This Summary of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can't be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2 Synopsis

Investigators:	The name of the principle investigator and co-investigators is given in Appendix 16.1.4.	
Clinical Trial Centers:	The study was conducted in 30 centres in Germany and 3 in Austria	
Publication:	None at the time of writing this report.	
Studied Period (Years): Date of First Enrolment: Date of Last Completed:	 20/04/2006 19/12/2008	**Phase of Development:** Phase IV Trial
Sponsor's Responsible Person:	Berlin-Chemie Menarini Glienicker Weg 125 D-12489 Berlin, Germany [redacted]	
Objectives:	Primary objective To evaluate the clinical efficacy (in terms of initial claudication distance [ICD]) and tolerability of nebivolol in comparison with hydrochlorothiazide in the treatment of patients with peripheral arterial disease (PAD) Fontaine's stage II and essential hypertension. Secondary objective(s) To assess all of the following: • Initial claudication distance (ICD) after 12 weeks treatment • Absolute claudication distance (ACD) after 12 weeks and 24 weeks treatment • ICD and ACD responders after 24 weeks of treatment • Ankle-brachial pressure index (ABI) after 12 weeks and 24 weeks treatment • Lipid profile after 24 weeks treatment • hsCRP (high sensitivity C-reactive protein) after 24 weeks treatment • Quality of life (QoL) ("Periphere Arterielle Verschlusskranktheit 86 Scale") after 24 weeks treatment • All-cause mortality • Cardiovascular mortality • Cardiovascular morbidity • Proportion of patients with cardiac catheter examinations, coronary angiography and hospitalizations.	
Methodology:	The clinical trial was conducted as a multicentre, pseudo-placebo controlled, randomized, double-blind, prospective phase IV parallel group trial with 2 independent treatment groups: 5 mg (once daily) nebivolol (Neb) and 25 mg (once daily) hydrochlorothiazide (HCT). The study included 7 scheduled visits (visit 1: day 0; visit 2: day 14 ± 2; visit 3: day 28 ± 2; visit 4: day 42 ± 2; visit 5: day 112 ± 7; visit 6:	

	day 196 ± 7; visit 7: day 224 ± 7). The study comprised three periods: • Run-in period of 4 weeks during which all patients were to adhere to a stable background anti-hypertensive medication. The adjustment of this medication was performed according to the ESH Guidelines 2003. This period also allowed exclusion of patients who showed a high variability in the measurement of the primary objective. • Double-blind treatment period lasting 24 weeks. At the end of the 4-week run-in period, those patients meeting the baseline selection criteria were allocated to nebivolol or hydrochlorothiazide for 24 weeks under double-blind conditions. • Follow-up period of 4 weeks. After withdrawal of study medication, patients underwent a follow-up period in order to assess a possible rebound phenomenon regarding the measurement of their ICD and ACD. The first visit was the screening visit at which patients were examined according to the protocol after giving written informed consent. Patients with a diagnosis of PAD Fontaine's stage II and essential hypertension and meeting the screening selection criteria underwent a 4-week run-in period. The second visit was scheduled two weeks after the screening visit (visit 2: day 14 ± 2) and was considered a screening control visit. At the end of the run-in period, the third visit or baseline visit took place (visit 3: day 28 ± 2). At this visit, all patients meeting the baseline selection criteria were randomised to be treated by either nebivolol or hydrochlorothiazide for 24 weeks. During the treatment period a safety visit (visit 4: day 42 ± 2) was scheduled 2 weeks after treatment initiation and a safety/efficacy visit (visit 5: day 112 ± 7) 12 weeks after starting the study medication. At the end of the study treatment period, patients were scheduled for visit 6 (day 196 ± 7) in which the main efficacy assessment was performed, and the study medication was withdrawn. The final visit (visit 7: day 224 ± 7) took place at the end of the 4 week follow-up period. Concomitant medication and vital signs were recorded at all visits. Patients underwent a Treadmill testing for ICD and ACD measurement at all visits except for visit 4. Doppler ultrasonography to measure the ABI was performed at visits 1, 3, 5, 6 and 7. The lipid profile and hsCRP levels were assessed at the beginning (visit 3) and end (visit 6) of treatment. Quality of life was assessed using an abbreviated version of the PAVK-86 questionnaire at visits 1, 3 and 6. Adverse events were recorded at all visits after the screening visit. Females with childbearing potential had a pregnancy test done at screening.

BERLIN-CHEMIE MENARINI	EudraCT Number:	2004-004863-32
	Trial Number:	BCBe/04/Neb-Pao/087
	Integrated Clinical Trial Report	

No. of Patients:	planned			realized				
	total	Neb	HCT	total	Neb		HCT	
	n	n	n	n	n	%	n	%
Randomized	172	86	86	177	91	51.4	86	48.6
Evaluable - safety	172	86	86	177	91	51.4	86	48.6
- efficacy*								
- ITT	172	86	86	163	84	51.5	79	48.5
- PP	128	64	64	127	65	51.2	62	48.8

Neb = Nebivolol, HCT = Hydrochlorothiazide, ITT = Intention To Treat, PP = Per Protocol.
*A 20% drop out was considered.

Diagnosis / Indication and Main Criteria for Inclusion:

Indication: peripheral arterial disease with intermittent claudication in patients with essential hypertension.
The screening inclusion criteria were:

1. Written informed consent
2. ≥40 years
3. PAD Fontaine's stage II with:
   - History of typical intermittent claudication for at least 6 months with documented lesions by duplex sonography or angiography within the last 36 months prior to inclusion,
   - Actual proven PAD by objective means such as haemodynamics and non-invasive imaging or angiography,
   - History (> 1 month before study inclusion) of previous peripheral (lower extremity) vascular intervention such as surgical endarterectomy, by pass grafting or aortic abdominal aneurysm repair or PTA with or without stenting was allowed,
   - Ankle-brachial pressure index (ABI) of the worse leg < 0.90,
   - Advice on smoking cessation had been given and documented prior to inclusion in the trial; smoking habit had to be stable for at least 3 months prior to inclusion in the trial.
4. No further improvement in previous exercise training or failure of previous tried exercise training or experience of patient's lack of compliance regarding exercise training or patients unable to perform exercise training. Walking training had to be applied during the trial.
5. Hypertension according to the European Society of Hypertension Guidelines 2003 (ESH) Grade 1 (mild) and Grade 2 (moderate) (systolic blood pressure (SBP) 140-179 mmHg and/or diastolic blood pressure (DBP) 90-109 mmHg) with or without treatment with antihypertensive drugs

The baseline inclusion criteria were:

6. ASA 100 mg and/or Clopidogrel 75 mg or Phenprocoumon (Phenprocoumon stable at least three months prior screening visit) and stable background medication for the prevention or therapy of cardiovascular events like ACE inhibitors and/or AT1 inhibitors and/or calcium-channel blockers and/or statins (statins stable for ≥ 3 month before study inclusion")
7. Treadmill variability in ACD of ≤ 25% between treadmill test at visit 2 (screening control) and visit 3 (baseline)
8. ACD between 100 m and 300 m at visit 3 (baseline)
9. SBP > 130mmHg and/or DBP > 85 at baseline (visit 3)

The exclusion criteria were:

1. PAD with rest pain or leg ulcer or gangrene (Fontaine stage III –IV

	resp. critical limb ischemia (CLI): systolic ankle pressure ≤ 50 mmHg or systolic toe pressure ≤ 30 mmHg or transcutaneous partial oxygen pressure (tcpO2) ≤ 10 %) 2. Any concomitant disease limiting the exercise capacity of the patient (e.g. but not limited to: angina pectoris, heart failure, respiratory disease, orthopaedic disease, neurological disorder) 3. Standardized exercise training during the study (e.g. supervised physical group-training or individual training) or walking exercises during the study exceeding the all-day habits of the patient as compared to the patient's habits prior to study inclusion 4. Poorly controlled diabetes mellitus (HbA1c > 8.5%) 5. Orthopedic, neurological or pulmonary concomitant diseases, which limited or could have limited the walking distance. 6. Anticipated need for limb, coronary, or carotid vascular surgery or angioplasty during the trial 7. Previous treatment within the last 4 weeks prior to screening or concomitant treatment with rheologic agents (including herbal substances like Ginkgo Biloba (or Padma28)) or substances that may had influenced the progression of the PAD or the walking distances except for the trial medication and the background medication 8. Treatment with alpha-blockers or vasodilators as prostaglandin E1, prostaglandin I2 analogs, pentoxiphyllin, naftidrofuryl and buflomedil at dose stable for < 3 month before visit 1 9. Regular use of analgesics with anti-inflammatory potential, i.e. NSAIDs. Treatment on demand and ≤ 7 days, e.g. for headache was allowed 10. Treatment with COXII-Inhibitors 11. Anticipated need of newly prescribed treatment with nitrates during the study in patients not pre-treated at stable dose for ≥ 3 month with those agents at screening 12. Newly diagnosed or unstable angina pectoris (acute coronary syndrome) 13. Concomitant treatment with other beta-blockers (pre treatment can be discontinued until visit 2), HCT or diuretic agents (including combinations) except for the study medication started at visit 3. Concomitant medication Verapamil. 14. Contraindication to the study drugs: • Cardiogenic Shock • Heart failure NYHA class III or IV • Sick-sinus-syndrome including heart blocks (SA node) and/or AV block 2nd and 3rd degree and/or significant arrhythmias and/or bradycardia < 50 bpm • Hypotension with systolic blood pressure < 100 mmHg • Bronchial hyperreagibility, bronchial asthma, or history of bronchospasm • Patients with known SGPT (ALAT) and SGOT (ASAT) levels exceeding three times the upper limit of the investigator's normal range, known serum bilirubin > 1.75 mg/dl (> 30 µmol/l) or clinical evidence of severe hepatic disease or hepatic failure • Untreated phaeocromocytoma • Known metabolic acidosis • Known severe renal disease (renal failure with oliguria or

	unuria, creatinine clearance < 30 ml/min and/or serum creatinine level > 150 µmol/l [1.8 mg/100ml]) • Known acute glomerulonephritis • Known coma and praecoma hepaticum • Known articular gout • Known hypocaliaemia, hyponatriaemia, hypovolaemia, hypocalcaemia • Fructose incompatibility 15. Acute myocardial infarction and/or stroke during the last 6 months prior to screening 16. Acute pathologic haemorrhage 17. Known Hyperthyroidism 18. Patients with psychiatric diseases 19. Known hypersensitivity to nebivolol or HCT or to any of the ingredients of the study drugs, or any known hypersensitivity to beta-blocker or HCT 20. Prior or active malignancy in the previous 5 years except adequately treated basal cell/ squamous cell carcinoma of the skin or carcinoma in situ of the cervix 21. Women of childbearing potential without adequate contraception; medically acceptable methods were contraceptive implant (contraceptive injection, intrauterine device (IUD), or oral contraceptives taken for at least 3 months, which the patient agreed to continue using during the study 22. Applied for female patients with childbearing potential: pregnancy or lactation (pregnancy should be ruled out by pregnancy test) 23. Patients with a history of alcohol and/or drug abuse 24. Patients currently participating in another clinical study or who have received an investigational drug within 30 days prior to entering the study or who had participated in this trial before 25. Patients unwilling or unable to provide informed consent or to participate satisfactorily for the entire trial period.
Test Product, Dose, Mode of Administration, Batch-No.:	Trial medication: Nebilet® Active ingredient: Nebivolol Dose: 5 mg Mode of administration: oral, once daily in the morning with a glass of water Batch number: A1105081 (until 30 September 2007), A1107061 (from 1 October 2007)
Duration of Treatment for Each Patient:	24 weeks
Reference Therapy, Dose, Mode of Administration, Batch-No.:	The comparator medication was HCT Hexal® Active ingredient: Hydrochlorothiazide Dose: 25 mg Mode of administration: oral, once daily in the morning with a glass of water Batch number: A1105081 (until 30 September 2007), A1107061 (from 1 October 2007)
Criteria for Evaluation: **Efficacy:**	Primary and secondary efficacy parameters as well as the method used to assess them are listed below. Primary variables Method

	ICD	Treadmill testing to assess both ICD (= meters until onset of pain) and ACD (= total distance; pain free meters + meters walked with pain). Treadmill testing was performed in all study sites according to protocol LABS: constant speed of 3.2 km/h and a constant inclination of 12%.
	<u>Secondary variables</u> ICD and ACD	<u>Methods</u> Treadmill test
	ABI	Doppler ultrasound with a continuous wave, hand-held Doppler machine.
	Laboratory safety parameters, lipid profile, hsCRP	Standardized laboratory methods to assess laboratory safety parameters, the lipid profiles and hsCRP.
	QoL	QoL assessed with “Periphere Arterielle Verschlusskrankheit 86 Scale”.
	All-cause mortality	According to data in CRF.
	Cardiovascular mortality	Death due to a cardiovascular event including myocardial re-infarction, acute heart failure, sudden cardiac death, stroke, etc.
	Cardiovascular morbidity	Cardiovascular morbidity to be assessed upon cardio-vascular adverse events (i.e., any adverse event coded (MedDRA) to the SOC “cardiac disorders” or “Vascular disorders” or if they represented a cardiovascular procedure).
	Proportion of patients with cardiac catheter examination, coronary angiography, hospitalizations	According to data in CRF.
<u>Safety:</u>	The safety parameters were the following: - Incidence and type of adverse events - Changes of laboratory parameters (Hemoglobin, hematocrit, erythrocytes, leukocytes, thrombocytes, SGOT (ASAT), SGPT (ALAT), gamma-GT, alkaline phosphatase, bilirubin, serum creatinine, HbA1c, sodium, total cholesterol, potassium, calcium) - Changes of vital signs (heart rate and blood pressure) Adverse events were registered from visit 2 to visit 7; laboratory parameters at screening and at the end of the treatment period, while vital signs were measured at all visits.	
Statistical Methods:	Continuous variables were summarized with descriptive statistics, and categorical data were described by the number (n) and percentage (%) of subjects in each category. All data calculations were based on available data; a separate category was used to	

	present the missing observations. Comparisons among treatment groups of demographics and other baseline variables were performed using a one-way Analysis of Variance (ANOVA) for continuous measures and a chi-square test for categorical measures. For the primary efficacy variable (percent change in ICD), a two-sided 95% confidence interval for the difference was conducted in order to investigate non-inferiority as well as superiority in case of proven non-inferiority. The lower margin for the non-inferiority analysis was set as -10%. The hypothesis of non-inferiority was to be adopted if the lower bound of confidence interval was > -10%. An ANOVA model was used to adjust for any centre effect on ICD percent change. In secondary efficacy variables, the chi-square test or Fisher's exact test was used for dichotomous variables and the Wilcoxon-Mann-Whitney test for treatment comparisons of the secondary efficacy variables. The Wilcoxon rank sum test for paired data was applied to assess changes within each group. The primary efficacy analysis (non-inferiority test) was conducted in the PP set (Neb: n=65; HCT: n=62); the ITT set (Neb: n=84; HCT: n=79) was used for all secondary efficacy analysis.

SUMMARY - CONCLUSIONS

Efficacy Results

Demographics and medical history

Both treatment groups were similar in terms of demographics and baseline characteristics. At baseline, the proportion of patients with PAD Fontaine's stage II A (Neb: n=28, 33.3%; HCT: n=22, 27.8%) and PAD Fontaine's stage II B (Neb: n=56, 66.7%; HCT: n=57, 72.2%) was similar in both groups (p=0.448, chi-square test). The mean duration of hypertension and PAD was also similar between groups.

The most frequent group of concomitant diseases (besides hypertension) was metabolism and nutrition disorders SOC (132 [82%] patients) with hyperlipidemia in 67 patients (41.6%) and diabetes mellitus in 33 patients (20.5%).

Primary efficacy variable

The percentage ICD from visit 3 to visit 6 increased in both groups. In the PP set (Neb: n=65; HCT: n=62), the percent increase in ICD from visit 3 to visit 6 was 26.4 (95% CI [13.40; 39.42]) in the nebivolol group, and 32.1 (95% CI [18.41; 45.67]) in the hydrochlorothiazide group.
The difference in percent increase between groups was -5.65 (95% CI: [-23.98; 12.68]) for nebivolol. As the lower bound of the confidence interval of the difference was inferior to the pre-set non-inferiority margin of 10%, the non-inferiority of nebivolol compared with hydrochlorothiazide regarding the effects on ICD could not be confirmed. Non-inferiority could not be rejected either, as the confidence interval of the difference contained the value zero.
In absolute value, the mean ICD in the nebivolol group increased by 23.4 m (95% CI: [10.80; 35.95]) between visit 3 and visit 6 and by 32.5 m (95% CI: [16.05; 48.99]) in the hydrochlorothiazide group.
The increase in ICD observed in both groups was similar to that expected for placebo (25%); this suggests that nebivolol does not have a negative effect on the ICD in patients with PAD.

Secondary efficacy variables

For the ITT set (Neb: n=84; HCT: n=79), the percent increase in ICD between visit 3 and visit 6 was 28.3 (95% CI [15.57; 41.04]) in the nebivolol group and 26.5 (95% CI [14.43; 38.53]) in the hydrochlorothiazide group. The mean between groups difference in percent increase between these two

visits was 1.26 ± 8.67 (95% CI [-15.91; 18.43]; p=0.885) for nebivolol when adjusted for the centre.
The absolute mean ICD increase between visit 3 and visit 6 was 24.8 m (95% CI: [12.57; 36.97]) for nebivolol and 26.1 m (95% CI: [11.67; 40.44]) for hydrochlorothiazide.

An increase in ACD was also observed after 12 (visit 5) and 24 weeks (visit 6) of treatment with both study medications. The mean increase and mean percent increase was similar in both groups (p>0.4). The mean percent increase after 24 weeks of treatment was 15.79 (SD: 33.17) for nebivolol and 20.17 (SD: 46.60) for hydrochlorothiazide.

No significance between group differences were observed for the percentage of ICD and ACD responders at visit 6. The percentage of ICD responders was 27.0% (n=20) in the nebivolol group and 29.7% (n=22) in the hydrochlorothiazide group. The percentage of ACD responders was 21.6% (n=16) for nebivolol and 23.0% (n=17) for hydrochlorothiazide group.

The ankle-brachial index (ABI) increased during the double-blind treatment period in both groups. In the nebivolol group, the mean increase between visit 3 and visit 6 was 0.038 (SD: 0.142) and 0.054 (SD: 0.138) for hydrochlorothiazide.

No patients underwent cardiac catheter examination or coronary angiography during the study. Eight patients required hospitalisation between visit 3 and visit 7 (Neb: n=5, 6.0%; HCT: n=3, 3.8%).

The PAVK-86 questionnaire (2 visual analogue scales and 6 domains with 4-point Likert items) was completed by most patients at each visit. The percentage of patients assessable for each domain and VAS was >89% in both groups throughout the study.
At visit 3, the mean PAVK-86 score for all 6 domains and both VAS were similar between patients randomised to nebivolol and hydrochlorothiazide. In both groups, the highest score (worst outcome) was for the Pain domain, followed in decreasing score order by the Functional Status, Worries, Mood, Expectations from Treatment and Social Life.
At the end of the 24 week treatment period, a significant decrease (i.e., improvement) from baseline was observed for the Pain domain (Δ: -0.179 points; p=0.003, Wilcoxon test for paired data) and for the QoL assessment VAS in the nebivolol group. In the hydrochlorothiazide group, a significant decrease in the mean score was observed for Pain (Δ: -0.243; p=<0.001) and Functional Status (Δ: -0.149; p=0.029) domains.
None of the changes observed for the domains scores after 24 weeks of treatment respect baseline visit were significantly different between groups (p>0.2).

Safety Results

The safety profile of nebivolol and hydrochlorothiazide was assessed in the safety population which included 177 patients (Neb: n=91; HCT: n=86). Exposure to the study medication was similar between groups (mean of 156.6 days for nebivolol and 161.7 days for hydrochlorothiazide).

There were no important differences between groups with regards to the overall adverse events experience, laboratory parameters, and vital signs.

Overall, 87 patients (Neb: n=41, 45.1%; HCT: n=46, 53.5%) reported a total of 155 adverse events (Neb: n=82 AEs; HCT: 73 AEs), including 17 SAEs (Neb: n=14; HCT: n=3). The intensity of most adverse events was considered as mild or moderate. Overall, 8 AEs (9.8%) in the nebivolol group and 5 AEs (6.8%) in the hydrochlorothiazide group were considered severe.

Eight patients (8.8%) in the nebivolol group and 16 patients (18.6%) in the hydrochlorothiazide group had 10 and 20 adverse drug reactions (ADRs), respectively. None of these ADRs were serious.

One patient randomised to nebivolol died during the study, a massive hemorrhage 2 weeks after a stroke being the cause of the fatality; however, the SAE was considered not related to the study

medication.

Laboratory evaluations did not reveal any major changes throughout the study. A minor reduction was observed in systolic and diastolic blood pressure during the double-blind treatment period in both groups. A decrease in heart rate was observed at the beginning of the randomised treatment period in the nebivolol group (visit 3: 76.2 ± 10.3 bpm; visit 4: 67.0 ± 8.2 bpm; visit 5: 67.7 ± 9.0 bpm; visit 6: 67.2 ± 9.2 bpm), but not in the hydrochlorothiazide group.

A progressive decrease in the percentage of patients reporting to feel cold feet was observed in both treatment groups (Neb: 40.7% at visit 3 and 33.3% at visit 6; HCT: 45.3% at visit 3 and 33.3% at visit 6)

Conclusion

Both nebivolol and hydrochlorothiazide treatments resulted in a small increase in the ICD. A non-inferior effect of nebivolol compared with hydrochlorothiazide on ICD could not be accepted nor rejected as the 95% CI included both the -10 and 0 values in the non-inferiority analysis. Both medications increased also the mean values of ACD and ABI. A similar percentage of ICD and ACD responders was observed in both treatment groups.
The increase observed in ICD, ACD and ABI with nebivolol suggest that this medication does not have a negative effect on patients with symptomatic PAD.

Overall, the results do not suggest a beneficial effect of nebivolol in the ACD, ABI or QoL of patients with PAD Fontaine's stage II and essential hypertension. The influence of this medication in all these parameters was at the best equivalent to that of hydrochlorothiazide.

Both agents had a similar capacity to maintain systolic blood pressure under control. None of these agents was associated with PAD progression in terms of ICD, ACD and ABI.

Date of the Report:
03. May 2010