SUMMARY REPORT OF EARLY TERMINATED CLINICAL TRIAL

Title of study:

Influences of angiotensin-neprilysin inhibition with Sacubitril/Valsartan (ENTRESTO®) on centrally generated sympathetic activity in heart failure patients

EudraCT number : 2017-000394-36

Protocol code number: M17-05-LCZ-ARNI

Sponsor:
Hannover Medical School
Carl-Neuberg-Str. 1
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Protocol version 1.6, 27.11.2017
Protocol version 2.0, 13.12.2017

Investigators:

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Publication (reference):
None.

Studied period:	Phase of development:
Date of first enrolment: 16.07.2018 Early termination: 06.09.2018	Phase IV

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Objectives:

Primary objective:

To test the hypothesis that angiotensin-neprilysin inhibition reduces sympathetic activity compared to standard heart failure therapy including Valsartan. The primary endpoint is muscle sympathetic nerve activity (MSNA) measured in bursts/minute during a five-minute resting period at the end of at least 4 weeks' treatment.

Secondary objectives:

To test the hypotheses that (compared to Valsartan) angiotensin-neprilysin inhibition:

1. is non-inferior regarding diastolic BP reduction (end of period – baseline) assuming a non-inferiority-margin of 4 mmHg
2. reduces activity of pre-motor sympathetic brainstem centers as measured by fMRI
3. reduces resting MSNA burst incidence
4. reduces MSNA burst area
5. improves baroreflex regulation of heart rate (HR)
6. improves baroreflex regulation of MSNA
7. attenuates MSNA increases during sympathetic stimuli (handgrip testing)
8. reduces venous plasma norepinephrine levels

Assessment of safety:

SAEs, AEs and safety laboratory tests will be collected throughout the study.

Methodology:

Prospective, monocentric, active-controlled, double-blind, cross-over study with randomized sequence of treatments

Number of patients (planned and analysed):

Planned: 35
Analysed: None

Diagnosis and main criteria for inclusion:

Diagnosis:

Heart failure patients with reduced left ventricular ejection fraction (NYHA II-III)

Inclusion criteria:

1. Women or men at the age ≥ 18 years, ≤ 80 years and able to give written informed consent
2. Heart failure NYHA class II-III
3. Ejection fraction of 40 % or less (any measurement made within the past 6 month using echocardiography, multi-gated blood-pool aquisition (MUGA), computertomography (CT) scanning, magnet resonance tomography (MRT) or ventricular angiography is acceptable, provided no subsequent measurement above 40%)
4. Angiotensin-Converting-Enzyme (ACE) inhibitor or Angiotensin-Receptor-Blocker (ARB) at a stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks before visit 1 (screening)
   (A 2-day ACE inhibitor washout is scheduled before run-in.)
5. Stable dose of a beta-blocker for at least 4 weeks before visit 1 unless contraindicated or not tolerated
6. Patient has to be in sinus rhythm
7. Patients capable of understanding the investigational nature, potential risks and benefits of the clinical trial

8. Women without childbearing potential defined by:
   - at least 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral oophorectomy or
   - hysterectomy or uterine agenesis or
   - ≥ 50 years and in postmenopausal state ≥ 1 year or
   - < 50 years and in postmenopausal state ≥ 1 year with serum FSH > 40 IU/l and serum estrogen < 30 ng/l or a negative estrogen test

   OR

   Women of childbearing potential with a negative urine ß-HCG pregnancy test at screening who agree to meet one of the following criteria from the time of screening, during the study and for a period of 7 days following the last administration of study medication:
   - correct use of at least an acceptable effective contraceptive measure. The following are deemed acceptable in this study: hormonal contraceptives (combined oral contraceptives and estrogen-free pills with desogestrel, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release), intrauterine device (IUS))
   - true abstinence (periodic abstinence and withdrawal are not acceptable methods of contraception)
   - sexual relationship only with female partners and/or sterile male partners

   OR

   Male
9. Signed written informed consent and willingness to comply with treatment and follow- up procedures.

Test product, dose and mode of administration, batch number:

1. Sacubitril/Valsartan (ENTRESTO®) 49 mg/51 mg, study-specifically labelled, p.o.,
   2×1 or 2×2 tablets per day.
   Batch number: S0007 2010708
2. Valsartan (Diovan®) 80 mg, study-specifically labelled, p.o.,
   2×1 or 2×2 tablets per day.
   Batch number: B5061 2015812
3. Sacubitril/Valsartan (ENTRESTO®) 49 mg/51 mg, study-specific additionally labelled, p.o.,
   2×1 or 2×2 tablets per day.
   Batch number: TL971
4. Valsartan (Diovan®) 80 mg, study-specific additionally labelled, p.o.,
   2×1 or 2×2 tablets per day.
   Batch number: BF930

Duration of treatment:

The trial duration per patient was planned for approximately 18 weeks.

Cross-over treatment period: 4 weeks per treatment arm; two treatment periods per patient, at least 2 weeks wash-out period

Reference therapy, dose and mode of administration, batch number:

Placebo for test product 1.; mode of administration as for test product 1. Batch number: H235IK 2011469

Placebo for test product 2.; mode of administration as for test product 2. Batch number: B0005 2012069

Criteria for evaluation/statistical methods:

No evaluable data are available.

Summary - Conclusions

The sponsor and the principal investigator of the study suggested and announced on 6th SEP 2018 to terminate the study prematurely because of severe difficulties to successfully recruit patients and to achieve the planned numbers of patients to be recruited within a reasonable time frame. Despite intensive, daily screening of all heart failure patients admitted to the Dept. of Cardiology and Angiology of Hannover Medical School and patients identified with a left ventricular ejection fraction ≤ 40% in the department's central echocardiography laboratory by study physicians, unexpectedly, only few patients fulfilled the inclusion/exclusion criteria of the study. Therefore, cardiologists collaborating with the Dept. of Cardiology and Angiology were particularly informed about the study and asked to report all patients potentially eligible for study participation (e.g. all patients identified by echocardiography with an left ventricular ejection fraction ≤ 40% or if start of/switch to therapy with sacubitril/valsartan is indicated for medical reasons), however, without success. Finally, the few patients eligible for study participation were not willing to spend the according to the study protocol necessary amount of time only for study purpose and finally refused study participation after having received detailed information about the study schedule.

No subject received study treatment. Two patients gave their written consent for participation in the clinical trial. Both patients were screening failures and were not randomized. Therefore no evaluable data are available.

Prof. Dr. med. Udo Bavendiek
Principal Investigator

11.04.19
Date