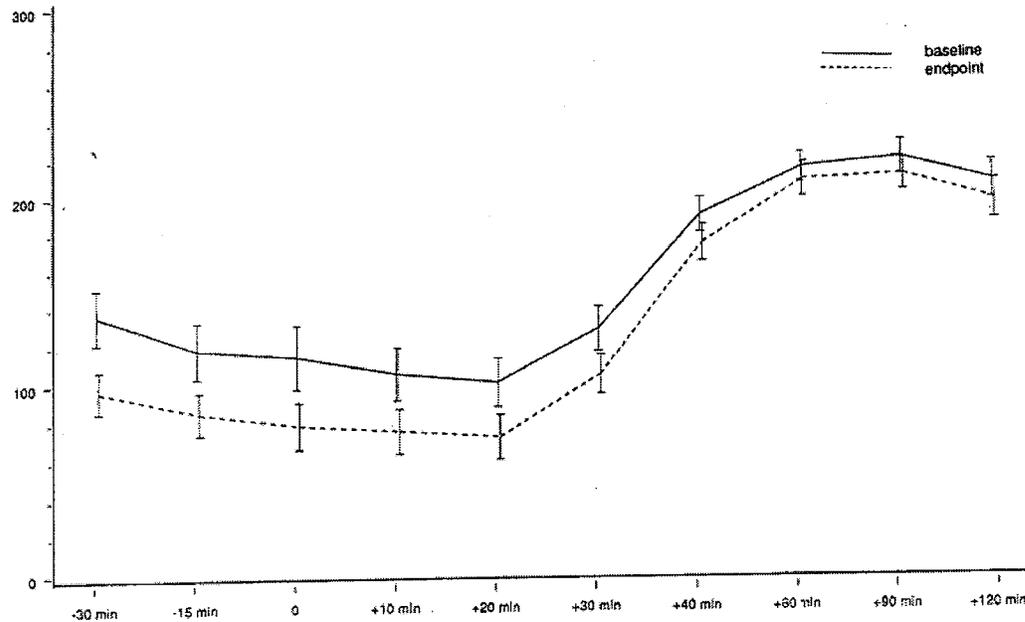


Reviewer's comments: Since ACTH is often interpreted in the setting of cortisol levels, please see my comments after the cortisol section below.

Cortisol: Although the responsiveness of cortisol levels to insulin provocation was similar between at baseline and Day 7 (i.e. C_{max} was not statistically different), the mean AUC at endpoint was significantly less than that at baseline ($p=0.016$). This difference in AUC was attributed to reduced steady state levels of plasma cortisol after 7 days of treatment with nebivolol.

| Changes in Plasma Cortisol Levels ($\mu\text{g/dL}$) During the Insulin Tests | | | | | |
|---|-------------------|-------------------|-------------------|-------------------|--|
| Time (minutes) | Baseline (Day 0) | | Endpoint (Day 7) | | Change from baseline to endpoint p-value |
| | Mean (SEM) | 95% CI of mean | Mean (SEM) | 95% CI of mean | |
| -30 | 13.6 (1.5) | 10.4, 16.9 | 9.7 (1.1) | 7.3, 12.0 | |
| -15 | 11.8 (1.5) | 8.5, 15.0 | 8.5 (1.1) | 6.1, 10.9 | |
| 0 | 11.4 (1.7) | 7.8, 15.0 | 7.8 (1.2) | 5.2, 10.5 | |
| +30 | 12.8 (1.2) | 10.2, 15.4 | 10.4 (1.0) | 8.2, 12.6 | |
| +60 | 21.4 (0.8) | 19.7, 23.1 | 20.8 (0.9) | 18.8, 22.8 | |
| +90 | 21.9 (0.9) | 19.9, 23.9 | 21.0 (0.9) | 19.1, 22.9 | |
| +120 | 20.7 (1.0) | 18.5, 22.9 | 19.6 (1.1) | 17.3, 22.0 | |
| AUC | 2175 (84) | 1990, 2361 | 1994 (93) | 1789, 2199 | 0.016 |
| Cmax | 23.1 (0.9) | 21.2, 24.9 | 21.9 (0.9) | 20.0, 23.9 | 0.519 |

A plot of plasma cortisol levels in response to insulin provocation is shown below.



Reviewer's comments: The ACTH findings complement the cortisol findings. The basal, unstimulated ACTH levels were slightly lower post- vs. pre-treatment with nebivolol. This likely explains the lower basal cortisol levels post-nebivolol treatment. Additionally, the urinary cortisol findings (see below) parallel the serum findings – there was a statistically significant reduction in 24-hour urinary cortisol levels post-nebivolol.

The post-nebivolol ACTH peak during the insulin test was also lower than that pre-nebivolol. This did not appear to affect the maximal cortisol response to hypoglycemia but the concern is that if there is a continued reduction in ambient ACTH levels with prolonged nebivolol use and/or higher nebivolol doses, adrenal atrophy and insufficiency could occur.

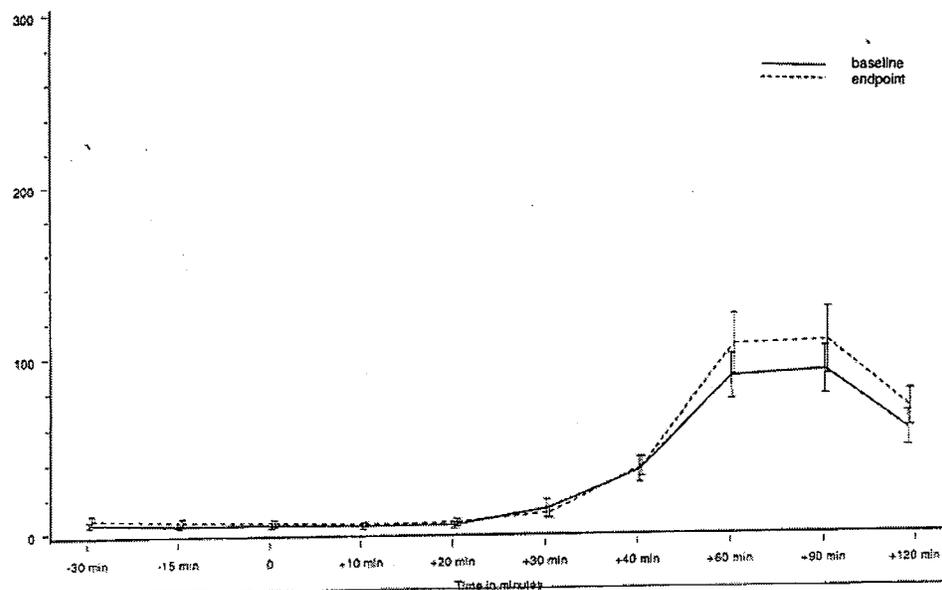
A longer duration study is required with doses up to 10 mg daily to adequately assess the effects of nebivolol on the HPA axis. Tests such as the low-dose ACTH test or the insulin tolerance test should be in addition to the high-dose ACTH test because the latter lacks sensitivity for detecting partial insufficiency states.

Growth Hormone: The response of growth hormone to insulin was numerically greater after treatment with nebivolol than at baseline, however, the AUC and C_{max} differences were not statistically significant.

| Changes in Serum Growth Hormone Levels (mU/L) During the Insulin Tests | | | | | |
|---|--------------------|----------------|---------------------|----------------|--|
| Time (minutes) | Baseline (Day 0) | | Endpoint (Day 7) | | Change from baseline to endpoint p-value |
| | Mean (SEM) | 95% CI of mean | Mean (SEM) | 95% CI of mean | |
| -30 | 5.5 (1.7) | 1.8, 9.2 | 8.0 (2.7) | 1.9, 14.0 | |
| -15 | 3.9 (1.1) | 1.5, 6.4 | 6.1 (2.4) | 0.9, 11.3 | |
| 0 | 4.2 (1.8) | 0.2, 8.2 | 5.4 (1.9) | 1.1, 9.6 | |
| +30 | 12.8 (5.2) | 1.3, 24.2 | 10.3 (3.0) | 3.8, 16.8 | |
| +60 | 87.1 (12.6) | 59.3, 114.9 | 105.3 (17.6) | 66.5, 144.0 | |
| +90 | 90.2 (13.7) | 60.2, 120.2 | 107.0 (19.3) | 64.6, 149.3 | |
| +120 | 56.9 (9.8) | 35.4, 78.4 | 68.8 (10.4) | 45.8, 91.7 | |
| AUC | 6480 (926) | 4442, 8518 | 7648 (1159) | 509, 10198 | 0.57 |
| Cmax | 98.4 (13.0) | 69.9, 126.9 | 113.9 (19.3) | 71.4, 156.3 | 0.79 |

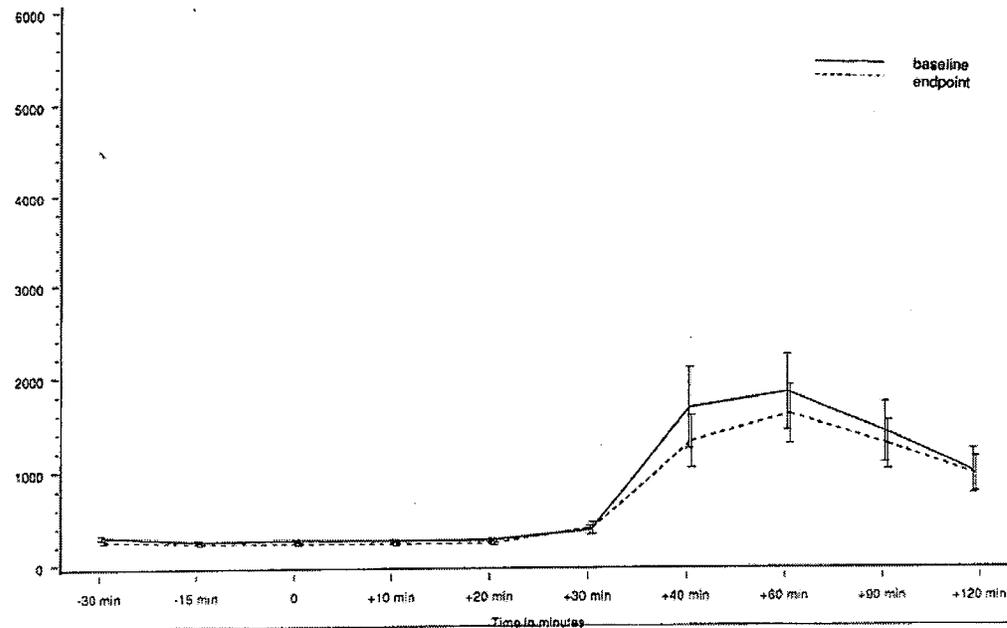
Reviewer's comments: This finding is of uncertain significance.

A plot of serum growth hormone levels in response to insulin provocation is shown below.



Prolactin: The response of prolactin to insulin was numerically smaller after treatment with nebigolol than at baseline, however, the AUC and C_{max} differences were not statistically significant.

| Changes in Serum Prolactin Levels (mU/L) During the Insulin Tests | | | | | |
|---|------------------|----------------|------------------|----------------|--|
| Time (minutes) | Baseline (Day 0) | | Endpoint (Day 7) | | Change from baseline to endpoint p-value |
| | Mean (SEM) | 95% CI of mean | Mean (SEM) | 95% CI of mean | |
| -30 | 306.3 (23.2) | 255.3, 357.2 | 260.3 (18.7) | 219.0, 301.5 | |
| -15 | 255.3 (15.7) | 220.6, 289.9 | 230.0 (17.5) | 191.5, 268.5 | |
| 0 | 264.6 (14.4) | 232.9, 296.2 | 226.4 (15.7) | 191.9, 260.9 | |
| +30 | 366.8 (49.4) | 258.2, 475.5 | 389.3 (63.9) | 248.8, 529.9 | |
| +40 | 1666.1 (430.0) | 719.7, 2612.5 | 1311.7 (274.4) | 707.7, 1915.6 | |
| +60 | 1832.9 (400.9) | 950.6, 2715.2 | 1601.0 (314.0) | 910.0, 2292.0 | |
| +90 | 1411.4 (319.5) | 708.2, 2114.7 | 1276.8 (255.9) | 713.5, 1840.0 | |
| +120 | 993.0 (235.1) | 475.5, 1510.5 | 962.1 (185.1) | 554.7, 1369.5 | |
| AUC | 138229 (28975) | 74455, 202003 | 122010 (22478) | 72537, 171483 | 0.62 |
| Cmax | 2004.6 (454.6) | 1004.1, 3005.1 | 1619.8 (314.0) | 928.7, 2310.8 | 0.62 |



Reviewer's comments: This finding is of uncertain clinical significance.

24-Hour Urinary Hormone Levels: Urinary cortisol levels (unadjusted and creatinine-adjusted) were significantly lower after nebivolol treatment that at baseline.

| Changes in 24-Hour Urinary Hormone Levels | | | | | |
|--|-------------------------|-------------------------|-----------------------------|---|-------------------------------------|
| Parameter | Mean (SEM) | | | 95% CI for the mean change from baseline | Change from baseline p-value |
| | Baseline (Day 0) | Endpoint (Day 7) | Change (Days 0 to 7) | | |
| Urine volume (mL) | 1467.5 (145.4) | 1389.2 (171.0) | -78.3 (121.3) | -345.3, 188.6 | 0.60 |
| Total creatinine (g) | 1.4 (0.2) | 1.6 (0.2) | 0.2 (0.1) | 0.0, 0.4 | 0.064 |
| Aldosterone, µg | 10.0 (2.4) | 10.2 (2.1) | 0.2 (2.2) | -4.6, 5.0 | 0.91 |
| Cortisol, µg | 52.9 (8.3) | 38.1 (3.9) | -14.8 (6.2) | -28.5, -1.1 | 0.034 |
| Aldosterone/creatinine (µg/g) | 7.3 (2.0) | 7.4 (1.5) | 0.1 (1.8) | -4.0, 4.1 | 0.91 |
| Cortisol/creatinine (µg/g) | 41.0 (6.1) | 26.6 (3.2) | -14.3 (4.2) | -23.6, -5.1 | 0.002 |

Reviewer's comments: Although cortisol levels likely remained within the normal range (based on the 95% confidence intervals), this finding is concerning and suggests reduced exposure to cortisol over a 24-hour time period. Further investigation needs to assess higher nebivolol doses and longer duration of therapy.

It is surprising that no clinical adverse events were reported during the trial, especially since symptomatic hypoglycemia would be anticipated during the insulin tests.

Sponsor's Conclusions: Nebivolol 5 mg daily for 7 days did not significantly alter the basal, nonstimulated levels of testosterone, LH, ACTH, aldosterone, renin, growth hormone or prolactin. There were statistically significant decreases in mean basal, non-stimulated plasma cortisol and 24-hour urinary cortisol levels. The observed reduction in the 2-hour AUC for plasma cortisol seen during the insulin provocation test was associated with the lower steady state levels of plasma cortisol and did not reflect reduced responsiveness to the hypoglycemic stimulus. Therefore, the Sponsor claims the HPA axis remained intact with treatment with nebivolol.

Reviewer's comments: The cortisol findings are worrisome. The reduced basal levels of cortisol in association with reduced ambient ACTH levels and lower 24-hour urinary free cortisol excretion post-nebivolol occurred with the 5 mg dose given for only 7 days. For chronic control of hypertension, subjects are likely to be exposed to this medication long-term and at higher doses. Therefore, the potential for nebivolol to cause adrenal insufficiency with long-term use at higher doses should be evaluated.

The Effect of Nebivolol on the State of the Pituitary-Gonadal System and on Lipid Peroxidation Processes in Young and Middle-Aged Men with Arterial Hypertension

Investigator: M.D. Rakhmatullaeva (Tashkent, Uzbekistan)

Reference: Kardiologiya 2003; 2: 53-55

Submitted for Publication: April 2002

Sponsor and Conflicts of Interest: Not listed, but the briefing packet claims the Sponsor did not support this study.

Reviewer's comments: The original article is in Russian – the Sponsor has provided a translated version

Objectives: To study the effect of nebivolol on (1) lipid peroxidation, (2) the antioxidant system, and (3) the pituitary-gonadal system in men with arterial hypertension.

Study Design: Non-randomized study assessing the endocrine effects of nebivolol in 32 men with hypertension. The results from the nebivolol group were compared to hormonal parameters that were measured in a control group that was not given nebivolol. This control group consisted of 10 normotensive (systolic blood pressure <130 mmHg; diastolic blood pressure <90 mmHg) “essentially” healthy men, each of whom underwent a single measurement of FSH, LH, and testosterone.

The ages of the entire group ranged from 30-65 years (mean 45.5±3.4 years).

Reviewer's comments: The author comments that the healthy men were “of the same age” as the hypertensive subjects - ages for subjects in each group are not explicitly stated.

For the hypertensive group, preceding anti-hypertensive medications were discontinued 1-2 weeks prior to starting nebivolol. These subjects started nebivolol 5 mg daily, but the dose was increased to 10 mg daily at 4 weeks if there was an inadequate blood pressure response. The total duration of therapy was 12 weeks.

Reviewer's comments: This study is of appropriate duration, but the control group was not well-defined in the manuscript – did the control group have any co-morbidities or were members in the control group taking any concomitant medications? A randomized, controlled study would have been a much more powerful design that would have produced more robust results. Also, the manuscript does not include the number of subjects who had an increase in nebivolol dose to 10 mg daily.

Primary Endpoints: Not explicitly stated

Secondary Endpoints: Not explicitly stated

Inclusion Criteria Included:

1. Hypertension Group: Young and middle-aged men (30-65 years old) with "mild" or "moderate" hypertension
2. Control Group: Essentially healthy men "of the same age [as the hypertensive patients]" with systolic blood pressure <130 mmHg and diastolic blood pressure <90 mmHg

Exclusion Criteria Included:

1. Prior myocardial infarction or stroke
2. Symptomatic or malignant arterial hypertension
3. Chronic renal or liver disease
4. Diabetes

Assessments Included:

Fasting, morning blood samples for testosterone, FSH, and LH (using RIA kits from Immunotech, Czech Republic and from the Scientific Research Institute of Endocrinology and of Regional Medicine of the Ministry of Health of the Republic of Uzbekistan).

Reviewer's comments: Hormone samples appear to have been drawn at the correct time of day. The manuscript does not describe the statistical tests used.

Results:

| Changes in Blood Pressure Over Time with Nebivolol Therapy (n=32) | | | | | |
|--|-----------------|----------------|----------------|----------------|-----------------|
| Blood Pressure | Baseline | 2 Weeks | 4 Weeks | 8 Weeks | 12 Weeks |
| Systolic, mmHg | 152.4±2.4 | 142.3±3.1 | 140.5±2.6 | 136.7±2.1 | 132.2±2.7* |
| Diastolic, mmHg | 104.1±1.5 | 94.2±1.7 | 90.1±1.9 | 86.1±1.2 | 82.2±1.3** |

*The author reports $p < 0.05$ compared with baseline

**The author reports $p < 0.01$ compared with baseline

Normalization of diastolic blood pressure occurred in 28 (87.5%) of the hypertensive subjects. The remaining 4 subjects had a partial response (diastolic blood pressure change >10%).

| Pituitary-Gonadal System in Patients with Hypertension as Compared with Control | | | | |
|--|---------------------------------|-------------------------------------|----------------|-----------------|
| Hormone | Control Group (n=10) | Hypertensive Patients (n=32) | | |
| | | Baseline | 4 Weeks | 12 Weeks |
| FSH, mIU/mL | 6.2±0.18 | 7.9±0.19* | 7.5±0.16† | 7.0±0.13§ |
| LH, mIU/mL | 6.4±0.12 | 8.4±0.19* | 7.6±0.18‡ | 6.9±0.15§ |
| Testosterone, ng/mL | 4.8±0.11 | 1.8±0.05* | 2.3±0.15§ | 3.6±0.13§ |

*The author reports $p < 0.05$ compared with control group

†The author reports $p < 0.05$ compared with the baseline values

‡The author reports $p < 0.01$ compared with the baseline values

§The author reports $p < 0.001$ compared with the baseline values

Reviewer's comments: In what proportion of subjects were baseline and post-treatment testosterone levels frankly low and in what proportion of subjects with abnormally low levels of testosterone was there normalization of levels with nebivolol?

The author claims that LH and FSH levels were statistically higher and testosterone levels were statistically lower in the hypertensive subjects at baseline compared with the corresponding hormones measured in the normotensive group. In the hypertensive group, the LH and FSH levels were progressively lowered and the testosterone levels were progressively raised from 4 to 12 weeks of treatment with nebivolol.

Reviewer's comments: Without information about the statistical tests used, I cannot determine whether the data were analyzed appropriately (e.g. was a paired test used?) However, at face value, there does appear to be an increase in testosterone and a lowering of LH and FSH with nebivolol therapy. I am reluctant to compare the results with the control group given the trial design and poor characterization of the control group.

The author stated that “when the dose of the drug is increased by 2.5-5 mg according to indications, the extent of its influence on PGS [pituitary-gonadal system] hormones increased somewhat.” No data are presented in the manuscript to support this claim.

In the Discussion section, the author mentioned that the effects of nebivolol on vasodilation (via nitric oxide modulation) in the vessels of the sex glands and corpora cavernosa in men may explain the elaboration of testosterone by the glands and improvement in erectile function.

Reviewer's comments: The manuscript does not contain information about hypogonadal symptoms (e.g. erectile dysfunction) pre- and post-treatment with nebivolol (even if it did, the unblinded, uncontrolled design would limit interpretation).

Sponsor's Conclusions: Although results from this uncontrolled published study should be interpreted with caution, the findings suggest that nebivolol 5 to 10 mg/day, administered over 12 weeks in hypertensive men, was associated with changes in mean pituitary-gonadal hormone levels, resulting in levels similar to those in normotensive control subjects.

Reviewer's comments: Conclusions are limited given the uncontrolled trial design and missing descriptions of the statistical tests employed. Also, the positive 4-week findings in this study contrast with the null 4-week testosterone results in NEB-CAN-09. Therefore, I would consider the results from this study as “hypothesis-generating” and recommend confirmation in a well-designed trial. In general, beta-blockers, are associated with erectile dysfunction and have been

shown to decrease testosterone levels in normal volunteers and hypertensive patients (the Sponsor has listed the applicable studies on page 42 of the "BetaBlockerComp" PDF file in the electronic submission).

Metabolic and Antihypertensive Effects of Nebivolol and Atenolol in Normometabolic Patients with Mild-to-Moderate Hypertension

Authors: Yves Pesant (Hotel-Dieu Hospital, St-Jerome), Julien Marc-Aurele (Sacre-Coeur Hospital, Montreal), Pierre Biemann (Centre Hospitalier de l'Université Laval, Quebec, Canada), Peter Alaupovic (Oklahoma Medical Research Foundation, Oklahoma City, OK), Pierre Cartier (Sacre-Coeur Hospital, Montreal), Daniel Bichet (Sacre-Coeur Hospital, Montreal), Gaetan Thibault (Clinical Research Institute of Montreal, Montreal, Canada), Paul Lupien (Centre Hospitalier de l'Université Laval, Quebec, Canada)

Reference: American Journal of Therapeutics. 1999; 6: 137-147.

Conflicts of Interest: Supported by an educational grant from Janssen-Ortho, Inc.

Primary Objectives: To study the effect of nebivolol in comparison to atenolol on lipids and on carbohydrate metabolism (hemoglobin A1C, glucose, insulin, C-peptide).

Secondary Objectives: To assess safety, tolerability, the hormone profile and hypertensive efficacy of nebivolol and atenolol in normo-metabolic patients with mild-to-moderate essential hypertension.

Study Design: Four-week single-blind, placebo washout phase followed by a 12-week double-blind treatment phase with either nebivolol (5 mg) or atenolol (50 mg) once daily.

Reviewer's comments: This study is of appropriate duration but, again, used only one-half the maximum recommended dose (10 mg/day) in humans for which the Sponsor is seeking approval.

Inclusion Criteria Included:

1. Mild-to-moderate essential hypertension (WHO grade I-II)
2. Normometabolic
 - a. Fasting total cholesterol <240 mg/dL
 - b. Fasting triglycerides <220 mg/dL
 - c. Fasting blood glucose <116 mg/dL
 - d. Hemoglobin A1C <6%

Reviewer's comments: Ages of participants were not mentioned. It is not clear why the authors chose 116 mg/dL for the glucose cut-off value. In 1999, impaired fasting glucose was defined as a blood glucose concentration 110-125 mg/dL (the lower limit of impaired fasting glucose has subsequently been reduced to 100 mg/dL). Even by 1999 standards, some of the subjects included in this study may

have had impaired fasting glucose. However, if subjects with this mild abnormality were included (i.e. fasting blood glucose 110-116 mg/dL) I doubt the results of the hormonal tests would be significantly affected.

Exclusion Criteria Included:

1. Diabetes mellitus or fasting blood glucose >116 mg/dL, or hemoglobin A1C >6%
2. Asthma or chronic obstructive pulmonary disease or heart failure
3. Weight >30% over ideal body weight
4. Serum creatinine >2.0 mg/dL
5. Conditions with possible clinical effects on lipids (e.g. liver disease, alcohol use)
6. Pregnant or nursing women and those of childbearing potential.
7. Cardiac arrhythmias
8. Significant liver disease (transaminitis >2.5x upper limit of normal)
9. Concomitant medications affecting blood pressure (e.g. NSAIDs) or lipids (e.g. glucocorticoids)

Assessments Included:

1. Lipid parameters
2. Two-hour, 75g oral glucose tolerance test at the end of the washout period (i.e. at randomization) and at the end of the 12-week treatment period
3. Hormonal profile – drawn at randomization and at the end of the treatment period
 - a. Plasma renin activity
 - b. Aldosterone
 - c. Prolactin
 - d. Cortisone
 - e. ACTH
 - f. Serum thyrotropin (TSH)

Statistical Plan: Intent-to-treat analyses. Lipids and hormonal variables were assessed with ANOVA and ANCOVA (covariate = last determination during baseline). Dunnett's procedure was used for multiple comparisons versus baseline. Bartlett's test was used to assess the significance of differences between variables. All analyses used a two-sided alpha of 0.05. No power calculations were presented.

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Results:

| Baseline Data | | | |
|--------------------------------|-------------------------|------------------------|----------------|
| | Nebivolol (n=21) | Atenolol (n=16) | p-value |
| Age, yr | 53.8±9.1 | 55.6±8.4 | NS |
| Weight, kg | 75.5±14.4 | 75.4±12.8 | NS |
| Male/female | 9/12 | 8/8 | NS |
| Cigarette non-smoker/smoker | 15/5 | 12/4 | NS |
| Alcohol, yes/no | 7/14 | 11/5 | <0.05 |
| Total cholesterol, mmol/L | 5.00±0.74 | 4.58±0.82 | NS |
| Total triglycerides, mmol/L | 1.49±0.39 | 1.47±0.18 | NS |
| Systolic blood pressure, mmHg | 150±17 | 160±20 | NS |
| Diastolic blood pressure, mmHg | 98±7 | 99±5 | NS |
| Sitting heart rate (beat/min) | 72±11 | 73±11 | NS |

Plus-minus values are mean±SD; NS, non-significant

Patient compliance was evaluated by tablet counting. During the 12-week active treatment period, 14 doses (<1% of all nebivolol doses) were missed by the nebivolol group and 7 doses (<1% of all atenolol doses) were missed by the atenolol group. Both drugs reduced blood pressure and heart rate to a similar extent. No drug-related adverse events were reported.

Oral Glucose Tolerance Test: The changes in the oral glucose tolerance test parameters observed at the end of 12 weeks between nebivolol and atenolol were not statistically significant.

Reviewer's comments: According to the Table, treatment with nebivolol or atenolol did not significantly alter basal glucose, insulin, or C-peptide levels nor did these medications alter the response of these variables to the oral glucose tolerance test. However, according to the text, atenolol caused a statistically significant increase in basal serum glucose from baseline to the end of treatment (mean increase from 92 to 100 mg/dL). Some beta-blockers, including atenolol have been shown to cause impaired glucose tolerance and worsening insulin sensitivity (Lithell 1991).

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| Oral Glucose Tolerance Results Before and After 3 Months of Nebivolol or Atenolol Treatment | | | | | | | |
|---|------------------|-----------------|----------------------------|----------------|---------------------------|----------------|-----------------|
| | Baseline (n=30) | | Nebivolol treatment (n=17) | P within group | Atenolol treatment (n=12) | P within group | P between group |
| | Nebivolol (n=17) | Atenolol (n=13) | | | | | |
| Basal glucose (mmol/L) | 5.22±0.45 | 5.09±0.72 | 5.29±0.51 | NS | 5.57±0.86 | NS | NS |
| Basal glucose (mg/dL) | 94±8 | 92±13 | 95±9 | NS | 100±15 | NS | NS |
| Basal insulin (mU/L) | 54.3±26.7 | 62.0±43.0 | 61.4±32.9 | NS | 56.6±32.2 | NS | NS |
| Basal C-peptide (µg/L) | 1.94±0.62 | 2.23±1.33 | 2.02±0.94 | NS | 2.28±1.39 | NS | NS |
| AUC Glucose 0-2h (h x mmol/L) | 1034±201 | 929±200 | 1043±225 | NS | 964±217 | NS | NS |
| AUC Insulin 0-2h (h x mU/L) | 57012±26173 | 53815±33067 | 61867±41212 | NS | 56109±42061 | NS | NS |
| AUC C-peptide 0-2h (h x µg/L) | 943±280 | 955±362 | 894±352 | NS | 974±413 | NS | NS |

Plus-minus values are mean±SD; NS, non-significant

ACTH:

Treatment with either nebivolol or atenolol significantly reduced ACTH levels from baseline (for nebivolol: 3.0±1.6 to 2.2±2.0 pg/mL; p=0.032. For atenolol: 5.0±3.6 to 2.4±2.7 pg/mL; p=0.038). The decreases in ACTH levels were not statistically different between the two treatment groups.

Reviewer's comments: ACTH levels were also reduced post-nebivolol in the insulin-induced hypoglycemia study.

Aldosterone:

Aldosterone levels increased with nebivolol and declined with atenolol. Neither of these changes were statistically significant. However, there was a statistically significant difference in aldosterone levels between the nebivolol and atenolol groups (p=0.03).

Reviewer's comments: These random aldosterone levels are uninterpretable, especially without knowledge of the subject's sodium balance and positioning.

Cortisol:

Cortisol levels declined in both treatment groups, but only the change in the atenolol group was statistically significant (p=0.039). Cortisol levels were not statistically different between treatment groups.

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| Endocrine Profile Before and After 3 Months of Nebivolol or Atenolol Treatment | | | | | | | |
|--|------------------|------------------|----------------------------|----------------|---------------------------|----------------|-----------------|
| | Baseline (n=30) | | Nebivolol treatment (n=17) | P within group | Atenolol treatment (n=12) | P within group | P between group |
| | Nebivolol (n=17) | Atenolol (n=13) | | | | | |
| ACTH (ng/L or pg/mL) | 3.0±1.6 (17) | 5.0±3.6 (11) | 2.2±2.0 (14) | 0.032 | 2.4±2.7 (10) | 0.038 | NS |
| Aldosterone (ng/dL) | 3.0±2.3 (17) | 3.0±2.0 (12) | 3.8±3.6 (14) | NS | 2.1±0.9 (8) | NS | 0.03 |
| Cortisol (nmol/L) | 14.2±5.3 (17) | 16.2±3.9 (13) | 12.1±5.9 (16) | NS | 13.6±? (12) | 0.039 | NS |
| PRA (ng/mL/h) | 0.998±0.882 (15) | 0.794±0.642 (12) | 1.181±1.401 (13) | NS | 1.187±0.937 (8) | NS | NS |
| Prolactin (µg/L or ng/mL) | 8.1±3.4 (17) | 7.4±2.4 (13) | 8.5±5.8 (16) | NS | 8.86±?9.6 (12) | NS | NS |
| TSH (mU/L) | 1.69±0.91 (17) | 1.43±1.18 (13) | 1.61±0.91 (16) | NS | 1.58±1.24 (12) | NS | NS |

Plus-minus values are mean±SD; NS, non-significant

Reviewer's comments: In the nebivolol group, cortisol levels were slightly lower post-treatment when compared to baseline but this did not reach statistical significance. There appeared to be a greater reduction in basal cortisol levels in the insulin study than in the current study. Differences between the studies include (1) healthy volunteers (insulin study) vs. hypertensive patients (current study) and (2) 1-week treatment with nebivolol (insulin study) vs. 4-week treatment (current study). Additionally, the current study did not do provocative testing of the HPA axis or 24-hour urine collections for cortisol.

Sponsor's Conclusions: There were no significant differences between treatments with respect to mean values for ACTH, cortisol, or plasma renin activity at endpoint. For mean aldosterone values, there was a non-significant increase in the nebivolol group and a non-significant decrease in the atenolol group, resulting in a significant difference between treatments for mean values for aldosterone at endpoint.

Reviewer's comments: Nebivolol significantly lowered ACTH levels but this only had a non-significant lowering effect on basal cortisol levels. The renin and aldosterone levels are uninterpretable based on the same issues raised throughout this review.

The hormone data from the five clinical nebivolol trials in this review are summarized by the Sponsor in the Table below. Methodological issues limit this consultant's ability to agree with some of these conclusions.

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Table 13 Hormonal effects of nebivolol in humans obtained from five clinical studies

| Hormone | NEB-CAN-09* | NEB-BEL-52 | | NEB-BEL-55 | | Pesant | Rakhmatullaeva |
|--------------|-------------|------------|--------|------------|--------|--------|----------------|
| | | Basal | Stim** | Basal | Stim** | | |
| Testosterone | ↔ | ↔ | NA | ↔ | NA | - | ↑ |
| LH | ↔ | ↔ | NA | ↔ | NA | - | ↓ |
| FSH | ↔ | - | - | ↔ | NA | - | ↓ |
| Estradiol | ↔ | - | - | ↔ | NA | - | - |
| Prolactin | - | ↔ | ↔ | ↔ | NA | ↔ | - |
| GH | - | ↔ | ↔ | - | - | - | - |
| Progesterone | ↔ | - | - | - | - | - | - |
| Renin | ↓ | ↔ | NA | - | - | ↔ | - |
| Cortisol | ↔ | ↓ | ↔ | ↔ | ↔ | ↔ | - |
| Aldosterone | ↔ | ↔ | NA | ↓ | ↔ | ↑ | - |
| ACTH | ↔ | ↔ | ↔ | - | - | ↔ | - |

* Data presented for *dl*-nebivolol

** Effect on response evoked by insulin-induced hypoglycemia (NEB-BEL-52) or exogenous ACTH administration (NEB-BEL-55)

↔ = no change, ↑ = increased, ↓ = decreased, - = not assessed, LH = luteinizing hormone, FSH = follicle stimulating hormone, GH = growth hormone, NA = not applicable, ACTH = adrenocorticotropic hormone, ANF-C = atrial natriuretic factor-C terminal, ANF-N = atrial natriuretic factor-N terminal, TSH = thyroid stimulating hormone

A Comparison of the Effects of Beta-Adrenoreceptor Antagonists on Endocrine Organs, Reproductive Toxicity, and Physiological Endpoints: Human Data

The Table below, compiled by the Sponsor, demonstrates the reported effects of various beta-blockers on hormones in humans. All references are provided in the Sponsor's electronic submission.

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Table 6 Clinical effects of beta-blockers other than nebivolol on hormone status in published literature

| Hormone | Effect on basal serum/plasma levels | Beta-blockers showing this effect * | Effect on stimulated serum/plasma levels | Beta-blockers showing this effect * |
|--------------|-------------------------------------|--|--|---|
| Testosterone | ↑ | Propranolol | ↑ | Propranolol |
| | ↓ | Anapraline, Atenolol, Metoprolol, Nadolol, Pindolol, Propranolol | ↓ | Metoprolol |
| | ↔ | Acebutolol, Metoprolol, Oxprenolol, Propranolol | ↔ | Metoprolol |
| LH | ↑ | Anapraline | ↑ | NA |
| | ↓ | Atenolol, Nadolol, Propranolol | ↓ | NA |
| | ↔ | Acebutolol, Propranolol, Tolamolol | ↔ | Metoprolol Propranolol |
| FSH | ↑ | Anapraline | ↑ | NA |
| | ↓ | Acebutolol, Atenolol, Nadolol, Propranolol | ↓ | NA |
| | ↔ | Propranolol | ↔ | Metoprolol Propranolol |
| Estradiol | ↑ | Anapraline, Nadolol | ↑ | NA |
| | ↓ | Atenolol | ↓ | NA |
| | ↔ | Atenolol | ↔ | Metoprolol |
| Prolactin | ↑ | Anapraline, Labetalol, Medroxalol, Nadolol, Tolamolol | ↑ | Metoprolol Propranolol Timolol |
| | ↓ | Acebutolol, Pindolol, Propranolol | ↓ | Pindolol |
| | ↔ | Atenolol, Bopindolol, Labetalol, Medroxalol, Metoprolol, Oxprenolol, Pindolol, Propranolol, Timolol | ↔ | Atenolol, Propranolol |
| GH | ↑ | Propranolol, oxprenolol | ↑ | Alprenolol, Atenolol, Betaxolol, Metoprolol, Practolol, Propranolol |
| | ↓ | NA | ↓ | Bupranolol, Metoprolol, Pindolol |
| | ↔ | Acebutolol, Atenolol, Labetalol, Medroxalol, Metoprolol, Oxprenolol, Pindolol, Propranolol, Timolol, Tolamolol | ↔ | Atenolol, Metoprolol, Propranolol, Timolol |

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| Hormone | Effect on basal serum/plasma levels | Beta-blockers showing this effect * | Effect on stimulated serum/plasma levels | Beta-blockers showing this effect * |
|--------------|-------------------------------------|---|--|--|
| Cortisol | ↑ | Atenolol, Pindolol, Propranolol | ↑ | Metoprolol, Pindolol, Propranolol, Timolol |
| | ↓ | Atenolol, Propranolol | ↓ | Pindolol |
| | ↔ | Acebutolol, Atenolol, Bopindolol, Dilevalol, Medroxalol, Metoprolol, Penbutolol, Pindolol, Propranolol, Timolol | ↔ | Acebutolol, Alprenolol, Betaxolol, Metoprolol, Pindolol, Propranolol |
| ACTH | ↑ | Propranolol | ↑ | Metoprolol, Pindolol, Propranolol |
| | ↓ | Atenolol, Propranolol | ↓ | Pindolol, Propranolol |
| | ↔ | Propranolol | ↔ | Betaxolol |
| Aldosterone | ↓ | Amosulalol, Atenolol, Bisoprolol, Dilevalol, Penbutolol, Propranolol | ↓ | Propranolol |
| | ↔ | Oxprenolol, Pindolol, Propranolol | ↔ | Propranolol |
| Plasma renin | ↓ | Amosulalol, Bisoprolol, Dilevalol, Oxprenolol, Penbutolol, Propranolol | ↓ | Metoprolol, Propranolol, Timolol |
| | ↔ | Atenolol, Dilevalol, Metoprolol, Pindolol, Timolol | ↔ | Propranolol |

* A given beta-blocker may have shown different results in clinical studies of various designs and therefore may be listed more than once.

↑ = increase; ↓ = decrease; ↔ no change, ACTH = adrenocorticotrophic hormone, LH = luteinizing hormone, FSH = follicle-stimulating hormone, GH = growth hormone

As is readily apparent from the Table above, inconsistent results on the hormonal system have been described for different beta-blockers and sometimes even for the same beta-blocker. Therefore, the inconsistent results obtained for nebivolol across the 5 clinical studies is in line with inconsistencies obtained for other beta-blockers. However, it is important to realize that there are significant limitations in most of the nebivolol trials, which have likely contributed substantially to this variability – limitations that most assuredly exist in the other beta-blocker studies.

Other than fetal growth restriction, little has been reported regarding adverse effects of beta-blocker treatment during pregnancy.

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Response to Questions from Cardio-Renal

1. For the clinical studies (NEB-CAN-09, NEB-BEL-52, NEB-BEL-55, Pesant, and Rakhmatullaeva):
 - a. Do the above studies rule out a possible endocrine effect of nebivolol? If not, why not?

DMEP Response: In general, the 5 clinical studies do not rule out a possible endocrine effect of nebivolol, mostly because of methodological issues, which are summarized for the individual studies below. All but one of these studies tested only 5 mg/day of nebivolol, which is one-half the maximum recommended dose (10 mg/day) in humans for which the Sponsor is seeking approval. The one study (Rakhmatullava; n=32) that included titration to 10 mg/day of nebivolol did not specify the proportion of participants exposed to this higher dose. For all 5 studies, random aldosterone and renin levels provide limited data about the integrity of the renin-angiotensin-aldosterone system and are dependent on body position and dietary sodium intake, which were not specified in any of the studies. None of the studies evaluated free sex-hormone (e.g. free testosterone and free estradiol) levels.

CAN-09:

The protocol does not describe the methodological details regarding determination of the hormone levels. For example, no information was provided as to the types of hormonal assays used. The timing of the hormone collections was not specified (cortisol, ACTH and testosterone levels are highest in the mornings – were these hormones consistently drawn in the mornings for all subjects?). Estradiol and progesterone levels vary widely in healthy premenopausal women depending on the timing of the draw with regard to the menstrual cycle – the study did not take this into account.

BEL-52:

This was one of the better designed nebivolol hormonal studies, but it only provides data from short-term (7-day) nebivolol 5 mg/day exposure. Basal ACTH levels were slightly lower post- vs. pre-treatment with nebivolol, which likely explains the lower basal cortisol levels post-nebivolol treatment. Additionally, there was a statistically significant reduction in 24-hour urinary cortisol levels post-nebivolol, which parallels the serum findings. The ACTH peak during the insulin test performed post-nebivolol was also lower than that pre-nebivolol. This did not appear to affect the maximal cortisol response to hypoglycemia but the concern is that if there is a continued reduction in ambient ACTH levels with prolonged nebivolol use and/or higher nebivolol doses, adrenal atrophy and insufficiency could occur.

BEL-55:

The high-dose ACTH test, which was used to assess the integrity of the hypothalamic-pituitary-adrenal (HPA) axis has several limitations. First, this dose causes ACTH levels to increase ~1,000 times higher than what is observed in maximally stressed individuals, thereby potentially causing a falsely normal cortisol response by an adrenal gland that is in fact partially impaired. Second, this test will be falsely negative in patients with newly-acquired (i.e. <1 month) secondary adrenal insufficiency (e.g. ACTH deficiency) because adrenal atrophy only occurs in the setting of chronic ACTH deficiency. Since the BEL-55 study was only 7 days in duration and used the high-dose ACTH test, we are not reassured by the negative HPA results for nebivolol.

Rakhmatullaeva:

This study (translated from Russian) provided exposure to doses of nebivolol up to 10 mg/day for 3 months. However, this was a non-randomized study and the control group was not well-defined in the manuscript. Furthermore, the author did not include a statistical methods section so there is no way of knowing which statistical tests were used to compare the hormone values.

Pesant:

Nebivolol significantly reduced ACTH levels in this study (as it did in NEB-52), but there were no statistically significant differences in pre- and post-nebivolol basal cortisol levels. However, basal cortisol levels provide limited information about the integrity of the HPA axis and no provocative testing (e.g. insulin-induced hypoglycemia or ACTH stimulation testing) was performed.

- b. As some of these studies were performed 10 years ago, do you agree with the methods used in these studies to obtain hormone measurements? Could more accurate results of hormone measurements be made with the technology we have today?

DMEP Response: Not all the studies have provided a description of the assays used to measure hormone levels. For those studies that have provided details, the analytic methods appear appropriate even by today's standards. Issues related to blood collection (e.g. timing of day, timing during menstrual cycle, dietary sodium intake for aldosterone, etc.) appear to be more problematic in these studies.

- c. In these studies, was the duration of nebivolol therapy adequate for detecting any possible endocrine changes? If not, what would be the recommended duration of therapy prior to hormonal testing?

DMEP Response: Please also see response to 1a above. The two studies that tested the integrity of the HPA axis with provocative testing (BEL-52 and BEL-55) only exposed subjects to nebivolol for 7 days. In the insulin study (NEB-52), the reduced basal levels of cortisol in association with reduced ambient ACTH levels and lower 24-hour urinary free cortisol excretion post-nebivolol occurred with the 5 mg dose given for only 7 days. Patients are likely to be exposed to this medication long-term and possibly at higher doses. Therefore, the potential for nebivolol to cause adrenal insufficiency with long-term use at higher doses should be evaluated. Since significant ACTH deficiency on the order of 1 month is needed to develop some degree of adrenal atrophy, the normal ACTH stimulation test after 7 days of nebivolol exposure (BEL-55) also does not rule out potential long-term adrenal insufficiency with this agent. Even though the CAN-09 study provided a 4-week exposure to nebivolol, the methodological flaws (please see response to 1a) significantly impair interpretation of most of the hormonal values from that study. The Rakhmatullaeva and Pesant studies each provided 3 month exposure to nebivolol. However, the Rakhmatullaeva study only evaluated men and only evaluated gonadotropins (LH, FSH) and testosterone levels. The Pesant study was of appropriate duration but did not include provocative testing or measurement of gonadotropins or sex-hormones. Finally, virtually all subjects in these studies were exposed to only a 5 mg daily dose of nebivolol.

Therefore, we would recommend a randomized, well-designed study of ~3 months duration testing up to the 10 mg recommended maximum dose of nebivolol in both men and women (see response to 1e for further details regarding this study).

- d. Do we agree with the Sponsor's interpretation of the study results regarding the hormone effects?

DMEP Response: No. We have addressed each of the Sponsor's claims one-by-one below. Additional details are included in our responses to other questions.

Sponsor's Claim: Nebivolol had no effects on the HPA axis in humans based on testing using insulin-induced hypoglycemia and ACTH-stimulated glucocorticoid and mineralocorticoid production.

DMEP Response: The insulin-induced hypoglycemia study (BEL-52) did show changes in the HPA axis, including slightly lower basal ACTH levels post- vs. pre-treatment with nebivolol, lower basal cortisol levels post-nebivolol treatment, a statistically significant reduction in 24-hour urinary cortisol levels post-nebivolol, and a lower post-nebivolol ACTH peak during the insulin test. The ACTH-stimulation study (BEL-55) used high-dose ACTH and will be falsely negative in patients with newly-acquired (i.e. <1 month) secondary adrenal insufficiency (e.g. ACTH deficiency) because adrenal atrophy only occurs in the setting of chronic ACTH deficiency.

Sponsor's Claim: Nebivolol did not affect basal, non-stimulated cortisol levels in three clinical studies (NEB-CAN-09, NEB-BEL-55, and the Pesant study). Another study (BEN-BEL-52) showed a statistically significant decrease in basal, non-stimulated cortisol levels and urinary cortisol levels in subjects given nebivolol for 7 days, but the Sponsor questions the relevance of this study because the maximal cortisol response to acute ACTH stimulation was unchanged and the 4-week NEB-CAN-09 and 12-week Pesant studies did not show an effect on basal, non-stimulated cortisol levels.

DMEP Response: Basal cortisol levels provide only limited information about the integrity of the HPA axis. Provocative testing is needed to fully assess this axis. Unchanged results to acute ACTH stimulation (BEL-55) are not reassuring (please see responses to 1a).

Sponsor's Claim: Nebivolol did not have consistent effects on aldosterone and renin levels across clinical studies. The Sponsor attributed the statistically significant decrease in basal, non-stimulated plasma renin levels in NEB-CAN-09 to the known class effect of beta-blockers on the renin-angiotensin-aldosterone system.

DMEP Response: The aldosterone and renin results from all the studies are uninterpretable because the investigators did not control for dietary sodium intake and body position. These confounders probably contributed to the inconsistent results. Additionally, even correctly obtained random aldosterone and renin measurements offer limited information about the integrity of the renin-angiotensin-aldosterone system, unless there are large changes in results.

Sponsor's Claim: Nebivolol did not affect basal, non-stimulated LH, FSH, estradiol, progesterone, or testosterone in men and women in the 4-week NEB-CAN-09 study.

DMEP Response: The LH, FSH, estradiol, and progesterone results are uninterpretable in women because these were not timed appropriately with regard to the menstrual cycle in the pre-menopausal group. Furthermore, progesterone levels were lowered in men, but for unclear reasons no statistical tests were applied to that data. The null results with regard to LH, FSH, and testosterone in men contradict the 4-week data from the Rakhmatullaeva study.

Sponsor's Claim: Nebivolol did not affect basal, non-stimulated LH, prolactin, or testosterone levels in men and women in the 7-day NEB-BEL-52 study. Nebivolol did not affect basal, non-stimulated FSH, LH, estradiol, prolactin, or testosterone levels in men in the 7-day NEB-BEL-55 study.

DMEP Response: These were only short-term studies using 5 mg/day nebivolol and do not rule-out an effect of long-term nebivolol on these parameters. The lack of difference in estradiol levels in BEL-55 cannot be definitely concluded because in this cross-over study there was a carry-over effect of nebivolol on estradiol levels measured at the end of the placebo treatment period for the subjects who received nebivolol first.

Sponsor's Claim: In NEB-BEL-52, there was a normal response of ACTH, cortisol, prolactin, and growth hormone to insulin-induced hypoglycemia, confirming overall integrity of the HPA.

DMEP Response: There were documented changes to the HPA axis after only 7 days of therapy with nebivolol 5 mg daily – please see response to 1a.

Sponsor's Claim: In Rakhmatullaeva's study (12-weeks of 5 or 10 mg daily nebivolol), baseline LH and FSH were significantly higher and mean baseline testosterone levels were significantly lower in a group of hypertensive men compared with normotensive controls. At the end of treatment, mean values for these hormones in patients with hypertension approached the baseline values of the control group

DMEP Response: Please see responses to 1a and 1f.

- e. If none of the above studies are sufficient to rule out a possible endocrine effect of nebivolol in humans, what are our recommendations for further testing or clinical trials in humans to better determine this?

DMEP Response: We recommend a randomized, well-designed study of 3 months duration testing up to the 10 mg recommended maximum dose of nebivolol in both men and women. Comparison could be to placebo and to an active treatment (e.g. another commonly used beta-blocker, such as atenolol). Compliance with study medication should be assessed to ensure adequate nebivolol exposure. This study should collect bloods for hormones at the appropriate time of the day and the appropriate time of the menstrual cycle. Detailed methods of hormone collection and analyses should be presented. In addition to basal, unstimulated hormone levels, provocative testing should be performed to more fully test the reserve of the hormonal system (where appropriate) with long-term nebivolol use. For the cortisol response, relying solely on a high-dose ACTH test is inadequate. Other testing (e.g. insulin-induced hypoglycemia, low-dose ACTH test) should also be performed. Free sex-hormones concentrations should be measured in addition to total sex-hormone levels. Finally, the clinical significance of changes in the hormonal parameters should be assessed (e.g. sexual dysfunction questionnaire, menstrual changes, etc.).

- f. In the Rakhmatullaeva study, nebivolol decreased luteinizing hormone (LH) and follicle stimulating hormone (FSH) and increased testosterone. Rakhmatullaeva attributes this finding to the antihypertensive effect of nebivolol. Do we agree or do these changes reflect nebivolol's endocrine effect in humans?

DMEP Response: Assuming the results are valid, it is not possible to determine from the Rakhmatullaeva study whether the changes in LH, FSH, and

testosterone are due to the anti-hypertensive effect or an endocrinologic effect of nebivolol. Furthermore, the positive 4-week findings in this study contrast with the null 4-week testosterone results in NEB-CAN-09. Therefore, we would consider the results from this study as “hypothesis-generating” and recommend confirmation in a well-designed trial. Such a trial could compare the LH, FSH, and testosterone effects of nebivolol to that of another anti-hypertensive agent that does not alter these parameters and also capture clinical information regarding hypogonadal symptoms.

2. In the 13 week study in mice and rats (Appendix 7), there appears to be a significant dose-related decrease in the percentage of normal sperm and sperm count in the mouse. There was also a significant dose-dependent increase in adrenal and prostate weight and a significant decrease in the weight of the seminal vesicles that did not completely normalize during recovery. Dose-dependent Leydig cell hyperplasia was noted. LH increased significantly and estradiol decreased by Week 13 in the nebivolol 40 mg/kg/day mouse model. Several estradiol measurements were not obtained because they were apparently below the limit of quantification of the assay. Is the assay adequate for appropriately interpreting the changes in estradiol seen in this study? Do these study results rule out a possible endocrine effect of nebivolol?

DMEP Response: Defer to Pharmacology-toxicology.

3. Do we agree that nebivolol exerts no unique or clinically relevant adverse effects on adrenal function at therapeutic dosing regimens?

DMEP Response: No. There is a signal from the 7-day insulin study (BEL-52) suggesting that nebivolol may affect the integrity of the HPA axis. Methodological issues with most of the studies limit conclusions and do not assure us that the endocrinologic profile of nebivolol has been adequately studied.

4. Do we agree that the pre-clinical reproductive tract observations are not clinically relevant?

DMEP Response: Defer to Pharmacology-toxicology.

5. Do we agree that the reproductive/developmental toxicity profile of nebivolol is consistent with the beta-antagonist class?

DMEP Response: Defer to Pharmacology-toxicology.

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NDA 21,742

References:

Lithell H. Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. Diabetes Care. 1991; 14: 203-9.

Salvatori R. Adrenal insufficiency. JAMA. 2005; 294: 2481-8.

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6/21/05

Memorandum

To: File: NDA 21-742 nebivolol _____ for hypertension
Stockbridge, Norman: Acting Director, HFD-110

From: Director, ODEI

Date: June 21, 2005

Subject: Nebivolol

Nebivolol is a long-marketed (European) beta blocker with some in vitro cardioselectivity and complex, incompletely studied metabolism. As all reviewers indicate, the striking increase in leydig cell tumors in mice must be "explained" before N can be approved. There may indeed be an "endocrine mechanism," but this needs to be established and shown to be irrelevant to humans. I note also that there is not yet an acceptable trade name.

There are, I believe 3 issues of interest: cardioselectivity, the presence of active metabolites and complex mixtures of parents (both isomers) and metabolites and subset differences in response. Given the flat dose-response, I am not concerned about the second of these but the situation could make assessment of cardioselectivity difficult.

1. Cardioselectivity

Based on Dr. Hicks' reviews (pg 68) of supportive studies, it appears that essentially all beta-1 blockade is contributed by d-N with little by L-N, and that it is quite selective (250-350 fold). In the past we have required studies in asthmatics (single dose) showing a smaller effect on airway resistance for a drug seeking a "cardioselective" claim. There is in fact a study (GBR-22) in normals examining the effect of N atenolol and propanolol on specific airway conductance (SGaw), showing less effect by N. We need to decide whether this study provides sufficient evidence for a cardio-selective claim.

2. Complex Metabolites

Given the 2D6 metabolism and active metabolites, and the marked affect of hepatic failure on AUC, it could be very difficult to know how any individual would respond to N. Fortunately, and like most beta blockers, the DIR for BP is pretty flat, over a 30 fold range in the case of N, so these concerns are clinically minimal. It would therefore be of interest to study DIR for summarized beta blockade i.e., capturing effects of both parents and

metabolites using steady state exercise HR or, conceivably, isoproterenol infusions, in normals and 2D6 poor metabolizers over the dose range of 1.25 to 30-40 mg. In fact there is an isoproterenol infusion study (Hicks pg 75), showing increasing effects of N 5, 10 and 20 mg, pretty similar to atenolol and propranolol, as well as an exercise study (Hicks pg 76), in which I-N had no effect on an exercise induced heart rate increase, indicating little or no activity. In another study I-N had no effect at all on HR and BP. It thus seems fairly clear that the seemingly complex situation may be simpler than it first appears. The I-isomer may have little activity. I could not find data on the metabolites, but as noted, over the 5-20mg range, N looks like any other BB.

3. Racial and other subset differences in response

The DIR for S/D pressure in 4 studies is shown in the table below (from Karkowsky review)

| Studies | | Change in BP (S/D), plbo – subtracted, sitting | | | | | | |
|---|----|--|---------|---------|---------|---------|---------|----------|
| | | Dose | 1.25 | 2.5 | 5 | 10 | 20 | 40 |
| 302 12 week n=909 PM=6.5% Mean baseline=100 BP=60 909 | n | | 83 | 82 | 165 | 166 | 166 | 166 |
| | BP | | 6.6/5.1 | 8.5/5.6 | 8.1/5.5 | 9.2/6.3 | 8.7/6.9 | 11.7/8.3 |
| | | | | | | 244 | 244 | 244 |
| 305 12 week Mean baseline=99 n=807 PM=6.2% | n | | | | | | | |
| | BP | | | | | 3.5/2.8 | 3.1/3.9 | 6.3/4.5 |
| 202 12 week Mean baseline=100 N=300 PM=2% | n | | | 49 | 50 | 51 | 50 | 51 |
| | BP | | | 1.5/2.9 | 2.6/4.9 | 6.0/6.1 | 7.3/6.0 | 6.8/5.5 |
| 321 12 week n=669 PM=5.4% | n | | | | 168 | 168 | 166 | |
| | BP | | | | 5.7/3.2 | 3.7/3.3 | 6.2/4.7 | |

Although study 302 could suggest that although doses of 1.25 and 2.5 mg are effective in whites, 5mg is needed for blacks, and your figure could also suggest that the difference all turns on two data points in study 302, and study 305 in a mixed population looks very similar to 202. Probably 2.5-5mg, or even 10mg, is a reasonable starting dose for both races. There seems little consequence (see safety discussion below) to such a starting dose and needless titration simply delays control. If we agree that there is clear evidence of cardioselectivity, the higher starting dose might be a problem. As noted, peak and trough effects are essentially identical, even at low doses (Incidentally, I get peak/trough of 0.74 for study 302, dose 1.25 for sitting DBP, not the 1.4 Dr. Karkowsky has on pg 19; the 2.5 dose is similar. The reason is that the values in his table 9 are trough to peak, not peak to trough. See e.g., Hicks review pg 136).

As Dr. Karkowsky notes, there seems to be little effect of age (≤ 65 vs > 65) gender, or even metabolizer status an adverse effects.

As Dr. Karkowsky notes, there were 2 deaths (ANII, sudden death post pericarditis). Neither suggest a role for N. The discontinuation table and serious event table do not suggest increasing rates with dose, conceivably exceptive brachycardia (at 20mg). There was, as noted, a single case of angioedema (no ACEI), but also some cases in the Janssen database. The 3 cases of liver disease (Lemtouni) do not suggest a drug relationship. I note that there was an attempt at a thorough QT that did not manage more than 3/70 PMs, and that used a maximum dose of 40mg. Although I believe the 3 days at dose probably did get close to steady state for parent drug (> 4 half lives), that does not exactly stress the system, but the data captured from the clinical trials are pretty reassuring (QTc by Bazett or Fridiricia is decreased compared to placebo).

For non-serious ADR's, there is a suggestion that headache, diarrhea, and fatigue may be drug-induced.

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NDA 21-742

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Response to Consultation Request

Consult Date May 24, 2005

To Karen Hicks, M.D.
Medical Officer HFD 110

From Audrey Gassman, M.D.
Medical Officer HFD 580

Lynnda Reid, PhD
Pharmacology/Toxicology Team Leader HFD 580

Through Shelley R. Slaughter, M.D., Ph.D.
Team Leader, HFD 580

Daniel Shames, M.D.
Director, Reproductive and Urologic Drug Products, HFD 580

Subject Response to Consultation Request from Division of
Cardiorenal Drug Products (HFD-110) dated December 21, 2004,
regarding the reproductive toxicology of Nebivolol, a beta-1 antagonist
being developed for the treatment of mild to moderate hypertension.

Introduction

The Division of Cardiorenal Drug Products (HFD-110) has sent a Request for Consultation to the Division of Reproductive and Urologic Drug Products (HFD-580) requesting our advice concerning Nebivolol, a beta-1 antagonist being developed for the treatment of hypertension. Nebivolol will be used chronically, and the dosing will range from a starting dose of 2.5 mg daily to 20 mg daily. The specific questions posed from HFD-120 are:

1. How would one develop a study to further evaluate cyclicity in female mice and rats (and to rule out a stress-induced effect)? What study duration is required? Does cyclicity need to be evaluated in male rodents as well, and do we also need to be concerned about stress-induced effects in male rodents?
2. There is a concern that Nebivolol administration to women may result in disrupted cyclicity. Given this, what specific parameters would need to be followed in a future study? Could these parameters be evaluated in Protocol 324? Since men do not "cycle," am I correct in assuming no further testing in men would be required?

June 21, 2005

Materials Reviewed

Materials reviewed were from a brief Pharmacology/Toxicology Email Review of studies contained in IND 33,060 dated 19-May-05, and a Medical Officer's Review dated 30-Apr-04.

Brief Background

Janssen Pharmaceutica Products, LP, Bertek Pharmaceuticals, Inc., and A. Menarini LTD developed nebivolol. In the late 1980s and early 1990s, Janssen performed approximately 65 clinical trials in 2874 patients in the United States and Europe. According to the sponsor, 2,570 of these 2,874 patients received nebivolol for the treatment of hypertension. Most of the nebivolol doses studied were less than 10 mg; however, Janssen also studied doses up to 30 mg in short-term dose-finding studies. Approximately 400 patients received nebivolol for 12 months or longer at doses of 5 mg.

On May 1, 1998, Bertek Pharmaceuticals, Inc., a subsidiary of Mylan, assumed ownership of IND 33,060 and subsequently performed six pivotal studies with nebivolol in patients with mild to moderate hypertension in the United States, the United Kingdom, the Netherlands, and Belgium from May 2002 until present. The pivotal studies, comprised of NEB-302, NEB-305, NEB-202, NEB-321, NEB-306, and NEB-203, evaluated 2,800 patients with hypertension. A total of 2,464 out of these 2,800 patients received nebivolol in doses ranging from 1.25 mg to 40 mg. Additionally, NEB-122 studied electrocardiographic changes in 281 healthy subjects. NEB-323, performed by the sponsor, is a study assessing the safety and efficacy of long-term nebivolol exposure (up to 24 months) in patients with mild to moderate hypertension and is ongoing at the time of this NDA. For NDA 21-742, Bertek Pharmaceuticals performed and submitted 94 primary safety and efficacy studies included 6 primary studies and 62 supportive studies performed by Janssen.

The preclinical evaluation included a number of reports where the original sponsor (Janssen) simply states that the drug has affected cyclicity. The original applicant did not do vaginal cytology, but in the histopathology there are findings of decreased numbers of corpora lutea, increased numbers of atretic follicles, and other indicators of decreased activity. In some cases, there are changes in adrenal histology and body weight loss, but the panoply of clinical chemistry changes that one would expect to see is usually not there.

There are also reports of altered cyclicity where there are no indications of adrenal changes. In the teratogenicity studies some alterations in bone structure in both rats and rabbits were noted.

Reproductive Findings in Animals

Several of the preclinical studies may suggest that Nebivolol may affect the endocrine axis.

1. There have been statements in several study reports that the reproductive tract is one of the target organs of toxicity. One of the statements is quoted here:
“The adrenocortical, ovarian and testicular changes in the 160 mg/kg dosed groups are directly related to the interference of the test article with steroid metabolism. This interference results in a hormonal imbalance as evidenced by the organ weight changes of the adrenals and the ovaries, by the swelling of the adrenals and by the severely decreased serum cholesterol levels.”

Of note, the data supporting this statement were not made available to the reviewing Division.

2. Study EDMS-PSDB-2876162 reported drug-related changes in cyclic activity after 1 week of 40 mg/kg nebivolol followed by 1 week of 60 mg/kg nebivolol. There were no differences in body weight compared to the control group. There were insufficient doses in this study to assess either a dose-response effect or dependence upon adrenal changes. N88268, a one month intravenous administration study in rats showed a 9% ($p < 0.01$) decrease in female “gonad” weight at 5 mg/kg/day. There were no associated adrenal changes, body weight changes or other indicators of stress effects. The study did not provide the data to assess cyclicity in association with the organ weight changes. Changes in female “gonad” weight and histologic changes indicative of changes in cyclicity have been reported in multiple studies. In some cases, these changes have been associated with weight loss and adrenal changes. Overall, the effects upon the female reproductive tract are incompletely characterized.
3. Dystocia has been reported in at least 3 studies (N92750, N106655, N65774) but with incidences clearly reported for only 2 studies. Dystocia has been reported to occur with doses of nebivolol ≥ 5 mg/kg.
4. Prolonged gestation was reported in study N92570 with increased duration of gestation 0.5 days longer than control ($p < 0.01$) at 40 mg/kg. The report for study N106655 indicated increased duration of gestation at the HD of 20 mg/kg. The increase was 1 day longer than control ($p < 0.05$).
5. The Segment III developmental studies are inconsistent with regard to the effects of late gestation/lactation exposure on the offspring.

Recommendations

Questions:

1. **How would one develop a study to further evaluate cyclicity in female mice and rats (and to rule out a stress-induced effect)? What study duration is required? Does cyclicity need to be evaluated in male rodents as well, and do we also need to be concerned about stress-induced effects in male rodents?**

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The data in rodents is inconsistent and there does not appear to be any reported adverse effects on the adrenals or reproductive organs in the 12-month dog study. Although serum triglycerides and cholesterol levels were consistently decreased in rodent toxicology studies, mechanistic studies in mice demonstrated no change in ACTH stimulation, increases in testosterone levels in males, and inconsistent changes in corticosterone levels in males and females. In the multigenerational reproductive and developmental study in rats, this reviewer believes that there is no significant difference in the numbers of corpora lutea and implantations between F1 offspring exposed in utero to vehicle or Nebivolol. The fertility rate was reduced in offspring of dams treated at 5 mg; however, the cause of this reduction was not explored as to whether it was related to male or female infertility or potentially to delayed sexual maturation of the offspring.

To explore potential effects on disruption of estrus cyclicity in rodents it would be necessary to conduct a study specifically addressing this issue, preferable in female rats. Cyclicity should be monitored for at least 6 weeks. Histopathology of the adrenal glands and ovaries should be performed. If any changes in cyclicity are observed, a subset of animals should be observed to determine the time to restoration of normal estrus cycling and reversibility of any histopathology findings.

It is not necessary to evaluate cyclicity in male animals.

2. There is a concern that Nebivolol administration to women may result in disrupted cyclicity. Given this, what specific parameters would need to be followed in a future study? Could these parameters be evaluated in Protocol 324? Since men do not "cycle," am I correct in assuming no further testing in men would be required?

It is unclear what aspect of reproduction (hypothalamic, pituitary or ovarian axis) is being affected by Nebivolol, and whether these findings would be applicable to humans. A de novo clinical study to target disruption of cyclicity would be difficult to design given the limited human information available. Data obtained from previously collected clinical trial information would not be helpful as no baseline endocrinologic or menstrual diary information was collected. In addition, it would be difficult to estimate the number of patients that were reproductive aged that actually initiated treatment with normal menstrual cycles in the previously performed studies.

The Cardiorenal reviewer provided a copy of a new clinical protocol for Nebivolol. Protocol 324 is an open-label, randomized, titration to effect, multi-center study of up to 1000 patients, (18 years or older), of the safety, tolerability and blood pressure effects of metoprolol versus nebivolol alone or in combination with amlodipine or HCTZ.

Reviewer's comments: Protocol 324 could assist in determining the effect of nebivolol monotherapy on menstrual cyclicity by menstrual diary evaluations. In all reproductive age female subjects regardless of mode of contraception:

- *Perform gynecological examinations including a pap smear if needed at baseline. Repeat the gynecological exam at the end of therapy.*
- *In order to assess treatment effects on menstrual cycles, have subjects use diaries for at least two complete cycles to record menstruation and/or irregular bleeding. If there is a disruption of the menstrual cycle, provide post treatment follow-up to document return of normal function. Subjects would need 3 to 6 months of pretreatment menstrual cycle diary data to determine their true cyclicality.*
- *Follow on-treatment pregnancies for outcome information.*

However, the Applicant should decide whether they wish to better characterize the effects of Nebivolol in reproductive age women in a more detailed endocrine study. The Applicant could consider a more detailed endocrine study in a subset of women to better characterize the effects of treatment on hormonal and reproductive function. This would include serum concentrations of LH, FSH, and free and total testosterone obtained early in the proliferative phase of the cycle and a serum progesterone obtained in the midluteal phase of the cycle. These profiles should be done at baseline, on treatment, and post treatment.

Men do have a very short spermatogenic cycle (90 days) that requires an intact hypothalamic-pituitary-testicular axis. However, there is no evidence from the animal studies that Nebivolol significantly impacts spermatogenesis per se. In addition, there is no evidence that the reproductive effects of Nebivolol would not be reversible in men given the short spermatogenic cycle of 90 days. Therefore, no additional studies in men should be required at this time.

Clinical Recommendations:

- 1. Protocol 324 could assist in determining the effect of nebivolol monotherapy on menstrual cyclicality by menstrual diary evaluations. In all reproductive age female subjects regardless of mode of contraception:**
 - **Perform gynecological examinations including a pap smear if needed at baseline. Repeat the gynecological exam at the end of therapy.**
 - **In order to assess treatment effects on menstrual cycles, have subjects use diaries for at least two complete cycles on Nebivolol treatment to record menstruation and/or irregular bleeding. If there is a disruption of the menstrual cycle, provide post treatment follow-up to document return of normal function. Prior to this, the Applicant would need to document a minimum of 3 – 6 menstrual cycles prior to the treatment cycles to determine the true cyclicality of the patient.**
 - **The Applicant should follow any on-treatment pregnancies for pregnancy outcomes**
 - **The Applicant could consider collecting the menstrual cycle data obtained with metoprotolol as a control group.**
- 2. In contrast, the Applicant should consider whether they wish to better characterize the effects of Nebivolol in reproductive age women in a more detailed endocrine study. The Applicant could consider a more detailed**

endocrine study in a subset of women to better characterize the effects of treatment on hormonal and reproductive function. This would include serum concentrations of LH, FSH, and free and total testosterone obtained early in the proliferative phase of the cycle and a serum progesterone obtained in the midluteal phase of the cycle. These profiles should be done at baseline, on treatment, and post treatment. In addition to the endocrine profiles, menstrual cycle data would also be collected.

3. At this time, no male reproductive studies appear to be indicated.
4. Please feel free to reconsult us at the time of labeling negotiations.

DRUDP thanks you for the opportunity to provide consultation on the above issues. We are available to assist further if needed.

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/s/

Audrey Gassman
6/21/05 11:06:57 AM
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Lynnda Reid
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PHARMACOLOGIST

Shelley Slaughter
6/21/05 11:21:21 AM
MEDICAL OFFICER
I concur.

Daniel A. Shames
6/22/05 06:06:09 PM
MEDICAL OFFICER

5/9/05



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-742 (nebivolol for hypertension)

Sponsor: Bertek Pharmaceuticals

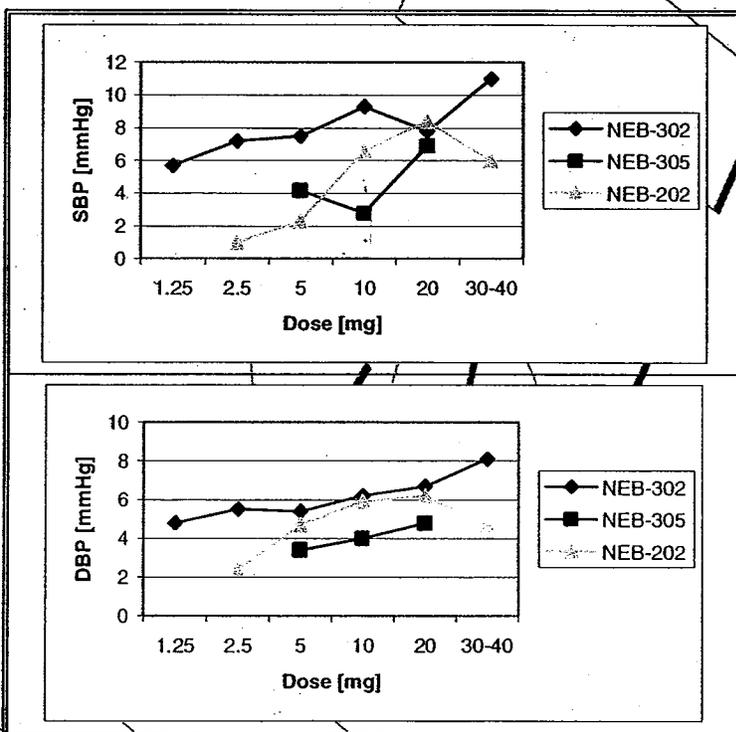
Review date: 8 May 2005

From: N. Stockbridge, M.D., Ph.D., Acting Director, HFD-110

To: Dr. Robert Temple, Director, ODE-I

This memo conveys my support for taking an "Approvable" action for this NDA.

For your convenience, I have extracted trough seated systolic and diastolic blood pressure data from the three dose-ranging studies. These are raw means; mostly Dr. Hicks's review focuses mainly on the least squares estimates.



I note that the lowest dose studies, 1.25 mg, had about half of the effect of the highest dose (40 mg). The trough-peak ratio is high and does not appear to be dose-related. Race makes a small difference, but the drug works well in blacks. Extensive or poor metabolizer status makes some difference pharmacokinetically, but the dose-response is so flat that it is of little consequence.

Aside from pretty clearly supporting once-daily dosing, there is nothing particularly advantageous about nebivolol for hypertension.

As you are aware, there are two possibly related findings that warrant resolution prior to approval. The first is a dose-related increase in Leydig cell tumors in mice. Two observations suggest that these findings relate to hormonal effects. One is that the finding was not seen in rats, consistent with differences in the hormonal regulation of rats and mice. The other observation is the lack of apparent gene toxicity. On the other hand, the rate of tumorigenesis in mice was remarkable high and was manifest at exposure levels close to clinical relevance.

The second finding is of reproductive toxicity in rats, again with exposure close to the clinically relevant levels.

These are unusual findings for a beta-blocker.

The sponsor and the review team have been in numerous discussions with the sponsor developing a plan to resolve these issues. As Dr. Karkowsky's memo summarizes, there are two parts to such a plan. The first is to develop an understanding of the endocrinological correlates of the phenomena in the affected species and the second part is to show that the endocrine effects do not occur in man. The animal studies are underway, I believe, without implementing a late suggestion to include another beta blocker.

Labeling negotiations have simply avoided the pharm-tox section.

There appears to be no ongoing development program for another indication.

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/s/

Norman Stockbridge
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4/22/05

**CLINICAL REVIEW: ALL INDIVIDUAL SUPPORTIVE
STUDIES**

Application Type NDA
Submission Number 21,742
Submission Code 000

Letter Date April 29, 2004
Stamp Date May 4, 2004
PDUFA Goal Date February 28, 2005

Reviewer Name Karen A. Hicks
Review Completion Date January 21, 2005

Established Name Nebivolol
(Proposed) Trade Name _____
Therapeutic Class Selective β 1 blockade
Applicant Bertek Pharmaceuticals, Inc.

Priority Designation S

Formulation PO
Dosing Regimen 2.5 mg, 5 mg, 10 mg
Indication Hypertension
Intended Population Adults

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1 REVIEW OF INDIVIDUAL SUPPORTIVE STUDIES

The Agency reviewed all supportive studies submitted by the sponsor. None of these studies altered the efficacy results of the Pivotal studies. Table 1 and Table 2 provide a list of the supportive studies. The reviews for the individual studies may be found either within the Tables or in the section following Table 1 and Table 2. The number prior to the study title corresponds to # in the Table.

The reviews were performed as follows:

- Dr. Maryann Gordon reviewed Studies #25 through #30 and #70 through #93.
- Dr. Karen A. Hicks reviewed Studies #1 through #24, #39, #40, #41, #43, #44, #46 through #69, and #134 through #151.
- Dr. Katharine R. Lillie reviewed Studies #73 and #76.
- Dr. Juan Carlos Pelayo reviewed Studies #94 through #133.
- Dr. Shari Targum reviewed Studies #31 through #38, #42, and #45.

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Table 1. List of Supportive Studies (all reviewed)

| # | LMD No. | Study ID | Title | Study Category/ Type/Design |
|----|---------|-------------------------------------|---|---|
| 1 | N/A | 1270_01_00 | Comparative Effects of Nebivolol, Nebivolol Enantiomers, Atenolol, Metoprolol, Carvedilol and Bucindolol on Human Endothelial Cell Nitric Oxide Release Following Acute Treatment | Molecular pharmacology, Nitric oxide effects, In vitro |
| 2 | N/A | 1273_01_00 | Comparative Effects of Nebivolol, Nebivolol Enantiomers, and Six Nebivolol Metabolites on Endothelial Nitric oxide Release from Human Endothelial Cells following Acute Treatment | Molecular pharmacology, Nitric oxide effects, In vitro |
| 3 | N/A | 1332_01_00 Same as 1332_00_00 | Comparative Effects of Nebivolol Metabolites 4,5'-dihydroxy, 4,8'-dihydroxy, Glucuronide, Nebivolol and Nebivolol Enantiomers on Endothelial Cells following Acute Treatment | Molecular pharmacology, Nitric oxide effects, In vitro |
| 4 | N/A | 1333_00_00 | Comparative Effects of Nebivolol and Atenolol on Nitric Oxide Release from Human Endothelial Cells following Chronic Treatment | Molecular pharmacology, Nitric oxide effects, In vitro |
| 5 | N/A | 1334_00_00 | Comparative Effects of Nebivolol and Atenolol on Nitric Oxide Release in Black and Caucasian Endothelial Cells following Chronic Treatment | Molecular pharmacology, Nitric oxide effects, In vitro |
| 6 | N/A | 1271_01_00 | Effects of Nebivolol and ACE-Inhibitors on Endothelial Nitric Oxide Release in Black and Caucasian Donor Endothelial Cells following Chronic Treatment | Molecular pharmacology, Nitric oxide effects, In vitro |
| 7 | N/A | 1269_01_00 | Separate and Combined Effects of Nebivolol and ACE-Inhibitors on Human Endothelial Cell Nitric Oxide Release following Acute Treatment | Molecular pharmacology, Nitric oxide effects, In vitro |
| 8 | N/A | 1268_01_00 | Effects of Acute Nebivolol Treatment on Nitric Oxide Release and Vascular Function in Normal versus Diseased Mesenteric Arteries | Molecular pharmacology, Nitric oxide effects, In vitro |
| 9 | N/A | 1312_01_00 | Adrenergic Receptor Pharmacology of Nebivolol in the Human Heart | Molecular Pharmacology, Beta adrenergic receptor affinity, In vitro |
| 10 | N/A | 1311_01_00 | Adrenergic Receptor Pharmacology of Nebivolol, its Enantiomers and Nine Metabolites in the Human heart | Molecular pharmacology, Beta adrenergic receptor affinity, In vitro |
| 11 | 59897 | N/A | Response to Isoprenaline after Single Intravenous and Oral Application of Nebivolol: Time Course. Clinical Research Report. January 1988. | Pharmacodynamics, Beta blockade, Open-label |

| # | LMD No. | Study ID | Title | Study Category/ Type/Design |
|----|--------------------------|----------|--|---|
| 12 | 59988 | NED-6 | Isoprenaline Dose-Response in Man after a Single 5 mg Intravenous Dose of Nebivolol and After Oral Application of Nebivolol 5 mg Once Daily for One Week. Clinical Research Report NEB-NED-6. February 1988. | Pharmacodynamics, Beta-blockade, Open-label |
| 13 | 84265 92890 106646 | GBR-20 | Clinical Pharmacology of Nebivolol (Drug Investigation; 3 (suppl. 1): 31-32, 1991) A Comparative Study of the Relative Beta-Blocking Potency, and Beta-1 selectivity of Nebivolol, Propranolol and Atenolol in Healthy Volunteers. A Comparative Study of the Potency and Relative Beta-1 Selectivity of Nebivolol, Propranolol and Atenolol in a Group of Healthy Volunteers. Clinical Research Report NEB-GBR-20, May 1994 | Pharmacodynamics, Beta-blockade, Single-blind, placebo-controlled |
| 14 | 108078 | BEL-20 | Determination of the Acute and Subacute Beta-Sympatholytic Activity of d-, l-, and dl Nebivolol compared to Atenolol and Placebo, in Inhibiting Exercise-Induced Tachycardia. Synoptic Clinical Research Report NEB-BEL-20. April 1994 | Pharmacodynamics, Beta-blockade, Double-blind, placebo-controlled |
| 15 | 108084 | NED-5 | Time Course of Beta-Blockade with Nebivolol. Synoptic Clinical Research Report NEB-NED-5. January 1988 | Pharmacodynamics, Beta-blockade, Open-label |
| 16 | 106922 | GBR-29 | A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol Isomers on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-29. | Pharmacodynamics, Vasodilation, Double-blind, cross-over |
| 17 | 107421 | GBR-23 | A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol Isomers on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-23. | Pharmacodynamics, Vasodilation, Open-label |
| 18 | 107422 | GBR-25 | A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-25. | Pharmacodynamics, Vasodilation, Open-label, cross-over |
| 19 | 107423 | GBR-28 | A Study to Investigate the Mechanism of the Vasodilator Effect of Nebivolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-28. | Pharmacodynamics, Vasodilation, Open-label, cross-over |
| 20 | 107424 | GBR-27 | A Study to Compare the Effect of Nebivolol and Atenolol on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-27. | Pharmacodynamics, Vasodilation, Open-label, cross-over |

| # | LMD No. | Study ID | Title | Study Category/ Type/Design |
|----|--------------------|----------|--|--|
| 21 | 136347 | GBR-31 | A Study to Investigate the Vasodilator Effect of Nebivolol Racemate and Isomers on Forearm Blood Flow in Healthy Volunteers. Clinical Research Report NEB-GBR-31. July 1997. | Pharmacodynamics, Vasodilation, Double-blind, cross-over |
| 22 | 101180 | SWE-5 | Nebivolol—Effects on Peripheral Arterial and Venous Blood Flow. Clinical Research Report NEB-SWE-5. November 1993. | Pharmacodynamics, Vasodilation, Double-blind, placebo-controlled, cross-over |
| 23 | 49278 | N/A | Effect of a Single Oral Intake of R67555 (5 mg and 10 mg) and of a 7-Day Intake of R67555 (5 mg/day) on ECG. Clinical Research Report. February 1986. | Pharmacodynamic, Hemodynamic, Open-label, cross-over |
| 24 | 59987 | N/A | Invasive Haemodynamics of Nebivolol: Effects of a Single 5 mg Intravenous Injection and a 5 mg Oral Dose of Nebivolol Once Daily for 1 week on Blood Pressure, Heart Rate, Central Venous Pressure, Cardiac Output, Stroke Volume and Total Peripheral Resistance. Clinical Research Report. February 1988. | Pharmacodynamic, Hemodynamic, Open-label |
| 25 | 64808 | BEL-19 | Effect of Nebivolol 10 mg and 20 mg versus Placebo on Heart Rate, Blood Pressure, Systolic Time Intervals and Side Effects. A Double-Blind Placebo-Controlled Cross-Over Study in Healthy Volunteers. Clinical Research Report NEB-BEL-19. January 1989. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, cross-over |
| 26 | 65661 | BEL-17 | Phase I Study: Effect of Nebivolol on Dopamine Related Phenomena. Part II: Haemodynamic Effects. Clinical Research Report NEB-BEL-17. February 1989. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled cross-over |
| 27 | 65662 65669 | BEL-32 | Cardiac Haemodynamic effects of d-, l-, dl-Nebivolol and Atenolol during a 7-day Double-Blind Cross-Over Study in Healthy Volunteers. Clinical Research Report NEB-BEL-32. March 1989. Effects of Isometric Handgrip on Blood Pressure and Heart Rate during a 7-day Double-Blind Cross-Over Treatment with dl-, d-, and l-Nebivolol and Atenolol in Healthy Volunteers. Clinical Research Report NEB-BEL-32, January 1989. | Pharmacodynamic, Hemodynamic, Double-blind, active-controlled |
| 28 | 68085 | BEL-21 | Phase I Study: Comparison of the Subacute Haemodynamic Effects of l-Nebivolol versus a Combination of l-Nebivolol and Atenolol in Healthy Volunteers. Clinical Research Report NEB-BEL-21. March 1989. | Pharmacodynamic, Hemodynamic, Double-blind, active-controlled, parallel groups |

| # | LMD No. | Study ID | Title | Study Category/ Type/Design |
|----|----------------------|---------------|---|---|
| 29 | 108085 106560 | NED-7 | Invasive Hemodynamics of Nebivolol in Hypertensive Patients. Synoptic Clinical Research Report NEB-NED-7. April 1994. Invasive Hemodynamics of Nebivolol in Hypertensive Patients. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, cross-over |
| 30 | 107433 | USA-2 | Evaluation of Left Ventricular Function Assessed with Doppler Echocardiography and Radionuclide Ventriculography in Hypertensive Patients after Chronic Treatment with Nebivolol and Atenolol. Clinical Research Report NEB-USA-2, April 1994. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, active-controlled, cross-over |
| 31 | 54549 45715 | BEL-30 | Haemodynamic Effects of a Single Oral Administration of R 65824, a New Selective Beta-1-Adrenoceptor Blocking Agent in Human Volunteers as Compared to the Effects of Atenolol, Pindolol and Propranolol. Clinical Research Report NEB-BEL-30, September 1985. Haemodynamic Effects in Man During Exercise of a Single Oral Dose of Nebivolol (R67555), a New Beta-1-Adrenoceptor Blocking Agent: a Comparative Study with Atenolol, Pindolol and Propranolol. (Drug Development Research; 8: 109-117, 1986) | Pharmacodynamic, Hemodynamic, Open-label, active-controlled, cross-over |
| 32 | 56952 | BEL-1/Part I | Hematological, Biochemical and Urinary Safety during Subacute Treatment with Nebivolol in a Double-Blind Placebo-Controlled Study. Part I, Clinical Research Report NEB-BEL-1. August 1987. | Pharmacodynamic, Safety, Double-blind, placebo-controlled, cross-over |
| 33 | 59056 | BEL-1/Part II | Double-Blind Placebo-Controlled Study Comparing the Haemodynamic Effects of Various Doses of Nebivolol during Subacute Treatment. Clinical Research Report NEB-BEL-1. June 1987. | Pharmacodynamic, Hemodynamic, double-blind, placebo-controlled, cross-over |
| 34 | 59580 | N/A | Randomized Cross-Over Study Comparing the Haemodynamic Effects during Exercise of a Single Administration of Nebivolol 0.5 mg I.V., 5 mg Tablet and 5 mg Solution in Healthy Volunteers. Clinical Research Report. March 1987. | Pharmacodynamic, Hemodynamic, Open-label, placebo-controlled, cross-over |
| 35 | 59899 | BEL-35 | Acute Haemodynamic Effects of Various Doses of Nebivolol in a Placebo-Controlled Cross-Over Study in Healthy Volunteers. Clinical Research Report NEB-BEL-35. February 1988. | Pharmacodynamic, Hemodynamic, Open-label, placebo-controlled, cross-over |

| # | LMD No. | Study ID | Title | Study Category/ Type/Design |
|----|--------------------|----------|--|---|
| 36 | 59922 | BEL-38 | Acute hemodynamic Effects of 2 Enantiomers of Nebivolol (R 67138 and R 67145) in Men at Rest and During Exercise. Clinical Research Report NEB-BEL-38. March 1988. | Pharmacodynamic, Hemodynamic, Open-label, cross-over |
| 37 | 59970 | BEL-36 | Double-Blind Study Comparing the Subacute Hemodynamic Effects in Men at Rest and During Exercise of the 2 Enantiomers of dl-Nebivolol, d-Nebivolol (R67138) and l-Nebivolol (R67145). Clinical Research Report NEB-BEL-36. March 1988. | Pharmacodynamic, Hemodynamic, Double-blind, cross-over |
| 38 | 64858 | RSA-1 | The Effects of Nebivolol on Heart Rate and Blood Pressure at Rest and During Exercise. A Dose Finding Study. Clinical Research Report NEB-RSA-1. | Pharmacodynamic, Hemodynamic, Open-label, cross-over |
| 39 | 65577 69017 | BEL-9 | Effects of Isometric Handgrip on Blood Pressure and Heart Rate During a 14-day Double-Blind Cross-Over Treatment with Nebivolol and Atenolol in Healthy Volunteers. Clinical Research Report NEB-BEL-9. January 1989. Non-Invasive Cardiac Haemodynamics of Nebivolol in Man. (Acta Antwerpiensa; 6(2): 2-21, 1989) | Pharmacodynamic, Hemodynamic, Double-blind, active-controlled, cross-over |
| 40 | 106561 | NED-11 | Pharmacological Properties of Nebivolol in Man | Hemodynamic, Single-blind, cross-over |
| 41 | 65660 | BEL-15 | Double-Blind Placebo-Controlled Cross-Over Study Evaluating the Acute Haemodynamic Effects of dl-Nebivolol 5 mg, d-Nebivolol 2.5 mg and l-Nebivolol 2.5 mg in Healthy Volunteers. Clinical Research Report NEB-BEL-15. February 1989. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, cross-over |
| 42 | 68099 | RSA-5 | The Effects of Nebivolol on Heart Rate and Blood Pressure at Rest and During Exercise. A Sub-Acute Dose Finding Study. Clinical Research Report NEB-RSA-5. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, parallel groups |
| 43 | 88216 | SWE-1 | Nebivolol—Blockade of Exercise Induced Tachycardia. Clinical Research Report NEB-SWE-1. March 1991. | Pharmacodynamic, Hemodynamic, Single-blind, placebo-controlled, active-controlled, cross-over |
| 44 | 88260 | GBR-19 | The Effect of Nebivolol on Heart Rate, Blood Pressure and Cardiac Output at Rest and During Exercise in Healthy Volunteers. February 1991. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled |
| 45 | 106914 | BEL-26 | Cardiovascular and Metabolic Effect of d-, l- and dl-Nebivolol. Synoptic Clinical Research Report NEB-BEL-26. September 1994. | Pharmacodynamic, Hemodynamic, Double-blind, cross-over, placebo-controlled, parallel group |

| # | LMD No. | Study ID | Title | Study Category/ Type/Design |
|----|---------|----------------|---|---|
| 46 | 106917 | BEL-25(a) | Comparison of the Metabolic Effects of Nebivolol and Atenolol During Dynamic Exercise Part 1: Healthy Volunteers. Synoptic Clinical Research Report NEB-BEL-25(a). September 1994. | Pharmacodynamic, Hemodynamic, Double-blind, active-controlled, cross-over |
| 47 | 106918 | BEL-25(b) | Comparison of the Metabolic Effect of Nebivolol and Atenolol During Dynamic Exercise Part 2: in Patients with Borderline HT and/or Abnormally Quick Rise of BP During Exercise. Synoptic Clinical Research Report-NEB-BEL-25(b). September 1994. | Pharmacodynamic, Hemodynamic, Double-blind, active-controlled, cross-over |
| 48 | 108077 | BEL-16 | Comparative Study on the Effects of Nebivolol (2.5 and 5 mg) and Atenolol (50 mg) on Renal Blood Flow at Rest and on Energy Liberation During One Hour Submaximal Dynamic Exercise in Normal Individuals. A Pilot Study. Synoptic Clinical Research Report NEB-BEL-16. June 1994. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, cross-over |
| 49 | 92970 | INT-2 | Effect of Nebivolol (5 mg) on Exercise Induced Tiredness in Essential Hypertension. A Double-Blind, Randomized Comparison with Atenolol (50 mg) and Placebo, After a 4-week Placebo Run-In Period. Clinical Research Report NEB-INT-2. August 1993. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-controlled, active-controlled, cross-over |
| 50 | 107426 | GBR-4 | A Comparison of the Haemodynamics of Nebivolol and Atenolol in Hypertensive Patients. Clinical Research Report NEB-GBR-4. December 1993. | Pharmacodynamic, Hemodynamic, Double-blind, placebo-run in, active-controlled, cross-over |
| 51 | 59898 | N/A | Haemodynamic Effects of Subacute Treatment with Nebivolol: A Comparison Between Poor and Normal Metabolizers. February 1988. | Pharmacodynamic, Hemodynamic, Open-label, parallel group |
| 52 | 62826 | BEL-4/Part I | Comparison of the Subacute Haemodynamic Effects of Nebivolol in Poor and Normal Metabolizers. Part I. Clinical Research Report NEB-BEL-4. May 1988. | Pharmacodynamic, Hemodynamic, Open-label, parallel group |
| 53 | 62269 | BEL-4/Part II | Effect of an 8-day Intake of Nebivolol 5 mg/day on ECG in 6 poor and 6 Normal Metabolizers. Part II. Clinical Research Report NEB-BEL-4. May 1988. | Pharmacodynamic, Hemodynamic, Open-label, parallel group |
| 54 | 62270 | BEL-4/Part III | Multiple Dose Study of Nebivolol in Poor and Normal Metabolizers. Analysis of the Safety Data. Part III. Clinical Research Report NEB-BEL-4. May 1988. | Pharmacodynamic, Hemodynamic, Open-label, parallel group |
| 55 | 69145 | BEL-17/Part I | Effect of Nebivolol on Dopamine Related Phenomena. Part I: Hormonal Effects. Clinical Research Report NEB-BEL-17. June 1989. | Pharmacodynamic, metabolic/endocrine, Double-blind, placebo-controlled, cross-over |

| # | LMD No. | Study ID | Title | Study Category/ Type/Design |
|----|---------|----------|---|--|
| 56 | 101048 | BEL-52 | Effects of Nebivolol on Hormonal Responses to Insulin Induced Hypoglycaemia. Clinical Research Report NEB-BEL-52. December 1993. | Pharmacodynamic, Metabolic/endocrine, Open-label |
| 57 | 107434 | BEL-39 | The Influence of Chronic Treatment with Nebivolol or Atenolol on the Control of Glucose Levels in Diabetic Patients. Clinical Research Report NEB-BEL-39. August 1994. | Pharmacodynamic, Metabolic/endocrine, Double-blind, placebo-controlled, cross-over |
| 58 | 113227 | BEL-55 | The Effects of a One Week Administration of Nebivolol 5 mg o.d. on the Endocrine System and on Lipid Peroxidation in Healthy Male Volunteers. Clinical Research Report NEB-BEL-55. January 1996. | Pharmacodynamic, Metabolic/endocrine, Double-blind, placebo-controlled, cross-over |
| 59 | 106748 | ITA-5 | Efficacy and Tolerance of Nebivolol Compared to Atenolol in Non-Insulin Dependent Diabetics with Essential Hypertension. Clinical Research Report NEB-ITA-5. October 1994. | Pharmacodynamic, Metabolic/endocrine, Double-blind, placebo-run in, active-controlled, parallel groups |
| 60 | 125153 | CAN-7 | Clinical Evaluation of the Effects of Nebivolol vs. Atenolol on Plasma Lipid Profile and Carbohydrate Metabolism in Normometabolic Patients with Mild-to-Moderate Hypertension. Clinical Research Report NEB-CAN-7. October 1997. | Pharmacodynamic, Metabolic/endocrine, Double-blind, active-controlled, parallel groups |
| 61 | 126525 | CAN-8 | A Prospective Comparison of the Effects of Nebivolol and Atenolol on Glucose, Insulin and Lipid Metabolism During Long-Term Treatment in Patients with Mild to Moderate Essential Hypertension and Impaired Glucose Intolerance. Clinical Research Report NEB-CAN-8. February 1998. | Pharmacodynamic, Metabolic/endocrine, Double-blind, active-controlled, cross-over |
| 62 | 92864 | N/A | A Study to Assess the Effects of Nebivolol on Sedation and Psychomotor Performance. | Pharmacodynamic, Psychomotor/sedation, Double-blind, placebo-controlled, cross-over |
| 63 | 107425 | GBR-14 | A Study of the Possible Pharmacokinetic and Psychomotor Interactions of Alcohol and Nebivolol in Healthy Volunteers. Clinical Research Report NEB-GBR-14. March 1994. | Pharmacodynamic, Psychomotor/sedation, Double-blind, placebo-controlled, cross-over |
| 64 | 106642 | GBR-22 | Effect of Nebivolol on Lung Function in Normal Subjects: A Comparison with Atenolol and Propranolol. Clinical Research Report NEB-GBR-22. December 1989. | Pharmacodynamic, Pulmonary, Double-blind, placebo-controlled, active-controlled, cross-over |
| 65 | 92579 | ITA-2 | Open Trial with Nebivolol 5 mg Once Daily in Hypertension with Renal Artery Stenosis. Clinical Research Report NEB-ITA-2. March 1993. | Pharmacodynamic, Renal, Open-label, placebo-run in |

| # | LMD No. | Study ID | Title | Study Category/ Type/Design |
|----|---------|----------|--|--|
| 66 | 49643 | N/A | Randomized Double-Blind Cross-Over Study of the Effects of Topical R67555 as Compared with Timolol on the Intraocular Pressure, Blood Pressure and Heart Rate in Human Healthy Volunteers. April 1986. | Pharmacodynamic, Ophthalmic, Double-blind, active-controlled, cross-over |
| 67 | 51686 | N/A | Randomized Double-Blind Cross-Over Study of the Effects of Topical R67555 as Compared with R67555 Solvent and Timolol, on the Intraocular Pressure, Blood Pressure and Heart Rate in Human Healthy Volunteers. July 1986 | Pharmacodynamic, Ophthalmic, Double-blind, active-controlled, cross-over |
| 68 | 46816 | N/A | Safety Data after Oral Administration of R65824 5 mg/day for 7 Consecutive Days in 6 Human Volunteers. December 1985. | Pharmacodynamic, Safety, Open-label |
| 69 | 46817 | N/A | Safety Data After a Single Oral Administration of 5 mg and 10 mg of R65824 in 8 Human Volunteers. December 1985. | Pharmacodynamic, Safety, Open-label |

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Studies Sponsored by Janssen

| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|----|---------------------|---------------------------------|---|---|---|
| 70 | 88035 | INT-1 US Study Results | Report of U.S. Study Results in an International Trial: Nebivolol in the Treatment of Essential Hypertension (A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study). Clinical Research Report NEB-INT-1. March 1992. | Janssen, Hypertension Double-blind, Placebo- controlled, Parallel groups | Sample size/Mean change from baseline at endpoint intent-to-treat (supine or sitting DBP at trough mm Hg) [^] Placebo: 42/-3.0 0.5 mg: 42/-5.4 1 mg: 42/-4.7 2.5 mg: 43/-5.5 5 mg: 44/-9.1 10 mg: 41/-8.7 [^] unless otherwise noted |
| 71 | 101220 | INT-1 Non- US | The Effect of Nebivolol (0.5, 1, 2.5, 5, and 10 mg) in the Treatment of Essential Hypertension. A Double-Blind, Randomized Comparison with Placebo in an International Dose-Finding Trial. Clinical Research Report NEB-INT-1. March 1992. | Janssen, Hypertension Double-blind, Placebo- controlled, Parallel groups | Placebo: 84/-3.3 0.5 mg: 83/-4.0 1 mg: 87/-6.0 2.5 mg: 85/-7.1 5 mg: 86/-9.2 10 mg: 84/-10.1 |
| 72 | 106572 92891 | USA-1 | A Pilot Study to Compare the Cardiac Effects of Nebivolol and Atenolol. Synoptic Clinical Research Report NEB-USA-1. April 1994. Comparison of Antihypertensive and Beta-1-Adrenoceptor Antagonist Effect of Nebivolol and Atenolol in Essential Hypertension. (Clinical and Experimental Hypertension; 15(3): 501-509, 1993). | Janssen, Hypertension Double-blind, Placebo- controlled, Parallel group, Active-controlled, Cross-over | 1. Diastolic and systolic blood pressures were reduced to the same extent by nebivolol and atenolol; 2. PEP/LVET as an indirect measure for left ventricular performance shows a favorable decrease in the nebivolol 10 mg group compared to the unchanged value after atenolol. |
| 73 | 84315 | USA-3 | Double-Blind, Placebo-Controlled Study of Nebivolol 30 mg in Hypertensive Patients. Clinical Research Report NEB-USA-3. February 1991. | Janssen, Hypertension Double-blind, Placebo- controlled, Parallel groups | N=8 nebivolol, N=4 placebo. See complete review for full details. |
| 74 | 88185 | USA-4 | Nebivolol in the Treatment of Essential Hypertension (A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study). Clinical Research Report NEB-USA-4. May 1992. | Janssen Double-blind, Placebo- controlled, Parallel groups | Placebo: 46/-3.7 2.5 mg: 46/-6.4 5 mg: 44/-7.2 30 mg: 44/-10.1 |

| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|----|---------|-----------|---|---|---|
| 75 | 106916 | USA-6 | Nebivolol in Congestive Heart Failure: a Placebo-Controlled, Double-Blind, Dose-Titration, Pilot Study. Clinical Research Report NEB-USA-4. November 1994. | Janssen, Other cardiovascular condition Double-blind, Placebo-controlled, Parallel groups | Placebo: 19 Nebivolol: 19 6-Minute Walk Test At the overall endpoint, the walking distance for subjects on placebo was significantly increased compared to baseline ($p \leq 0.04$), whereas there was no significant increase in subjects on nebivolol. |
| 76 | 101044 | BEL-3/6 | Double-Blind, Placebo-Controlled, Multicentre Trial with Oral Nebivolol 2.5, 5 and 10 mg Once Daily in Essential Hypertension, Followed by an Open Nebivolol 5 mg Treatment for Up to 4 Years. Clinical Research Report NEB-BEL-3/6. November 1993. | Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups | Placebo: 35/-11.3 2.5 mg: 35/-15.7 5 mg: 34/-16.1 10 mg: 32/-15.7 See complete review for full details. |
| 77 | 101219 | BEL-12/18 | The Effect of Nebivolol (0.5, 1, 2.5 and 5 mg) in the Treatment of Essential Hypertension. A Double-Blind, Randomized Comparison with Placebo in a Dose Finding Trial Followed by an Open Long-Term Follow-Up. Clinical Research Report NEB-BEL-12/18. June 1994. | Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups, Open-label | Placebo: 41/-9.4 0.5 mg: 37/-12.5 1 mg: 41/-10.6 2.5 mg: 42/-17.0 5 mg: 42/-14.4 |
| 78 | 122133 | FRA-6 | Comparison of Efficacy and Tolerability of Nebivolol Combined with Nitrendipine and Placebo Combined with Nitrendipine in the Treatment of Hypertension Resistant to Nitrendipine. Clinical Research Report NEB-FRA-6. June 1998. | Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups | Nebivolol + nit: 12/-12.4 Placebo + nit: 12/-9.4 |
| 79 | 92707 | GBR-1 | Effect of Nebivolol (5 mg) in Essential Hypertension. A Double-Blind, Randomized Comparison with Atenolol (50 mg) and Placebo. Clinical Research Report NEB-GBR-1. April 1994. | Janssen, Hypertension Double-blind, Placebo-controlled, Active-controlled, Parallel groups | Nebivolol: 119/-12.6 Atenolol: 121/-12.2 Placebo: 124/-4.9 |
| 80 | 111607 | GER-12 | Clinical Evaluation of the Antihypertensive Efficacy and Safety of Nebivolol versus Amlodipine in Elderly Patients with Confirmed Mild to Moderate Essential Hypertension. Clinical Research Report NEB-GER-12. May 1995. | Janssen, Hypertension Double-blind, Active-controlled, Parallel groups | Nebivolol: 41/-13.4 Amlodipine: 27/-14.6 |

| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|----|---------------------|----------|--|---|--|
| 81 | 101221 | INT-3 | Nebivolol versus Enalapril in the Treatment of Essential Hypertension. Multicenter International Nebivolol Trial. Clinical Research Report NEB-INT-3. May 1994. | Janssen, Hypertension Double-blind, Active-controlled Parallel groups | 5 mg Nebivolol: 205/-12.3 10 mg Enalapril: 205/-9.8 |
| 82 | 92909 109101 | INT-4 | Effect of Nebivolol and its Enantiomers in Hypertensive Patients. Comparison with Placebo and Atenolol. Clinical Research Report NEB-INT-4. June 1993. Nebivolol Long-Term Treatment in Patients with Essential Hypertension. Synoptic Clinical Research Report NEB-INT-4. December 1994. | Janssen, Hypertension Double-blind, Placebo-controlled, Active-controlled, Cross-over, Open-label | N=30 d,l nebivolol: -11.8 d nebivolol: -11.5 Atenolol: -11.5 l nebivolol: -2.1 Placebo: -4.3 |
| 83 | 106562 | INT-7 | Nebivolol versus Enalapril in the Treatment of Essential Hypertension. Multicenter International Long-Term Follow-Up Nebivolol Trial. Clinical Research Report NEB-INT-7. November 1994. | Janssen, Hypertension Double-blind, Active-controlled, Parallel groups | Nebivolol: 31/-1.2 Enalapril: 32/-0.3 |
| 84 | 10122 | INT-5 | Nebivolol versus Nifedipine in the Treatment of Essential Hypertension. Multicenter International Nebivolol Trial. Clinical Research Report NEB-INT-5. July 1994. | Janssen, Hypertension Double-blind, Active-controlled, Parallel groups | Nebivolol: 92/1.3 Nifedipine: 90/0.3 |
| 85 | 129816 | INT-8 | Nebivolol versus Nifedipine in the Treatment of Essential Hypertension (Long-Term Extension). Clinical Research Report NEB-INT-8. June 1998. | Janssen, Hypertension Double-blind, Active-controlled, Parallel groups | Nebivolol: 91/-11.2 Nifedipine: 85/-10.6 |
| 86 | 101182 | ITA-3 | Left Ventricular Hypertrophy and Systolic Function in Hypertensive Patients During Long-Term Treatment with Nebivolol. A Randomized, Double-Blind Trial versus Atenolol. Clinical Research Report NEB-ITA-3. June 1998. | Janssen, Hypertension Double-blind, Active-controlled Parallel groups | Primary parameter: Left ventricular mass index, g/m ² : <u>Mean at Baseline/endpoint</u> Nebivolol: 162.7/147.3 (n=24*) Atenolol: 168.0/149.9 (n=24*) * End systolic values for secondary echocardiography parameters were available in only half of the patients |

| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* | | | | | | | | |
|--|--------------------|-------------------|---|--|--|--|--------------------|--|------------------|-------------------|---|-------------|------------|
| 87 | 101224 | TCH-1/2 | A Double-Blind Comparative Trial of the Effects of Metoprolol and Nebivolol in Hypertensive Patients. Clinical Research Report NEB-TCH-1/2. December 1993. | Janssen, Hypertension Double-blind, Active-controlled, Parallel groups | See Table below. | | | | | | | | |
| <table border="1"> <thead> <tr> <th rowspan="2">Therapeutic results (n = number of patients with efficacy data)</th> <th colspan="2">Double-blind phase</th> </tr> <tr> <th>nebivolol (n=82)</th> <th>metoprolol (n=73)</th> </tr> </thead> <tbody> <tr> <td>Primary parameters • Supine DBP, mm Hg mean at baseline/endpoint</td> <td>102.6/85.3*</td> <td>102.8/87.5</td> </tr> </tbody> </table> <p>(Reproduced from Sponsor, Study ID TCH 1/2, page 8)</p> | | | | | | Therapeutic results (n = number of patients with efficacy data) | Double-blind phase | | nebivolol (n=82) | metoprolol (n=73) | Primary parameters • Supine DBP, mm Hg mean at baseline/endpoint | 102.6/85.3* | 102.8/87.5 |
| Therapeutic results (n = number of patients with efficacy data) | Double-blind phase | | | | | | | | | | | | |
| | nebivolol (n=82) | metoprolol (n=73) | | | | | | | | | | | |
| Primary parameters • Supine DBP, mm Hg mean at baseline/endpoint | 102.6/85.3* | 102.8/87.5 | | | | | | | | | | | |
| 88 | 107416 | CAN-9 | Protocol for the Clinical Evaluation of the Antihypertensive Efficacy and Safety of Nebivolol (R67555) and d-Nebivolol (R85547) in Patients with Confirmed Mild to Moderate Essential Hypertension. Clinical Research Report NEB-CAN-9. October 1994. | Janssen, Hypertension Double-blind, Cross-over | <p>DBP trough sitting (Mean at Baseline/Last Available Visit)</p> <p>Nebivolol: 30 (99/91)</p> <p>d-nebivolol: 30 (99/90)</p> <p>Hormones (renin, progesterone, testosterone, ACTH, aldosterone, cortisol, LH, FSH, estradiol): no clinically significant between treatment changes. Significant decrease from baseline in plasma renin concentration following nebivolol and d-nebivolol.</p> | | | | | | | | |

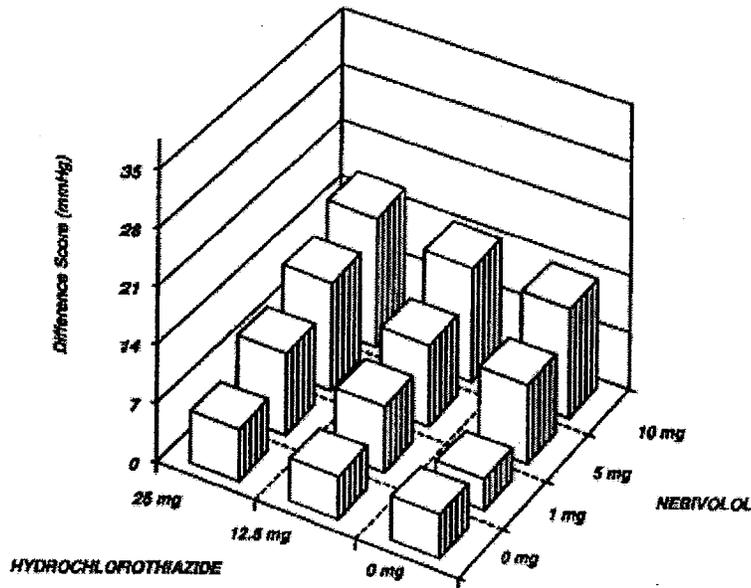
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| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|----------------|---------------|--|---|---|--------------------------------------|--|---------------|--------------------|-----------------|----------------|------------------------|--|--|--|--|--|---|--|--|--|--|--|-------|-----------|-----------|-----------|-----------|-----------|----------------|----------|----------|----------|----------|-------|-----------|-----------|-----------|-----------|-----------|----------------|----------|----------|----------|----------|----------------------------|--|--|--|--|--|-------|-----------|----------|----------|----------|----------|----------------|----------|----------|----------|----------|-------|-----------|----------|----------|----------|----------|----------------|----------|----------|----------|----------|
| 89 | 108086 | RSA-6 | A Comparison of the Effects of Nebivolol and Atenolol Against Placebo and Nitrates on Venous Tone Using Plethysmography. A Double-Blind Cross-Over Controlled Study with Hypertensive Patients. Synoptic Clinical Research Report NEB-RSA-6. March 1994. | Janssen, Hypertension Double-blind, Placebo-controlled, Active-controlled, Cross-over | See Table below. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1"> <thead> <tr> <th colspan="2">Pharmacodynamic and clinical results</th> <th>end of run-in</th> <th>nebivolol (n = 21)</th> <th>atenolol (n=20)</th> <th>placebo (n=21)</th> </tr> </thead> <tbody> <tr> <td colspan="6">Plethysmography</td> </tr> <tr> <td colspan="6">• maximum venous outflow, ml/min/100 ml: mean ± SEM</td> </tr> <tr> <td rowspan="2">• arm</td> <td>pre nitro</td> <td>41.2±1.63</td> <td>39.9±1.77</td> <td>42.1±2.08</td> <td>40.4±2.01</td> </tr> <tr> <td>post-pre nitro</td> <td>5.7±0.80</td> <td>4.6±0.89</td> <td>5.7±0.81</td> <td>6.3±0.84</td> </tr> <tr> <td rowspan="2">• leg</td> <td>pre-nitro</td> <td>40.7±2.23</td> <td>39.2±1.90</td> <td>41.0±1.81</td> <td>40.1±2.33</td> </tr> <tr> <td>post-pre nitro</td> <td>6.8±0.62</td> <td>4.9±0.88</td> <td>6.0±0.81</td> <td>6.0±0.65</td> </tr> <tr> <td colspan="6">• venous volume, ml/100 ml</td> </tr> <tr> <td rowspan="2">• arm</td> <td>pre nitro</td> <td>2.4±0.08</td> <td>2.5±0.07</td> <td>2.6±0.07</td> <td>2.6±0.05</td> </tr> <tr> <td>post-pre nitro</td> <td>0.3±0.02</td> <td>0.3±0.02</td> <td>0.3±0.03</td> <td>0.2±0.03</td> </tr> <tr> <td rowspan="2">• leg</td> <td>pre nitro</td> <td>2.6±0.14</td> <td>2.6±0.12</td> <td>2.7±0.10</td> <td>2.7±0.08</td> </tr> <tr> <td>post-pre nitro</td> <td>0.1±0.03</td> <td>0.2±0.05</td> <td>0.2±0.03</td> <td>0.2±0.02</td> </tr> </tbody> </table> <p>(Reproduced from Sponsor, Study ID RSA-6, page 2)</p> | | | | | | Pharmacodynamic and clinical results | | end of run-in | nebivolol (n = 21) | atenolol (n=20) | placebo (n=21) | Plethysmography | | | | | | • maximum venous outflow, ml/min/100 ml: mean ± SEM | | | | | | • arm | pre nitro | 41.2±1.63 | 39.9±1.77 | 42.1±2.08 | 40.4±2.01 | post-pre nitro | 5.7±0.80 | 4.6±0.89 | 5.7±0.81 | 6.3±0.84 | • leg | pre-nitro | 40.7±2.23 | 39.2±1.90 | 41.0±1.81 | 40.1±2.33 | post-pre nitro | 6.8±0.62 | 4.9±0.88 | 6.0±0.81 | 6.0±0.65 | • venous volume, ml/100 ml | | | | | | • arm | pre nitro | 2.4±0.08 | 2.5±0.07 | 2.6±0.07 | 2.6±0.05 | post-pre nitro | 0.3±0.02 | 0.3±0.02 | 0.3±0.03 | 0.2±0.03 | • leg | pre nitro | 2.6±0.14 | 2.6±0.12 | 2.7±0.10 | 2.7±0.08 | post-pre nitro | 0.1±0.03 | 0.2±0.05 | 0.2±0.03 | 0.2±0.02 |
| Pharmacodynamic and clinical results | | end of run-in | nebivolol (n = 21) | atenolol (n=20) | placebo (n=21) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Plethysmography | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| • maximum venous outflow, ml/min/100 ml: mean ± SEM | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| • arm | pre nitro | 41.2±1.63 | 39.9±1.77 | 42.1±2.08 | 40.4±2.01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | post-pre nitro | 5.7±0.80 | 4.6±0.89 | 5.7±0.81 | 6.3±0.84 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| • leg | pre-nitro | 40.7±2.23 | 39.2±1.90 | 41.0±1.81 | 40.1±2.33 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | post-pre nitro | 6.8±0.62 | 4.9±0.88 | 6.0±0.81 | 6.0±0.65 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| • venous volume, ml/100 ml | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| • arm | pre nitro | 2.4±0.08 | 2.5±0.07 | 2.6±0.07 | 2.6±0.05 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | post-pre nitro | 0.3±0.02 | 0.3±0.02 | 0.3±0.03 | 0.2±0.03 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| • leg | pre nitro | 2.6±0.14 | 2.6±0.12 | 2.7±0.10 | 2.7±0.08 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | post-pre nitro | 0.1±0.03 | 0.2±0.05 | 0.2±0.03 | 0.2±0.02 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 90 | 101046 | NED-12/8 | Nebivolol in the Treatment of Essential Hypertension. A Multicenter, Double-Blind, Cross-Over, and Single-Treatment Trial with An Open Long-Term Follow-Up. Clinical Research Report NEB-NED-12/8. April 1994. | Janssen, Hypertension Double-blind, Placebo-controlled, Cross-over | Placebo: 80/-2.3 Nebivolol: 80/-10.6 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 91 | 92691 | NED-13/10 | The Efficacy and Safety of Nebivolol in Severe Hypertension. A Randomized, Placebo-Controlled Cross-Over Trial Followed by 11 Months of Open Nebivolol Treatment. Clinical Research Report NEB-NED-13/10. September 1993. | Janssen, Hypertension Double-blind, Placebo-controlled, Cross-over | Placebo: 19/-5.3 Nebivolol: 19/-14.4 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|----|---------|----------|--|---|-------------------|
| 92 | 107414 | CAN-3 | Multicentre Clinical Evaluation of Antihypertensive Efficacy and Safety of the Combination of Nebivolol and Hydrochlorothiazide: HANS (Hydrochlorothiazide and Nebivolol Study). Clinical Research Report NEB-CAN-3. October 1994. | Janssen, Hypertension Double-blind, Placebo-controlled, Parallel groups | See Figure below. |

Display 5c: Mean Difference from Baseline Scores for Trough Sitting Diastolic Blood Pressure (mmHg) - Week 4



(Reproduced from Sponsor, Study ID CAN-6, Display 5c, page 62)

| | | | | | |
|----|--------|-------|---|---|---|
| 93 | 107415 | CAN-6 | Clinical Evaluation of the Antihypertensive Efficacy and Safety of Nebivolol versus Lisinopril in Patients with Confirmed Mild to Moderate Essential Hypertension. Clinical Research Report NEB-CAN-6. July 1994. | Janssen, Hypertension Double-blind, Active-controlled, Cross-over | (Clinic BP: A responder is defined as patients having a sitting DBP < 90 mm Hg or decrease \geq 10 mm Hg) % Responders: Lisinopril: 29/52% Nebivolol 29/41% |
|----|--------|-------|---|---|---|

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| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|-----|---------|----------|---|---|--|
| 94 | 101047 | POR-1/5 | Nebivolol in the Treatment of Essential Hypertension. A Multicenter Open and Double-Blind Trial with An Open Long-Term Follow-up. Clinical Research Report NEB-POR-1/5. December 1993. | Hypertension Double-blind, Placebo- controlled, Open- label | 2.5 mg: 133/-12.2 Placebo: 46/+8.2 2.5 mg: 47/+3.6 |
| 95 | 109042 | BEL-23 | Tolerability of Nebivolol in Patients with Essential Hypertension. Synoptic Clinical Research Report NEB-BEL-23. November 1994. | Hypertension Open-label, Dose- escalation | Week 1: 22/10 mg; Week 2: 22/15 mg; Week 3-6: 22/20 mg. No DBP results, dosage-dependent AEs |
| 96 | 108081 | GER-5 | Double-Blind Trial of Nebivolol versus Placebo in the Treatment of Essential Hypertension. Synoptic Clinical Research Report NEB-GER-5. September 1994. | Hypertension Double-blind, Placebo- controlled, Parallel groups | Placebo: 15/-1.7 2.5 mg: 15/-3.6 5.0 mg: 15/-11.0 |
| 97 | 108083 | NED-4 | Efficacy, Pharmacodynamics, Pharmacokinetics and Safety of Open Nebivolol Treatment (2.5 mg and 7.5 mg) in Hypertensive patients. Synoptic Clinical Research Report NEB-NED-4. December 1993. | Hypertension Open-label | 2.5 mg: 6/-9.0 7.5 mg: 6/-16.0 |
| 98 | 109089 | NED-9 | Tolerability of Nebivolol in Patients with Essential Hypertension. Synoptic Clinical Research Report NEB-NED-9. November 1994. | Hypertension Open-label | Week 1: 10/10 mg; Week 2: 10/15 mg; Week 3-4: 10/20 mg. No DBP results, dosage-dependent AEs |
| 99 | 84288 | MEX-1 | Long-Term Therapy with Nebivolol in Patients with Hypertension. (Drug Investigation; 3 (suppl. 1): 180-182, 1991). | Hypertension Open-label | 5.0 mg (3 mos.): 40/-13.1 5.0 mg (6 mos.): 35/-15.2 |
| 100 | 84283 | NED-1 | Nebivolol. An Acute and Long Term Study in Essential Hypertension. (Drug Investigation;(suppl. 1): 152-154, 1991). | Hypertension Single-blind, Placebo- controlled | Placebo: 9/+7.0 5.0 mg (4 wks.): 9/-18.0 |
| 101 | 108082 | NED-2 | Effect of a Single Dose of Nebivolol in Hypertensive Patients: Dose-Finding. Synoptic Clinical Research Report NEB-NED-2. December 1987. | Hypertension Open-label | Single dose 10 mg (n=5), BP ↓ > with nebivolol vs. placebo |

| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|-----|----------------------|----------|---|--|---|
| 102 | 109065 111589 | AUS-3 | A Study to Establish the Acute Effects of Nebivolol on Blood Pressure and Whether or Not There are First Dose Postural Effects in Middle Aged and Elderly patients. Synoptic Clinical Research Report NEB-AUS-3. October 1994. A Study to Establish the Acute Effects of Nebivolol on Blood Pressure and Whether or Not There are First Dose Postural Effects in Middle Aged and Elderly patients. Clinical Research Report NEB-AUS-3. March 1995. | Hypertension Double-blind, Placebo-controlled, Active-controlled, Cross-over | (n=11) Efficacy data not reported 1 st dose effect on BP & postural change (n=12): placebo, nebivolol 5 mg, labetalol 200 mg, atenolol 50 mg. Nebivolol = atenolol, labetalol worse |
| 103 | 106715 | AUS-5 | Effect of Single and Combination Therapy with Nebivolol and Enalapril and Comparison with Placebo in the Treatment of Essential Hypertension. Clinical Research Report NEB-AUS-5. October 1994. | Hypertension Double-blind, Placebo-controlled, Active-controlled, Cross-over | Placebo: 16 Nebivolol 5 mg: 19 Enalapril 10 mg: 17 Neb+Enal: 20 Neb > effect on BP Placebo & Enalapril. |
| 104 | 76693 | ARG-1 | Effects of Nebivolol on Left Ventricular Function in Patients with Essential hypertension. (Drug Investigation; 3 (suppl. 1): 155-160, 1991). | Hypertension Double-blind, Active-controlled, Parallel groups | Nebivolol 5 mg: 15/-15.1 Atenolol 100 mg: 15/-11.4 |
| 105 | 107413 | FRA-5 | Effect of Nebivolol on Arterial Hemodynamics and Compliance in Patients with Essential Hypertension. Clinical Research Report NEB-FRA-5. October 1994. | Hypertension Double-blind, Active-controlled, Parallel groups | Nebivolol 5 mg: 12/-15.7 Atenolol 100 mg: 12/-12.4 |
| 106 | 106599 | GER-9 | Double-Blind Placebo-Controlled Phase II Study of dl-Nebivolol and its d- and l-Enantiomers in Patients with Mild to Moderate Hypertension. Clinical Research Report NEB-GER-9. April 1994. | Hypertension Double-blind, Placebo-controlled, Parallel groups | Placebo: 8/+5.1 Nebivolol-dl 5 mg: 8/-7.9 Nebivolol-l 2.5 mg: 8/+1.1 Nebivolol-d 2.5 mg: 7/-16.4 |
| 107 | 106921 | MEX-2 | Nebivolol in Hypertensives; Diastolic Function. Synoptic Clinical Research Report NEB-MEX-2. October 1994. | Hypertension Double-blind, Active-controlled, Cross-over | Nebivolol 5 mg: 14/-12 Atenolol 100 mg: 14/-13 |
| 108 | 64696 | BEL-10 | Double-Blind, Placebo-Controlled Cross-Over Study with Nebivolol in Hypertensive Patients. Analysis in Haematological and Biochemical Safety Data. Clinical Research Report NEB-BEL-10. December 1988. | Hypertension Double-blind, Placebo-controlled, Cross-over | Placebo: 23/0.0 Nebivolol 5 mg: 23/-10.0 |

| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|-----|----------------------|----------|--|--|---|
| 109 | 84062 | HKG-2 | The Application of Nebivolol in Essential Hypertension: A Double-Blind, Randomized, Placebo-Controlled Study. (International J. Cardiology; 35: 387-395, 1992). | Hypertension Double-blind, Placebo-controlled, Parallel groups | Placebo: 14/0.0 Nebivolol 5 mg: 18/-5.0 |
| 110 | 109079 106927 | GBR-2 | Nebivolol and 24 Hour Blood Pressure Monitoring: A Comparison with Placebo. Synoptic Clinical Research Report NEB-GBR-2. December 1994. Nebivolol and 24 Hour Blood Pressure Monitoring: A Comparison with Placebo. Clinical Research Report NEB-GBR-2. September 1993. | Hypertension Double-blind, Placebo-controlled, Cross-over | Placebo: 14/-16.6 Nebivolol 5 mg: 14/-14.7 Placebo: 14/-4.5 Nebivolol 5 mg: 14/-11.6 |
| 111 | 153127 | CAN-10 | Evaluation of the Safety of Nebivolol 5 mg o.d. in Mild to Moderate Hypertensive Subjects Characterized as Poor Metabolizers for Debrisoquine, in Comparison to Extensive Metabolizers. Clinical Research Report NEB-CAN-10. May 2000. | Hypertension Open-label, Parallel groups | Nebivolol 5 mg: EM 23/-10.2 Nebivolol 5 mg: PM 14/-9.3 |
| 112 | 106923 | BEL-11 | Open Long-Term Treatment with 5 mg Nebivolol in Patients with Essential Hypertension. Synoptic Clinical Research Report NEB-BEL-11. November 1994. | Hypertension Open-label | Nebivolol 5 mg 1 yr: 37/-10.0 Nebivolol 5 mg 2 yr: 28/-10.0 |
| 113 | 108080 | GER-2 | Oral Treatment with Nebivolol in Hospitalized Patients with Essential Hypertension. An Open Pilot Study. Synoptic Clinical Research Report NEB-GER-2. September 1988. | Hypertension Open-label | Nebivolol 1 mg: 22/-33.5 |
| 114 | 92596 | RSA-8 | Long-Term (3-month) Effects of A New Beta-Blocker (Nebivolol) on Cardiac Performance in Dilated Cardiomyopathy. (JACC; 21(5): 1094-1100, 1993) | Other cardiovascular condition, Double-blind, Placebo-controlled, Parallel groups | Placebo: 13/+1.0 Nebivolol 1-5 mg: 11/-6.0 Nebivolol +chronotropic & -inotropic effect |
| 115 | 106915 | BEL-46 | Long-Term Effects of Nebivolol on Ischaemic Left Ventricular Dysfunction. Clinical Research Report NEB-BEL-46. October 1994. | Other cardiovascular condition, Double-blind, Placebo-controlled, Parallel groups | Placebo: 10/? Nebivolol 2.5 mg: 10/? Nebivolol 5 mg: 10/? Atenolol 50 mg: 10/? Nebivolol > exercise tolerance than atenolol |

| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|-----|------------------|----------|--|---|--|
| 116 | 101223 | TCH-4 | Clinical and Haemodynamic Effects of Nebivolol in Patients with Mild to Moderate Congestive Heart Failure. Clinical Research Report NEB-TCH-4. April 1994. | Other cardiovascular condition, Double-blind, Placebo-controlled, Parallel groups | Placebo: 29/+2.1 Nebivolol 2.5 mg: 29/-2.4 Nebivolol 5 mg: 33/-3.1 |
| 117 | 106563 | BEL-42 | Postoperative Haemodynamic Effects of Racemic Nebivolol Compared to d- and l-Nebivolol in Patients with Coronary Artery Bypass Grafting. Synoptic Clinical Research Report NEB-BEL-42. January 1994. | Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups | Nebivolol-dl 5 mg: 17/-1.3 Nebivolol-l 2.5 mg: 16/+1.8 Nebivolol-d 2.5 mg: 16/-0.2 |
| 118 | 76730 | ITA-1 | Antianginal and anti-ischæmic activity of nebivolol in stable angina of effort. (Drug Investigation; 3 (suppl. 1): 86-96, 1991). | Other cardiovascular condition Double-blind, placebo-controlled, parallel groups | Placebo: 16/? Nebivolol 5 mg: 16/? |
| 119 | 84268 | FRA-3 | Pilot Study of Cardiovascular Effects of Nebivolol in Congestive Heart Failure. (Drug Investigation; 3 (suppl. 1): 69-81, 1991). | Other cardiovascular condition, Double-blind, Placebo-controlled, Parallel groups | Placebo: 6/+6 Nebivolol 1,2.5,5 mg: 6/-1 |
| 120 | 92860 | GER-7 | Determination of the Anti-Ischemic Activity of Nebivolol in Comparison with Atenolol. (International J. Cardiology; 43: 279-289, 1994). | Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups | Nebivolol 5 mg: 12/? Atenolol 100 mg: 12/? |
| 121 | 106920 | TCH-3 | Effect of Nebivolol and Metoprolol in Patients with Coronary Artery Disease and Depressed Left Ventricular Function. Synoptic Clinical Research Report NEB-TCH-3. October 1994. | Other cardiovascular condition, Double-blind, Parallel groups | Nebivolol 5 mg: 18/-4.8 Metoprolol 50 mg: 18/-4.8 |
| 122 | 79247 | BEL-14 | Comparison of Left Ventricular Haemodynamics of Nebivolol and Metoprolol in Patients with Acute Myocardial Infarction. (Drug Investigation; 3 (suppl. 1): 140-141, 1991). | Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups | Nebivolol 5 mg: 40/-5.0 Metoprolol 100 mg: 40/-3.0 |
| 123 | 154909 107432 | NED-14 | Nebivolol versus Atenolol in Postinfarction Patients with Left Ventricular Dysfunction. Analysis Tables and Graphs. June 1993. | Other cardiovascular condition, Active-controlled, Parallel groups | Nebivolol 5 mg: 13/-7.0 Atenolol 100 mg: 15/-8.0 |

| # | LMD No. | Study ID | Title | Disease State/ Design | Efficacy Results* |
|-----|---------|-----------|--|--|---|
| 124 | 92597 | BEL-28 | Administration of Nebivolol after Coronary Artery Bypass in Patients with Altered Left Ventricular Function. (J. Cardiovascular Physiology; 22: 253-258, 1993) | Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups | Nebivolol 5 mg: 15/? Atenolol 50 mg: 15/? |
| 125 | 109097 | FRA-7 | Comparative Study of Intravenous Nebivolol, Propranolol and Labetalol in Obese Subject: Part I-Hemodynamics. Synoptic Clinical Research Report NEB-FRA-7. November 1994. | Other cardiovascular condition, Double-blind, Active-controlled, Cross-over | Nebivolol 0.07mg/kg: 19/-6 Propranolol 0.1mg/kg: 19/-4 Labetalol 0.9mg/kg: 19/-8 |
| 126 | 106528 | SWE-2 | Nebivolol – The Effect on Anginal Attacks and Exercise Tolerance in Patients with Stable Effort Induced Angina Pectoris. Clinical Research Report NEB-SWE-2. January 1994. | Other cardiovascular condition, Open-label, Placebo-controlled, Cross-over | Placebo: 10/-2 Nebivolol 2.5 mg: 10/-3 Nebivolol 5 mg: 10/-2 Nebivolol 10 mg: 10/-8 |
| 127 | 109017 | GER-10 | The Influence of Nebivolol on Haemodynamics and the Pressure-Volume Relationship in Patients with Coronary Artery Disease Undergoing Diagnostic Cardiac Catheterization. Synoptic Clinical Research Report NEB-GER-10. October 1994. | Other cardiovascular condition, Open-label | Nebivolol 2.5 mg: 7/? |
| 128 | 82501 | BEL-33 | The Effect of Nebivolol in Patients with Left Ventricular Diastolic Dysfunction. (Acta Anterwerpiensia; 1991). | Other cardiovascular condition, Open-label | Nebivolol 5 mg: 12/? |
| 129 | 80800 | BEL-24/41 | Effects of d-Nebivolol and l-Nebivolol on Left Ventricular Systolic and Diastolic Function: Comparison with d-l-Nebivolol and Atenolol. (J. Cardiovascular Pharmacology; 22: 183-190, 1993) | Other cardiovascular condition, Double-blind, Active-controlled, Parallel groups | Nebivolol-dl 2.5 mg: 9/? Nebivolol-l 1.25-2.5 mg: 22/? Nebivolol-d 1.25-2.5 mg: 22/? Atenolol 15 mg: 9/? |
| 130 | 108079 | BEL-34 | An Open Pilot Study on the Hemodynamic Effects of Nebivolol in Patients with Acute Congestive Heart Failure. Clinical Research Report NEB-BEL-34. February 1994. | Other cardiovascular condition, Open-label | Nebivolol 5 mg: 5/+4 |
| 131 | 72317 | GER-1 | Hemodynamic Effects of Nebivolol at Rest and On Exertion in Patients with Heart Failure. (Angiology; 41: 696-701, 1990). | Other cardiovascular condition, Open-label | Nebivolol 5 mg: 10/? |

[*Sample size/Mean change from baseline at endpoint intent-to-treat (supine DBP at trough mmHg).
?denotes data not available.]

Studies Sponsored by A. Menarini Ltd

| # | Study ID | Title | Sponsor/Design | Efficacy Results |
|-----|-----------------|--|---|--------------------|
| 132 | NAP 01 | Randomized, Multicenter, Multinational, Dose Ranging Placebo-Controlled Comparative Study of Nebivolol, 2.5, 5, 10 and 20 mg / day in Patients with Stable Angina Pectoris | Double-Blind, Placebo-Controlled, Parallel groups | Data not available |
| 133 | MR/01-99/01-Nhf | Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure | Multi-Centre, Multi-National, Randomized, Parallel group, Placebo-Controlled, Double-Blinded Study, Phase III | Ongoing |

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Table 2. Clinical Pharmacology Studies (all reviewed)

| # | LMD No. | Study ID | Title | Study Category/ Type/Design | Results |
|-----|---------|-----------|---|--|--|
| 134 | N/A | NEBI-0126 | Single-Dose, Dose-Proportionality Pharmacokinetic Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status | Pharmacokinetic, ADME Open-label | See complete review. |
| 135 | N/A | NEBI-0127 | Single-Dose, Relative Bioavailability and Food Effect Study of Nebivolol Hydrochloride in Healthy Volunteers Characterized According to Their Metabolizing Status September 14, 2001 – November 27, 2001 | Pharmacokinetic, ADME Open-label Single dose | No efficacy results. Single dose PK. 19 subjects enrolled, 18 subjects completed study. 1 subject did not complete the study due to personal reasons. Healthy male and female volunteers, ages 18 – 52. 8 AEs experienced by 4 subjects (headache, neck pain, chest bruising, pain, dry eyes). No deaths. Nebivolol 10 mg tablet or solution (fed and fasting) <u>For d,l-nebivolol:</u> Increased AUCL, AUCI, Cpeak with food. PMs with 20 fold increase in fasting AUCL and AUCL. PMs with 3.7 fold increase in t1/2 fasting and 4.5 fold increase in t1/2 fed. No significant ECG abnormalities. |
| 136 | N/A | NEBI-0136 | Absorption, Metabolism, and Excretion of Nebivolol in Healthy Male Volunteers after a Single Oral Dose of 15 mg ¹⁴ C-Nebivolol HCL July 27, 2001. | Pharmacokinetic, ADME Open-label | 6 fasting healthy male subjects (3 EM and 3 PM) drank a 60 mL solution containing approximately 100 µCi/15 mg (free base equivalent) ¹⁴ C-nebivolol HCL and 180 mL of water. <u>Results:</u> a. No serious AEs. b. Maximum radioactivity levels in blood plasma attained in 2 hours in EM and at 4 hours in PM c. CPEAK values of total radioactivity in blood or plasma comparable between EM and PM, but systemic exposure values based on AUCL differed 2.6 fold between EM and PM. d. The apparent terminal elimination half-lives of total radioactivity obtained from PM were longer in blood (73.1 hr) than that in plasma (60.1 hr). e. Mean blood-to-plasma total radioactivity ratios of less than 1 were observed for both CPEAK and AUCL. |
| 137 | N/A | NEBI-0142 | Metabolism of [¹⁴ C]-Nebivolol in Human: Mass Balance and Metabolite Profiling/Identification in | Pharmacokinetic, ADME Open-label | 6 male subjects (3 EMs and 3 PMs). Single oral dose of nebivolol 15 mg. Blood, urine, and feces collected up to either 14 days for EM subjects or 18 days for PM subjects. In general, 38.36% and 66.49% of administered |

| # | LMD No. | Study ID | Title | Study Category/ Type/Design | Results |
|-----|---------|-----------|--|----------------------------------|---|
| | | | <p>Plasma and Excreta</p> <p>? May 23, 2001 - February 14, 2003</p> | | <p>dose was recovered in urine and 43.57% and 13.06% of radioactivity was recovered in feces for EMs and PMs, respectively. Tmax was 2 hrs for EMs and 4 hrs for PMs.</p> <p>Major metabolic pathways include formation of glucuronides of unchanged drug, mono- to multiple-hydroxylations on alicyclic and/or aromatic rings followed by glucuronidation, and formation of N-dealkylated derivatives. Glucuronidation of d-nebivolol occurred much more rapidly than on the l-enantiomer. The ratio of d-nebivolol glucuronide/l-nebivolol glucuronide in urine was ca. 80:20. In plasma, most of the metabolites detected were glucuronides of unchanged drug in addition to oxidative N-dealkylated acid. Some oxidative hydroxylated conjugates were also detected in plasma of EM subjects, however, they were low in PM subjects.</p> <p>19 metabolites identified in feces, plasma, and urine</p> |
| 138 | N/A | NEBI-0223 | <p>A Phase I Open-Label Single-Dose Study Assessing the Pharmacokinetics of Nebivolol HCL and the Formation of Metabolites in Healthy Volunteers</p> <p>April 27, 2002</p> | Pharmacokinetic, ADME Open-label | <p>8 healthy nonsmoking males and females (4 EM and 4 PM), ages 22-38. Open-label, one period study. Single dose of nebivolol HCL 10 mg. All subjects completed the study.</p> <p><u>Results:</u> Higher nebivolol plasma concentrations (7 hrs vs. 1 hr) and a longer half-life seen in PMs compared to EMs (57 hrs for PMs, 10 hrs for EMs). 5 fold difference in maximum plasma concentration of d,l nebivolol between EM and PM subjects. Large differences in AUC between EM and PM subjects were observed (EMs: 8.982, 2.836, and 6.082 vs. PMs 272.2, 95.94, and 176.2 ng*hr/mL for d,l-nebivolol, d-nebivolol, and l-nebivolol, respectively).</p> <p>Lab, vital sign, and ECG monitoring—no safety risk. No AEs reported.</p> |

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| # | LMD No. | Study ID | Title | Study Category/ Type/Design | Results |
|-----|---------|-----------|---|-------------------------------------|---|
| 139 | N/A | NEBI-0270 | <p>A Phase I Open-Label Multiple-Dose Study Assessing the Pharmacokinetics of Nebivolol HCL in Healthy Volunteers</p> <p>Group A subjects dosed on September 7, 2002 and September 10, 2002 through September 23, 2002. Group B subjects dosed on September 28, 2002 and October 1, 2002 through October 14, 2002. Group C subjects dosed on November 2, 2002 and November 5, 2002 through November 18, 2002. Group D subjects dosed on November 30, 2002 and December 3, 2002 through December 16, 2002.</p> | Pharmacokinetic, ADME Open-label | <p>Open-label one period, multiple-dose study. 25 healthy adult, tobacco-free volunteers enrolled (17 EMs and 8 PMs). 22 subjects (16 EM and 6 PM) between the ages of 19 and 53 completed this study. Nebivolol 10 mg given on Day 1 post supervised overnight fast (at least 10 hours). Then, on Day 4, subjects received a single oral 10 mg nebivolol HCL tablet daily for 14 consecutive days.</p> <p>Results:</p> <ol style="list-style-type: none"> 1. TPEAK for EM subjects 1.2 hours for d-nebivolol, l-nebivolol, and d,l-nebivolol, compared with 2.7 hours for nebivolol glucuronides. 2. Mean TPEAK for PM subjects was 3.8, 5.7, 3.7, and 3.7 hours for d, l, d,l-nebivolol, and nebivolol glucuronides. 3. PM subjects had an approximately 5, 11, 9, and 4-fold higher mean CPEAK for d, l, d,l-nebivolol, and nebivolol glucuronides, compared with EMs. 4. PMs had mean AUCTAU values 14-fold, 43-fold, 32-fold, and 6-fold greater than their EM counterparts. 5. Mean t_{1/2} for EMS: 13, 17, 13, and 7 hours for d, l, d,l-nebivolol, and glucuronides. 6. For PMs, mean t_{1/2}: 22, 73, 56, and 33 hours for d, l, d,l-nebivolol, and glucuronides. 7. In EMs, nebivolol glucuronides statistically significant (p < 0.05) for KEL. For PMs, AUCTAU, CPEAK and HALF values at steady-state displayed a statistically significant difference relative to a single-dose administration of nebivolol glucuronides. 7. PMs will experience a 3-fold increase in peak plasma levels relative to their single-dose values following achievement of steady-state conditions. For EMs, single-dose PK disposition is indicative of what their steady-state PK disposition will be. <p>Subject 1 dropped out of study on Day 5 (9/11/2002) due to personal reasons that were not study related. Subject 16 dropped out of study on Day 12 due to an adverse experience (abdominal pain) that required hospitalization. Subject 23 dropped out on 11/2/2002 (Day 1) due to an adverse event (nausea).</p> |