

PROTOCOL SUMMARY

Name of Sponsor Company: Takeda Pharma GmbH Collaborators: -	Drug Under Study: Candesartan
Brief Title of Protocol: Candesartan “added” therapy for treatment optimization of symptomatic heart failure with diastolic dysfunction in diabetic and hypertensive patients. A randomized, placebo-controlled, double-blind, parallel-group and multicentre clinical phase III study investigating the effects on NT-proBNP over 6 months.	
Protocol Number: D-CAN-546	Phase: III
Interventions Study: drug, active control Intervention Type: Drug Intervention Name: Candesartan 8-32mg versus placebo	
Study Description: Patients with a diastolic heart failure have a preserved ejection fraction (pLVEF > 40%) and show diastolic abnormalities in the echocardiogram. The benefits of RAAS inhibition has been shown in CHARM-preserved, where a Candesartan-therapy was associated with significantly fewer hospitalizations and a non significant 11% reduction in the primary endpoint (cardiovascular death or hospitalization for HF). However, only 20% of the patients were on a background therapy with an ACE-I. It is supposed that a combined therapy could be a more favorable regimen, namely in diabetics. In D-CAN-546 the basic conditions for demonstration of diastolic dysfunction will be consistent regarding performance of echocardiography, measurement of natriuretic peptides, and background treatment with ACE-I and presence of hypertension and diabetes. Candesartan or matching Placebo will be used as additional treatment to basic HF-therapy with at least ACE-inhibitors alone or together with further preparations (e.g. β -blockers). The dosage of study medication will be 8, 16 and 32 mg during the 6-week titration period striving for a maintenance dose of 32 mg over 16 weeks, if possible, or less (i.e. 8 or 16 mg) in case of intolerances to the 16 or 32 mg doses. Primary Efficacy Variable Course of NT-proBNP (log-transformed) (mean change from baseline (V1) to final visit (V6) determined in a central laboratory) Secondary Efficacy Variables - Mean change from for NT-proBNP (log-transformed) - Mean changes for Adiponectin, Cystatin C, HbA _{1C} , UAE, kidney function (eGFR and Cystatin C), NYHA-class, body weight-, BP- and echocardiographic results - Correlations of NT-proBNP with NYHA-class, SF-36-score and BP-results - Subgroup evaluations regarding β -blocker therapy and NYHA-classI) - Transition from sinus rhythm to permanent atrial fibrillation (based on ECG recordings) - Progression of preserved to impaired systolic dysfunction based on echocardiographic results	
Study Type: : interventional, treatment, randomized, double blind, active controlled	
Study Status: recruiting	
Study Purpose: Efficacy of Candesartan in heart failure with preserved LVEF and diastolic dysfunction	
Condition or Disease: Congestive Heart failure	
Key Criteria for Inclusion: - Male or female patient of at least 45 years of age	

- Non insulin dependent diabetes mellitus type 2 orally treated for at least 3 months
- Normotension or controlled hypertension (sSBP < 140 and/or sDBP < 90 mmHg)
- Regular sinus rhythm or atrial fibrillation (rate control of < 100 bpm)
- Echocardiographic evidence of a preserved LVEF \geq 45% with further doppler-echocardiographic criteria for diastolic dysfunction grade I-IV.
- NYHA-classification of II or III in a stable condition since at least 3 months
- Existing background HF-therapy with an ACEI alone or together with further preparations in a constant regimen since at least 1 month, in case of β -blockers since at least 3 months
- NT-proBNP \geq 250 pg/ml
- No previous therapy with ARBs during the last 4 weeks prior to the study

Key Criteria for Exclusion:

- Impaired renal function (serum creatinine > 2.2 mg/dl or > 194 μ mol/l)
- Serum potassium > 5.5 mmol/l or HbA_{1C} > 9.5 %
- Cor pulmonale or primary pulmonary disease with dyspnea at rest
- Known disposition to episodes of symptomatic hypotension or sSBP < 95 mmHg
- Acute coronary syndrome or any form of unstable chronic CAD
- History of MI, PTCA with revascularization, stent-implantation, CABG
- Tachycardia at rest > 100 bpm
- Known clinically relevant rhythm disorders
- Primary valvular diseases and/or restrictive or obstructive cardiomyopathy

Location of Study Sites:

Bad Nauheim, Berlin, Darmstadt, Dresden, Erfurt, Frankfurt, Gelsenkirchen, Gießen, Hartmannsdorf, Herne, Jena, Kassel, Langenfeld, Leipzig, Leisnig, Ludwigsburg, Markkleeberg, München, Neunkirchen, Northeim, Nienburg, Paderborn, Siegen, Wiesbaden.