

**BCBe/04/Neb-PAO/087**

**Effects of Nebivolol on the walking distance in patients with essential hypertension and peripheral arterial occlusive disease (PAOD) Fontaine's stage II - A randomized, double blind, multicenter, active substance controlled clinical trial phase III**

**This study is currently recruiting patients**

**Sponsor:** Berlin Chemie AG

**Intervention:** Nebivolol 5 mg, HCTZ (hydrochlorothiazide) 25 mg

**Condition:** Patients with essential hypertension and PAOD Fontaine stage II(a+b)

**Study type & design:** Randomized, double-blind, multicenter, active substance controlled clinical trial phase IV

**Main criteria for inclusion:**

Subjects of 40 years to 75 years PAOD Fontaine's stage II with:

a 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,  
a history of (> 1 month before study inclusion) previous peripheral (lower extremity) vascular intervention such as surgical endarterectomy, bypass grafting or aortic abdominal aneurysm repair or PTA with or without stenting is allowed,  
an ankle-brachial pressure index (ABPI) of the worse leg < 0.90 and/or systolic ankle pressure > 70 mmHg,  
advice on smoking cessation has been given and documented prior to inclusion in the trial; smoking habit is stable for at least 3 months prior to inclusion in the trial.

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 must be applied during the trial. Hypertension according to the Joint National Committee on Hypertension (JNC) (systolic blood pressure (SBP) 140-159 mmHg and/or diastolic blood pressure (DBP) 90-99 mmHg) with or without treatment with antihypertensive drugs

### **Main criteria for exclusion**

. PAD with rest pain or leg ulcer or gangrene (Fontaine stage III & IV resp. critical limb ischemia (CLI): systolic ankle pressure  $\leq$  50-70 mmHg or systolic toe pressure  $\leq$  30-40 mmHg or transcutaneous partial oxygen pressure (tcpO<sub>2</sub>)  $\leq$  10-20 %) . 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)

. 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 . Poorly controlled diabetes mellitus (HbA<sub>1c</sub> > 8.5%) . Limb, coronary, or carotid vascular surgery or angioplasty within the last 3 months prior to screening Anticipated need for limb, coronary, or carotid vascular surgery or angioplasty during the trial . 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 influence the progression of the PAD or the walking distances except for the trial medication and the background medication Treatment with alpha-blockers or vasodilators as prostaglandin E<sub>1</sub>, prostaglandin I<sub>2</sub> analogs, pentoxifyllin, naftidrofuryl and buflomedil < 3 month stable before Visit 1. Regular use of analgesics with anti-inflammatory potential, i.e. NSAIDs. Treatment on demand and  $\leq$ 7 days, e.g. for headache is allowed. Treatment with COXII-Inhibitors Anticipated need of newly prescribed treatment with nitrates during the study in patients not pre-treated with those agents at screening stable for  $\geq$ 3 month Newly diagnosed or unstable angina pectoris (acute coronary syndrome) Concomitant treatment with other beta-blockers or HCT (including combinations) except for the study medication 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 arrhythmia 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 hypocalcaemia, hypopatraemia, hypovolaemia, hypocalcaemia

- Fructose incompatibility Acute myocardial infarction during the last 6 months prior to screening Acute pathologic hemorrhage Known Hyperthyroidism Patients with psychiatric diseases 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 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

Women of childbearing potential without adequate contraception; medically acceptable methods are contraceptive implant (contraceptive injection, intrauterine device (IUD), or oral contraceptives taken for at least 3 months, which the patient agrees to continue using during the study, or a double-barrier method which must consist of a combination of any of the following: diaphragm, cervical cap, condom, or spermicide) Applies for female patients with childbearing potential: pregnancy or lactation (pregnancy should be ruled out by pregnancy test) Patients with a history of alcohol and/or drug abuse Patients who are currently participating in another clinical study or who have received an investigational drug within 30 days prior to entering the study or who have participated in this trial before Patients who are unwilling or unable to provide informed consent or to participate satisfactorily for the entire trial period.