FULL TITLE OF THE TRIAL

Diuresis **E**fficacy in **A**mbulatory Chronic **H**eart **F**ailure Patients with Volume Overload- Intra -patient Comparison of Three Diuretics Regimens

SHORT STUDY TITLE / ACRONYM

The Heart Failure diuresis efficacy comparison (DEA-HF) study

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RESEARCH REFERENCE NUMBERS

Israel MOH number: 12490

0067-23-RMB

NCT number: TBD

1 Statistics and Data Analysis

1.1 Sample size calculation

A sample size of 28 was calculated in R version 4.2.2 using WebPower to provide a statistical power of 80%. The cutoff effect size was defined as the difference of 20 mmol in urine sodium measurement with an SD of 19, as described in a similar study design. Normal distribution, no cross-over effect, and sphericity were assumed for this calculation.

1.2 Planned recruitment rate and sample size correction

The recruitment process is estimated to be associated with a retention rate (participants recruited and completed the study follow-up, and assessed with valid primary outcome data) of 70%. Therefore, we aim to recruit 42 patients in total.

1.3 Statistical analysis plan

Descriptive analysis and statistical tests will be performed using the R software and Stata software. Data with a normal distribution will be presented as mean ± SD and data with a skewed distribution will be presented as median ± interquartile ranges (IQRs).

To balance the study for carryover effects, 6 subgroups of patients are needed to represent the 6 possible sequences of treatments. Generalized linear mixed models will be deployed to evaluate the differences among the effects of 3 different diuretic regimens (“treatments”). The treatments will be administered in a cross-over open-label trial (see section 8, “Trial design”), where each patient will receive every treatment exactly once with washout periods among the treatments. The sequence in which each patient will receive the 3 treatments will be randomized by a custom-made python script and determined a priori to balance for patients’ sex and HF type (i.e., male, female, HFrEF, HFpEF). Sequences will be designed using pairs of orthogonal Latin squares to balance for carryover effects (6 sequences in total). The dependent variables will be sodium weight (calculated as spot sodium concentration multiplied by the total volume of urine) and congestion score, with treatment type as an independent variable. To account for the crossover design effect, possible interactions between time (period of treatment) and intervention will be tested and the model will be adjusted for potential effects of the sequences of treatments, and the identity of the preceding treatment. To elucidate the differences between the 3 treatments, Tukey post-hoc testing and an adjustment for repeated measures will be performed whenever significant findings are observed. A value of $P < 0.05$ will be considered significant.

1.4 Interim Analysis

An interim analysis is planned after recruiting and completing the follow up of 22 patients. This is in order to assess the power of the study.

Three options exist:

1) Statistical significance is achieved- then the study recruitment may stop and full analysis will be pursued.
2) No statistical significance achieved and study is futile or one of the study interventions is causing severe side effects and the study should be stopped at once (recruitment and treatments).
3) The results are not significant- an additional power analysis calculation will be reassessed based on the realistic 1st endpoint data accumulated.

Using the O'brein & Fleming method it is estimated that one additional patient should be recruited to keep the study powered.