Mineralocorticoid Receptor Antagonists in End Stage Renal Disease

A double-blind, randomized, placebo-controlled, parallel group study to determine the effect of the mineralocorticoid receptor antagonist spironolactone on the left ventricular mass index in end stage renal disease patients on hemodialysis

Sponsor:
University Hospital Würzburg
Josef-Schneiderstr. 2, 97080 Würzburg

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EudraCT-No.: 2011-003179-12

Main Study Center:
University Hospital Würzburg
**Study Synopsis**

<table>
<thead>
<tr>
<th>Title of Trial</th>
<th>Mineralocorticoid Receptor antagonists in End stage renal DiseAse (The MiREnDa trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronym</td>
<td>MiREnDa</td>
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<tr>
<td>Indication</td>
<td>Hemodialysis</td>
</tr>
</tbody>
</table>
| Eligibility criteria - inclusion | Age >18 years  
- Hemodialysis treatment for at least 3 months  
- Written informed consent  
- At least 3 dialysis sessions per week |
| Eligibility criteria - exclusion | Contraindications for cardiac magnet resonance imaging (CMR)  
- Mineralocorticoid receptor antagonist treatment within the last 6 months  
- Estimated life expectancy < 12 months as judged by the nephrologist  
- History of hyperkalemia, defined as pre-dialysis potassium > 6.5 mmol/l occurring ≥ 3 times within the last 3 months prior to enrolment.  
- High risk to develop hyperkalemia defined as pre-dialysis potassium > 6.0 mmol/l  
- Hypotension (systolic blood pressure < 100 mmHg)  
- Planned kidney transplantation (living donor) within the prospected study duration  
- Any acute illness within the last 4 weeks precluding a study participation as judged by the nephrologist  
- Non-amenoarheic women with child bearing potential without reliable contraception, pregnancy/lactation  
- Allergy/hypersensitivity to spironolactone  
- Non-compliance suspected or demonstrated |
| Trial Design    | Phase II, prospective randomized, placebo-controlled, double-blind, parallel group, multi-center proof-of-concept trial |
| Primary Objectives | To investigate the effect of the mineralocorticoid receptor antagonist spironolactone on the left ventricular mass index in end stage renal disease patients on hemodialysis. |
| Secondary Objectives | To investigate the effect of spironolactone treatment on the following parameters/outcomes: cardiac function, serum potassium levels, blood pressure, hospitalization or death due to heart failure, kidney function, heart rate variability, cardiac arrhythmias, exercise capacity (6-minute walk test), vascular function (pulse wave analysis, flow-mediated dilatation, carotid intima-media thickness, carotid artery distensibility), body composition, quality of life and cardiovascular biomarkers. |
| Therapy/Interventions |  
**Experimental intervention:**  
Spironolactone 50 mg daily + standard medical care  
**Control intervention:**  
Placebo + standard medical care |
| Primary endpoints/ outcome(s) | **Primary efficacy endpoint:**  
Change in left ventricular mass index (LVMi) measured by CMR |
<table>
<thead>
<tr>
<th>Secondary endpoints / outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary endpoints:</strong></td>
</tr>
<tr>
<td>• Cardiac function parameters (cardiac volumes, systolic and diastolic function, cardiac output) measured by CMR and echocardiography</td>
</tr>
<tr>
<td>• Pre-dialysis serum potassium levels</td>
</tr>
<tr>
<td>• Frequency of hyperkalemic episodes (potassium ( \geq 6.5 \text{ mmol/l} ))</td>
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<td>• Office and 24h blood pressure</td>
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<tr>
<td>• Clinical measures of heart failure severity (New York Heart Association (NYHA) functional class, 6 minute walk test)</td>
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<tr>
<td>• Cardiac death and/or hospitalization due to heart failure (combined endpoint)</td>
</tr>
<tr>
<td>• Residual kidney function (urine volume, creatinine-, urea-clearance, electrolyte excretion)</td>
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<tr>
<td>• Heart rate variability (ECG)</td>
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<tr>
<td>• Cardiac arrhythmias</td>
</tr>
<tr>
<td>• Arterial stiffness (pulse wave analysis (PWA))</td>
</tr>
<tr>
<td>• Carotid intima media thickness (CIMT)</td>
</tr>
<tr>
<td>• Carotid artery distensibility (CD)</td>
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<tr>
<td>• Flow-mediated dilatation (FMD) of the brachial artery</td>
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<tr>
<td>• Body composition (bioimpedance spectroscopy)</td>
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<tr>
<td>• Biomarkers of fibrosis, inflammation and heart failure</td>
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<tr>
<td>• Quality of life</td>
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<tr>
<td>• Adherence to study medication</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Sample size</th>
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<tbody>
<tr>
<td><strong>To be assessed for eligibility:</strong> N=800</td>
</tr>
<tr>
<td><strong>To be allocated to trial:</strong> N = 120</td>
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</table>

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<thead>
<tr>
<th>Biometry</th>
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<tbody>
<tr>
<td><strong>Primary endpoint:</strong> ITT analysis on the change of LVMi from baseline to week 40 will be compared between groups using ANCOVA with follow-up value as target variable, baseline value as covariate, and group as factor.</td>
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<tr>
<td><strong>Major secondary analysis:</strong> Analyses will include t-test, ANCOVA or chi-square/Fisher’s exact tests as appropriate. Time to event analyses will be carried out by Kaplan-Meier analysis (log rank test) and by Cox proportional hazard regression after testing the proportional hazard assumption.</td>
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<tr>
<th>Trial duration</th>
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<tbody>
<tr>
<td><strong>First patient in to last patient out:</strong> 21 months</td>
</tr>
<tr>
<td><strong>Duration of intervention per patient:</strong> 9 months</td>
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<tr>
<td><strong>Duration of the entire trial:</strong> 24 months (first patient in to final report)</td>
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<td><strong>Duration of recruitment:</strong> 12 months</td>
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<tr>
<td><strong>Anticipated study start (Recruitment):</strong> 08/2012</td>
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<tr>
<td><strong>Anticipated study end (first report / final report):</strong> 12/2014</td>
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## Study Flow

![Study Flow Diagram]

### Visit Plan / Schedule of Assessment

<table>
<thead>
<tr>
<th>Visits</th>
<th>Screening</th>
<th>Placebo run-in</th>
<th>Baseline &amp; Randomization</th>
<th>Double-blind treatment</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Time (weeks)</td>
<td>-4 to -2</td>
<td>0</td>
<td>40</td>
<td>44</td>
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<tr>
<td>Assessment</td>
<td>1x</td>
<td>3x/week</td>
<td>1x</td>
<td>3x/week @ Week 13,26,39</td>
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<td>In-/exclusion criteria</td>
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<td>Informed consent</td>
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<td>Medical history</td>
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<td>Current medication</td>
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<td>Dialysis regime</td>
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<td>Routine blood tests</td>
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<tr>
<td>24h urine sample</td>
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<td>Office blood pressure</td>
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<td>Potassium / Sodium</td>
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<td>Adverse events</td>
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<td>Compliance with medication</td>
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<td>Randomization</td>
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<td>24h ABPM</td>
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<td>Flow mediated dilation</td>
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<td>Quality of life assessment</td>
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<td>Blood sample (biomarkers)</td>
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</table>

* Placebo medication will be dispensed during the screening visit; study medication will be dispensed following randomization and 13 and 26 weeks after randomization; drug accountability will be checked after randomization, week 13, week 26 and week 39.

* Routine blood tests (full blood count, electrolytes, liver function test, kidney function test and coagulation) will be performed at the screening visit and study visits: week 13, week 26, week 39 and week 44.

* Only study visit Week 39.