Transcatheter Perivascular Alcohol-Mediated Renal Denervation

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• I, Wojciech Wojakowski DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Transcatheter PeriVascular Alcohol-Mediated Neurolysis

PeriVascular Renal Denervation (PVRD™)

Distinctive Features

1. Controlled **perivascular** targeting to access nerves deep from artery
2. Efficient, **simultaneous** delivery of alcohol via micro-needles
3. Circumferential, axial, deep coverage achieved with single infusion
4. **Self-limited chemical diffusion** into adventitial space
5. **No obstruction of blood flow**
6. **No significant intimal/medial injury; No anatomical limitations**
7. Essentially painless
8. **No capital equipment**

Unique Mode of Action

- Renal nerves
- Micro-needles
- Renal Artery Section
Multiple Proprietary Design Elements Enable Consistent Performance

**Radio-opaque** distal components facilitate clear visualization across the arterial wall.

**Support structures** aid in precise needle positioning and centering of catheter.

**3 Retractable micro-needles** deliver fluid with homogeneous, circumferential, and axial spread.

**Handle** designed to be intuitive and easy to use as well as to ensure proper sequence of steps.
PeriVascular, Circumferential & Axial Alcohol Delivery

- Reproducible centering of catheter in vessel
- Precise perivascular, circumferential and axial fluid delivery into arteries
- No perforation or extravasation into surrounding tissues

Contrast Delivery

Needle delivery

Lateral Projection

Alcohol* Delivery

*Methylene Blue added as vital stain
Alcohol-Mediated Renal Nerve Injury at 4 Weeks: Composite Surrogate Efficacy with 4 Independent Markers*

Consistent alcohol-mediated dose response across numerous independent bio-markers

Alcohol-Mediated Ablation Area – Peregrine Catheter (Dose= 0.6 mL , Time= 3 Months)

1. Circumferential alcohol spread
2. Deep perivascular penetration
3. Nerve damage across entire ablation area (~52-57 mm²)
4. No, or insignificant, arterial change. No evidence of negative remodeling
5. No collateral damage to surrounding (peri-adventitial) tissue
Comparison of Alcohol at 2 Volumes to RF
(Values Are ± SD)°

Ablation Depth

Norepinephrine Reduction

Ablation Area

*Both doses of alcohol p<0.05 vs. RF

The Most Distant Damaged Tissue (mm from IEL)

Reduction in NE (ng/gm) vs. Control

Ablation Area (Section Containing Damage Within Adventitia), mm²

Both volumes of alcohol show increased efficacy, with both showing significance

°Bertog et al, in preparation

Key:  
- Symplicity RF (4 Ablations/Artery)  
- Peregrine Alcohol, 0.3 mL  
- Peregrine Alcohol, 0.6 mL
Pre-Clinical Studies: Safety, Efficacy & Durability (Surrogate)

**Pig model:**
- Precise Delivery
- Reproducibility
- Efficacy
- Safety
- Durability

(~100 pigs)
Acute & Chronic Studies

- Fluid delivery circumferentially and axially to the desirable and precise arterial wall depth
- Durable neurolysis confirmed by histologic, immuno-histochemical and neurochemical techniques
- Highly predictable alcohol-mediated dose-response
- Acute and chronic vascular safety confirmed with angiography, OCT and histologic techniques
- No systemic/renal toxicity when used as intended
- No renal toxicity when alcohol was injected directly into the renal arteries
- Improved performance compared to RF ablation across numerous parameters
First-Human-Use Study: Favorable Outcomes

**FEASIBILITY TRIAL**

- Prospective, Single Center, Non-randomized

- Subjects: Systolic OBP ≥ 160 mm Hg, stable regimen of ≥ 3 antihypertensive meds, including a diuretic

- Primary Endpoint – Safety: Freedom from procedural complications

- Secondary Endpoint – Performance: Reduction in systolic OBP from baseline at 6 months.

- N = 18

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**No acute complications:**
- No clots, spasm, perforation, or dissections
- No long-term effects on renal function
- Arteries appear unchanged from baseline at 6 months post-treatment (angiography evaluated by core laboratory)

**Excellent device performance:**
- 100% device success (37/37 vessels)
- Brief treatment time: ~10 minutes/artery (range 2-21 minutes)

**Successful navigation to the target site in all renal arteries, including challenging anatomies** -- short or tortuous segments

**Reduction in OBP,** including in patients who had a decrease in HTN medications. Response rate = 88%

Performed under minimal sedation with no additional analgesia or sedation required

Fischell et al, in preparation
Change in Office Blood Pressure

SBP and DBP Change Per Visit

<table>
<thead>
<tr>
<th></th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>175</td>
<td>95</td>
</tr>
<tr>
<td>1 Month</td>
<td>153</td>
<td>87</td>
</tr>
<tr>
<td>6 Months</td>
<td>151</td>
<td>83</td>
</tr>
</tbody>
</table>

SBP and DBP Reduction From Baseline Through 6 Months (Office BP)

Systolic BP and Diastolic BP Reduction

- 1 Month (N=16):
  - Systolic BP: -22 mm Hg
  - Diastolic BP: -8 mm Hg
- 6 Months (N=16):
  - Systolic BP: -24 mm Hg
  - Diastolic BP: -12 mm Hg

Reduction in systolic OBP at 6-Month = -24 ± 21
Reduction in diastolic OBP at 6-Month = -12 ± 21

Fischell et al, in preparation
**Peregrine Study**

**DESIGN**

- Prospective, multi-center, non-randomized, with follow-ups to 2 years
- Subjects: Refractory hypertension based on systolic OBP ≥ 160 mm Hg, ABPM of ≥ 135 mm Hg. Stable regimen of ≥ 3 antihypertensive meds, including a diuretic (4 week screening)
- Primary Safety Endpoint: Freedom from procedural complications
- Primary Performance Endpoint: reduction of 10% in OBP at 6-Month compared to baseline
- Secondary Safety Endpoints: Change in renal function, renal artery stenosis, adverse events
- Secondary Performance Endpoints: Changes in ambulatory blood pressure. Changes in antihypertensive medications

**STATUS**

- Closed for enrollment after treatment of 10 subjects: CE mark obtained, initiating a post-market study
- No procedural or post-procedural complications recorded (n=15 procedures)
- Overall short treatment times
- For initial procedures subjects received only standard level of sedation. Subsequent procedures performed with no sedation
- Follow-up is ongoing
Procedural Steps

1. Obtain baseline angio
2. Position Peregrine
3. Deploy guide tubes
4. Deploy Needles and Infuse alcohol
5. Retract the needles then the guide tubes
6. Post infusion angio
Case

- 56-years old woman with poorly controlled hypertension since 2000 on four antihypertensive medications (including diuretic) at their max doses
- No major medical history. Normal EF of 55%.
- Height: 160cm, Weight: 80 kg, waist circumference: 115, BMI: 32.1
- Laboratory and urine tests were normal
- She was seen by a nephrologist who recommended her for the renal denervation therapy
- Provided an informed consent on 18-AUG-14 and underwent the required tests prior to be confirmed eligible for the study treatment.
- She was treated for her left renal artery on 09-OCT-2014 and returned on 31-OCT-2015 for evaluation of the treated artery followed by treatment of the contralateral renal artery, per protocol requirements.
Procedure – Subject 002-012

1. Obtain baseline angio
2. Position Peregrine
3. Deploy guide tubes
4. Centering confirmed
5. Deploy Needles and Infuse alcohol
6. Post infusion angio
“Peregrine Post-Market” Study (EU)

A Post-Market Randomized Study of Transcatheter Perivascular Renal Denervation for the Treatment of Hypertension Using the Ablative Solutions Inc. Peregrine System™ Infusion Catheter

Co-Principal Investigators
Prof. Dr. med. Horst Sievert
Interventional Cardiology

Prof. Peter J. Blankestijn
Nephrologist / Hypertensionist

Steering Committee Co-Chairpersons
Prof. Atul Pathak, MD, PhD
Cardiology, Pharmacology

TBD
Transcatheter PeriVascular Alcohol-Mediated Neurolysis

• Preclinical studies have shown: efficient, dose-dependent, deep and circumferential inactivation of the sympathetic nerves with reduction of renal NE with no damage to intima and minimal media injury

• First Human Use (FHU) has demonstrated procedural and device safety, with strong trend toward significant reduction in blood pressure (office)

• Current experience in EU study is confirming performance: Device and procedure unchanged from FHU trial
  – Efficient procedure, good deliverability, ability to treat shorter and tortuous arteries
  – No-to-minimal sedation required, subjects not displaying symptoms of pain.