Externally delivered focused ultrasound for renal denervation

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Kona Medical, Medtronic, Recor, RoxMedical, Vascular Dynamics</td>
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<td>Consulting Fees/Honoraria</td>
<td>Kona Medical, Medtronic, Recor,</td>
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Advantages of Externally delivered focused ultrasound for renal denervation

**Invasive RDN Catheters**
- Energy through wall, may damage vessel
- Requires referral to interventional MD
- Dependency of user skills
- Radiation exposure
- Contrast medium application
- Resource intensive / expensive

**Duplex-songraphy guidance**
- Ultrasound surrounds vessel / no impact on artery
- Interventional or HTN treating MD can perform procedure
- Automated / robotic therapy delivery
- No cath lab, no contrast or radiation
Illustration of externally delivered focused ultrasound to the renal artery and surrounding nerves

After visualizing the renal artery with the diagnostic duplex ultrasound device (DD), and tracking of the kidney, the focal therapeutic ultrasound (TS) is delivered in a robotic way (14 spots around the kidney) within 3 minutes time frame.

Schmieder RE, LINC 2016
Updated Images of Ultrasound targeting and ablative field formation

- 14 ablations delivered in robotic manner
- 3 minutes per patient side
- 50-55° C
- Treatment volume of approx 2.5 cm³

Renal Bifurcation Target

Schmieder RE, LINC 2016
Noninvasive Renal Sympathetic Denervation by Extracorporeal High-Intensity Focused Ultrasound in a Pre-Clinical Canine Model

Qifeng Wang, MM,* Rui Guo, MD, PhD,† Shunkang Rong, MD,*‡ Gang Yang, MD, PhD,* Que Zhu, MD, PhD,* Yonghong Jiang, MD,* Changming Deng, MD,* Dicuhan Liu, MD,* Qi Zhou, MD, PhD,* Qi Wu, MD, PhD,* Shunhe Wang, MD,* Jun Qian, MM,* Qi Wang, MS,*

A

B

Freyhardt et al. Journal of Therapeutic Ultrasound 2014, 2:12
http://www.jtultrasound.com/content/2/1/12

MR-guided high-focused ultrasound for renal sympathetic denervation—a feasibility study in pigs

Patrick Freyhardt1, Lilian Heckmann1, Alexander Beck1, Nicola Stolzenburg1, Jörg Schnorr1, Julia Kamp1, Jan L Rinnenthal1, Bernd Hamm1, Rolf W Günther1 and Florian Streitparth1
Development of Clinical Trial Program

- **WAVE I**
  - First in Man

- **WAVE II**
  - Dose Optimization

- **WAVE III**
  - Non-Invasive

- **WAVE IV**
  - EU Sham RCT

- **WAVE V**
  - Pivotal RCT

- **69 Patients; Resistant HTN > 160 mmHg Systolic BP**
  - Age (years): 61.7 ± 10.9
  - Male / Females (N/%): 41 (59.4%) / 28 (40.6%)
  - Baseline systolic BP (mmHg): 180 ± 18 mmHg
  - Baseline diastolic BP (mmHg): 98 ± 14 mmHg
  - Number of antihypertensive meds: 4.57 ± 1.1
  - Patients on AH meds > 5 years: 57 (82.6%)
  - Patients on 5 or more AH meds: 34 (49.2%)

Schmieder RE et al, LINC 2016
Wave I-III Study aggregate office BP response (N=69)

Number of patients with medication number increases:  5  (7%)
Number of patients with medication number decreases:  16  (23%)
Number of patients with no medication change:             48  (71%)

Schmieder RE, LINC 2016
Wave III Study office BP response for patients with non-invasive image guidance (N=22)

<table>
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<tr>
<th>Time</th>
<th>SBP</th>
<th>DBP</th>
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<tbody>
<tr>
<td>3 Week</td>
<td>-18.0</td>
<td>-12.8</td>
</tr>
<tr>
<td>6 Week</td>
<td>-11.8</td>
<td>-6.2</td>
</tr>
<tr>
<td>12 Week</td>
<td>-29.6</td>
<td>-19.8</td>
</tr>
<tr>
<td>24 Week</td>
<td>-28.6</td>
<td>-11.3</td>
</tr>
<tr>
<td>52 Week</td>
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Schmieder RE, LINC 2016
Comparison of the baseline, 3-week and 24-week follow-up MRI angiogram images

No evidence of spasm, stenosis, thrombosis, dissection, aneurysm, pseudoaneurysm, fistula or any other vascular abnormalities at 3 weeks and 24 weeks post treatment. Neither were any filling defects detected.

No kidney pathology or vascular abnormalities were detected in any of the follow-up MRI images that were not present at the baseline examination.

The most common adverse event reported across the 3 studies was post-treatment back pain, which was reported in 35/69 subjects.
Representative OCT image performed on the treatment day immediately following the RDN treatment with the Surround Sound System and targeting catheter in the Wave I study (N=5)
WAVE Clinical Trial Program on Safety and Efficacy

- **WAVE I**: First in Man
- **WAVE II**: Dose Optimization
- **WAVE III**: Non-Invasive
- **WAVE IV**: EU Sham RCT
- **WAVE V/VI**: Pivotal RCT

- 69 Patients; Resistant HTN > 160 mmHg Systolic BP
- Average > 25 mmHg blood pressure reduction
- > 75% respond with drop ≥ 10 mmHg;
  More than half ≥ 20mmHg
- Excellent safety profile
- Therapy time / 3 minutes per side

Non-invasive renal denervation using externally delivered focused ultrasound emerged as an attractive treatment option in severe resistant hypertension.