Study protocol - Synopsis

PURE-HF: Peripheral Ultrafiltration for the RElief from Congestion in Heart Failure

Study code:	UF-HF-02-INT
NCT No:	NCT03161158
Investigational device:	Chiara, peripheral ultrafiltration device
Control device:	Not applicable
Control therapy:	Usual care including high-dose IV diuretics
Study design:	Multicenter, prospective, randomized, parallel-group controlled clinical trial
Protocol status:	Final version 5.0
Date of current version:	19. December 2018

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STUDY SYNOPSIS

Title:	**PURE-HF: Peripheral Ultrafiltration for the RElief from Congestion in Heart Failure**
Study code:	UF-HF-02-INT
Study design:	Multicenter, prospective, randomized, parallel-group controlled clinical trial
Investigational device:	Chiara, peripheral ultrafiltration
Control device:	not applicable
Control therapy:	Usual care including high-dose intravenous (IV) diuretics
Study objectives:	Primary objective

To evaluate whether tailored, peripheral ultrafiltration complementary to low-dose diuretics is associated with a reduction in cardiovascular mortality in 90 days after randomization and heart failure events in 90 days after discharge compared to usual care including stepped intravenous diuretics, in acutely decompensated chronic heart failure with fluid overload (not fully responsive to diuretic therapy).

Secondary objective

The secondary aims will be to examine the effect of the above treatment assignments on:

1. Heart failure rehospitalization analyzed as a recurrent event in 90 days after discharge
2. Time until first HF rehospitalization in 90 days after discharge
3. Time until first urgent HF visit in 90 days after discharge
4. Quality of life (Patient Global Assessment at baseline, discharge, FU30, FU90; Short Kansas City Cardiomyopathy Questionnaire and EQ-5D-5L at discharge, FU30, FU90)
5. Days alive and out of hospital up to 90 days after discharge
6. Cardiovascular mortality in 90 days after randomization
7. Resolution of congestion defined as resolution of at least two of the final eligibility criteria present at randomization (this does not include chest x-ray criterion, i.e. if x-ray criterion was one out of two final eligibility criteria, only resolution of the other criterion is necessary), thus:
   - Jugular venous pressure of <8cm H_2O
   - No orthopnea
   - Trace or no peripheral edema
   - Respiratory rate no longer ≥20/minute
8. In-hospital worsening heart failure until discharge
9. Weight loss at 96h after randomization and at discharge

Study hypotheses: In acutely decompensated chronic heart failure patients who are admitted to the hospital due to symptoms and signs of congestion and who are not fully responsive to diuretic therapy, tailored, peripheral ultrafiltration complementary to low-dose diuretics provides better 90 day outcomes than usual care (guideline-directed medical therapy including IV diuretics).

Patients: Acutely decompensated chronic heart failure patients who are admitted to the hospital due to symptoms and signs of congestion and who are not fully responsive to diuretic therapy

Sample size: Sample size including 10% loss to follow-up and 13% treatment failure is **864** (432 in each group), minimum age of 18 years, no maximum age, both sexes, regions (western, central and eastern Europe).

Inclusion criteria:

General:

- Informed consent signed and dated by study patient and investigator/authorized physician
- Minimum age of 18 years
- Ability to understand the nature and requirements of the study

Study-specific*:*

- Heart failure (HF) patients with preserved, mid-range or reduced ejection fraction (confirmed according to the current definitions of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) requiring echocardiographic assessment within the prior 12 months) who are admitted to the hospital due to signs/symptoms of congestion (left- or right sided)
- On regularly scheduled oral loop diuretics prior to admission
- Patients who have received IV loop diuretics for decongestion within 24 hours after hospital admission and prior to screening. The dosages are administered according to clinical judgment.
- Symptoms of congestion and clinical evidence at the time of screening for eligibility:
    - Fluid overload manifested by at least 2 of the following:
        - Pitting edema ≥2+ of the lower extremities
        - Jugular venous pressure >8 cm H_2O
        - Pulmonary congestion or pleural effusion on chest x-ray
        - Paroxysmal nocturnal dyspnea or ≥2− pillow orthopnea
        - Respiration rate ≥20 per minute

- Additional objective documentation of congestion: Lung or inferior vena cava ultrasound, chest x-ray or elevated filling pressures, if available, at the time of randomization (optional)

Exclusion criteria:

Candidates will be excluded from the study if **ANY** of the following conditions apply:

General:

- Any condition which could interfere with the patient's ability to comply with the study
- In case of female patients: pregnancy or lactation period
- Participation in an interventional clinical study during the preceding 30 days
- Previous participation in the same study
- Unwillingness or inability to complete follow up
- Active drug or alcohol abuse (smoking allowed)

Study-specific:

- Acute coronary syndrome requiring intervention during index hospitalization
- Severe renal dysfunction requiring renal replacement therapy
- Systolic blood pressure <90 mmHg at the time of randomization
- Pulmonary hypertension not secondary to left heart disease
- Pulmonary disease thought to be primarily responsible for symptoms
- Contraindication to systemic anticoagulation
- Severe concomitant disease expected to prolong hospitalization or to cause death in ≤90 days
- Sepsis
- Severe uncorrected valvular stenosis at the time of randomization
- Active myocarditis
- Hypertrophic obstructive cardiomyopathy
- Constrictive pericarditis or restrictive cardiomyopathy
- Liver cirrhosis due to primary liver disease
- Known infection with human immunodeficiency virus (HIV) or active hepatitis C
- Previous solid organ transplant
- Presence or requirement for mechanical respiratory support
- Presence or requirement of a mechanical circulatory support device
- Need for IV positive inotropic agents at the time of randomization

Treatment:

Ultrafiltration group:

Patients in the intervention group will be treated with veno-venous ultrafiltration (UF) complementary to low-dose diuretic therapy according to the low-dose IV diuretic treatment algorithm and other medical therapy as judged indicated by the investigator. Patients will receive 1-7 UF sessions (6-10h/session, number of sessions depending on clinical assessment according to algorithm) during a maximum time period of 10 days.

Control group:
Patients in the control group will be treated with high-dose diuretic therapy according to the high-dose diuretic treatment algorithm and other medical therapy as judged indicated by the investigator.

Target variables:

Primary endpoint:
Composite endpoint of cardiovascular mortality in 90 days after randomization and heart failure events in 90 days after discharge. HF events are defined as HF rehospitalization or an urgent HF visit.

Secondary endpoints:

1. Heart failure rehospitalization analyzed as a recurrent event in 90 days after discharge
2. Time until first HF rehospitalization in 90 days after discharge
3. Time until first urgent HF visit in 90 days after discharge
4. Quality of life (Patient Global Assessment at baseline, discharge, FU30, FU90; Short Kansas City Cardiomyopathy Questionnaire and EQ-5D-5L at discharge, FU30, FU90)
5. Days alive and out of hospital up to 90 days after discharge
6. Cardiovascular mortality in 90 days after randomization
7. Resolution of congestion defined as at least two of the final eligibility criteria present at randomization have resolved (this does not include chest x-ray criterion, i.e. if x-ray criterion was one out of two final eligibility criteria, only resolution of the other criterion necessary), thus:
    - Jugular venous pressure of <8cm H_2O
    - No orthopnea
    - Trace or no peripheral edema
    - Respiratory rate no longer ≥20/minute
8. In-hospital worsening heart failure until discharge
9. Weight loss at 96h after randomization and at discharge

Safety endpoints:

1. Increase in serum creatinine by 26.5 µmol/L (0.3 mg/dL) or more and/or a ≥25% increase in serum creatinine OR a ≥20% drop in GFR) at discharge
2. Access-related complications (bleeding, infection)

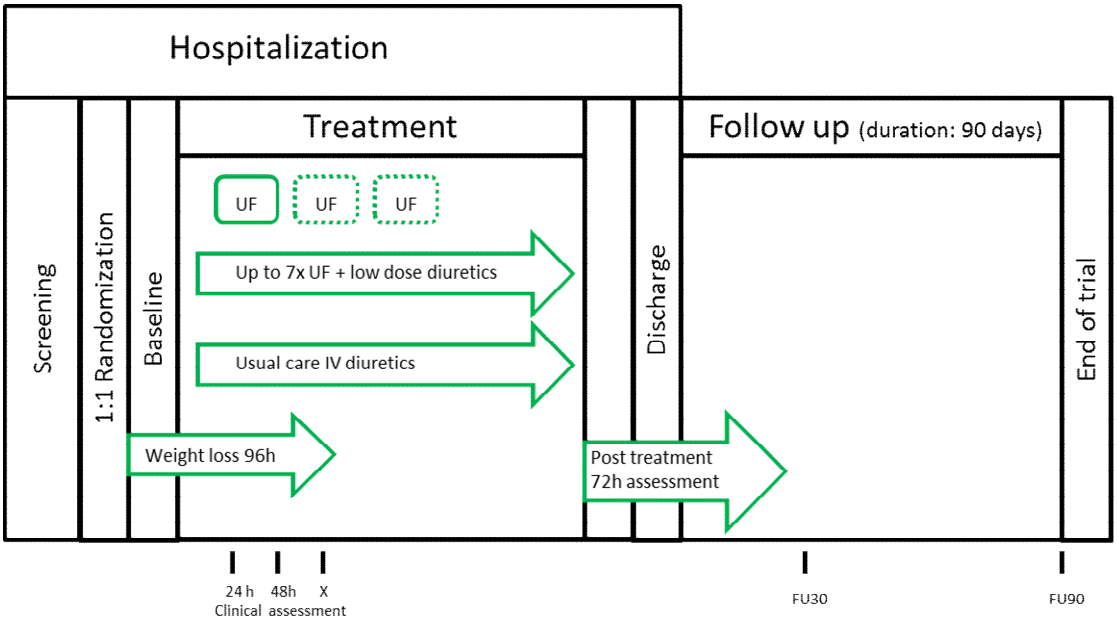
Exploratory variables:

1. Length of stay during initial hospitalization
2. Change in furosemide-equivalent dose from preadmission to discharge (in mg/day)
3. All-cause mortality rates up to 90 days after randomization

Planned start and end of study:

Start of Study Preparations	Q 3 2016
Start of Trial / First patient in	Q 3 2017
End of Trial / Last patient out	Q 3 2021
Data Base Lock	Q 3 2021
Statistical Analysis and Report	Q 4 2021

Intervention scheme and trial flow:



Of note, patients must be randomized within 24 hours after admission to designated hospital floor.

1. STATISTICS

1.1. PRIMARY ANALYSIS

The primary endpoint of the trial is the composite of cardiovascular mortality in 90 days after randomization or a heart failure event in the 90 days after discharge.

The primary analysis of the effectiveness of the UF treatment will be conducted in the ITT population (see section 1.5). The occurrence of cardiovascular deaths or heart failure event after discharge from hospital will be summarized using event proportions, i.e. number of patients with an event divided by the number of patients randomized to the respective treatment group.

The null hypothesis of no difference in event proportions between the randomized groups will be tested in a two sided test using logistic regression analysis adjusting for stratification variables (other than study site). Odds ratios including 95% confidence intervals (CI) will be presented as well as p-values (Wald methodology). In addition, descriptive analyses of the components of the primary outcome will be reported in the form of Kaplan-Meier (KM) curves for the time-to-event for each of cardiovascular mortality in 90 days after randomization and heart failure event within 90 days after discharge (Kaplan and Meier, 1958). Follow-up times will be censored at date of death, loss to follow-up or at the 90 day cut-off period.
Hazard ratios comparing the two treatment groups under study will be determined within the Cox proportional hazard model and provided along with the 95% HR confidence limits (Wald-CI).

1.2. SECONDARY ANALYSES

The analysis of secondary endpoints and exploratory variables (see section **Fehler! Verweisquelle konnte nicht gefunden werden.**) including the total number of recurrent HF hospitalizations, weight loss during index hospitalization, duration of index hospitalization (in days), changes in laboratory measurements (e.g. resolution of congestion) as well as "Quality of Life" (short form of KCCQ with EQ-5D as standardized measure of health status) and Patient Global Assessment (PGA) will included in formal analyses. There will be no structured analysis taking into account multiple testing. Summary statistics such as mean, standard deviation [SD], median, 25th [Q1] and 75th [Q3] percentiles, minimum [Min] and maximum [Max]) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical variables.

The comparison between treatment groups will be evaluated using logistic regression analysis adjusting for stratification variables (other than study site) or Fisher's exact test (in case of a rare outcome) for categorical variables, using joint modeling of death and recurrent events in the case of heart failure hospital admissions and linear regression analysis for continuous variables adjusting for stratification variables (other than study site) and, where appropriate for baseline levels of the variable. Non-parametic methods will be used where appropriate.

As described in section 1.1, patients who die or lost to follow-up after discharge are included in all secondary analyses with all available data up to the date of last contact.

Descriptive summaries of KM curves will be presented for all-cause mortality. Patients alive at the end of the study will be censored at the last date known to be alive.

More detailed descriptions of statistical methods and assumptions including calculated variables and the proposed format and content of tables and figures in the final report will be detailed in the Statistical Analysis Plan (SAP). Wherever reasonable, evaluation will be stratified by subgroups (i.e. age, other baseline characteristics) and pre-defined in the SAP. All statistical analyses will be performed using the software package SAS® [SAS Institute Inc., The SAS system for Windows, Cary, NC: SAS Institute Inc., 2013].

1.3. SAFETY ANALYSES

Standard procedures for reporting of adverse events will be used. Adverse events will be summarized as frequencies and percentages by treatment group.

1.4. FURTHER STATISTICAL CONSIDERATIONS

Sensitivity analysis

For sensitivity and robustness, the analyses of the primary and secondary endpoints will be repeated for the Per-Protocol-Population.

Handling of missing data

We will perform multiple imputation for subjects with missing data on the primary and secondary outcomes at 90 days, if applicable (details will be specified in the SAP).

1.5. ANALYSIS SETS

For this study, the following analysis populations will be defined:

Per-protocol-population (PP)
Includes all subjects who entered the study in accordance with both the inclusion / exclusion criteria without major protocol deviations and who finished the study in accordance with the study protocol.

(Modified) Intention-to-treat population (ITT=FAS)
Includes all subjects who were randomized and for whom complete efficacy data are available. We will analyze subjects lost to follow up based on subjects´ status at time of withdrawal of consent and add a sensitivity analysis using multiple imputation for those with missing outcomes at 90 days.

Safety-population (SP)
Includes all subjects who were randomized.

Assignment of patients to analysis populations will be done during the data review meeting. Primary analysis will be based on the ITT population; an additional analysis on PP will be performed to assess validity of results. Safety analyses will be performed on the SP.

The primary endpoint measured at 90 days will be analyzed on an intention to treat basis. It is anticipated that there may be some "crossover" from the intervention group to the control group or from the control group to the intervention group. The number of crossovers will be documented to provide context for interpreting the primary results; however, treatment crossovers will be analyzed according to the intention to treat principle and thus will be included in the arm to which they were randomized.

1.6. SAMPLE SIZE JUSTIFICATION

Previously published results from clinical trials comparing intravenous loop diuretics to mechanical fluid removal by isolated veno-venous ultrafiltration have yielded conflicting results regarding heart failure–related rehospitalization. The present PURE-HF study is similar to the AVOID-HF (Costanzo et al., 2015) in terms of study design and targets. The primary objective of the AVOID-HF study was to determine whether UF prolonged the time to first HF event within 90 days of hospital discharge. Regarding sample size considerations, the AVOID-HF trial refers to different publications in order to provide an estimate of the combined HF event rate for the control group and the assumed reduction of the HF event rate in the UF group (Felker et al., 2011, O'Connor et al., 2011, Costanzo et al., 2007, Konstam et al., 2007, Hernandez et al., 2010, Ross et al., 2010).

Taking into account the assumptions and observations actually made in the prematurely terminated AVOID-HF study published by Costanzo et al. (Costanzo et al., 2016) we estimated that 864 patients (432 in each arm) should be sufficient to test whether there is a difference between the event proportions of the test and the control treatment. The proposed sample size calculations based on the two-sided Z test with unpooled variance and include the following assumptions: 1) α of 0.05 (α/2=0.025); 2) power (1-β) of 0.90; 3) an HF event rate for the loop diuretics group of 25% plus 2% cardiovascular death and 4) a reduction of the event proportion for the UF group of 37,5 % (this leads to an event proportion for the UF group of 16,88%). The estimated total sample size is displayed with additional patients included to account for 10% of subjects lost to follow-up and 13% treatment failures due to crossover during the treatment period

Table 1: Sample size calculations according to assumptions of AVOID-HF trial.

Event proportion			**Sample size N**		
control group	UF group	Reduction	Crude	Incl. 10% loss to FU	Incl. 10% loss to FU and 13% treatment failure
27.00%	16.88%	37.50%	694	764	864

1) Test for two proportions,
2) two-sided α of 0.05,
3) power of 0.90,
4) HF event rate of control group of 25% + 2% in-hospital death
5) an event proportion for the loop diuretics group (control group) of 27%,
6) an event proportion for the UF group (treatment group) of 16.88% (37.50% reduction),
7) including 10% loss to follow up and 13% crossover (i.e. treatment failure),

The sample size calculation was carried out using PASS 14 [PASS 13. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.]

1.7. INTERIM ANALYSIS

No formal interim analysis will be performed. The requirements for safety are further defined in the context of the DMC and detailed in the DMC charter. Decisions will be

based on e.g. inspection of study-database, AE listings, event rates, etc. Thus, a statistical interim analysis is not applicable.