A Critical Evaluation of MIST Intervention in LUTS and BPH Treatment

Claus G. Roehrborn
Professor and Chairman

Department of Urology

Abbreviated Outcomes Tables
MIST Interventions

| Table LC-3: Comparison of mean micturition diaries, estimates of change in symptom scores rights |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | M12                          | M24                          | M36                          |
|                                | Symptom Score (points)       | Symptom Score (points)       | Symptom Score (points)       |
| M3-9 mo.                       | Medical                      | Min. Invasive                | Surgical                     |
|                                | Medical                      | Min. Invasive                | Surgical                     |
|                                | Medical                      | Min. Invasive                | Surgical                     |
|                                | Medical                      | Min. Invasive                | Surgical                     |
|                                | Medical                      | Min. Invasive                | Surgical                     |
|                                | Medical                      | Min. Invasive                | Surgical                     |
|                                | Medical                      | Min. Invasive                | Surgical                     |

Discussion of Therapeutic Options

Non Invasive Options

Invasive Therapies

Diagnostic Tests

Prostate, ultrasound, bone scan

Cystoscopy

Urodynamics

Ultrasonography

Nonevasive Options

Consultation with a urologist when choosing a more invasive therapy

Minimal Impact: Therapeus, or

Surgical Therapy

Invasive Therapies

Surgical Interventions

Medical Therapy

Minimal Invasive Therapies (MIST)

Watchful Waiting
Recommended Treatment Options

• Minimally invasive therapies (MIT)
  – Transurethral microwave heat treatments
  – CoreTherm™
  – Prostatron® (various versions)
  – Targis®
  – TherMatrx™
  – Transurethral needle ablation
  – UroLume® stent

• Surgical Therapies
  – Transurethral resection of the prostate
  – Transurethral electrovaporization
  – Transurethral incision of the prostate
  – Transurethral holmium laser resection/enucleation
  – Transurethral laser vaporization
  – Transurethral laser coagulation (e.g., visual laser ablation)
  – Open prostatectomy

Conflict of Interest
Claus G. Roehrborn MD

• Presenter has done investigational research for and consulted with the following companies:
  – VidaMed / Medtronics
  – Dornier Medtech
  – Urologix
  – AMS
  – ACMI
  – Boston Scientific
  – Ethicon Endosurgery / Johnson & Johnson

Disclaimer

• In the course of this presentation I will make critical comments about certain aspects of many devices, the manufacturers, trial designs, data gathering and analyses
• What I state regarding one company applies easily to other companies as well
• The shortcomings are not necessarily those of the involved company alone
• I wish to point out systematic problems and unfortunately have to use individual examples

U.S. BPH Treatment Market - 2004

Total 8.8 Million Symptomatic BPH Patients
Common Concerns

- Impact of trial design on efficacy data
- Quality control of data
- Mean/median changes hide individual results
- Early positive data from single centers vs multi-center trial results
- Sham versus true effect on symptoms
- Chosen direct comparator
- Overstated claims
- Technology changes occur faster than clinical experience can be accumulated
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- Differing patient population between controlled trials vs clinical practice

Effects of Editorial Peer Review
A Systematic Review

Tom Jefferson, MD
Philip Alderson, MD/PhD
Elizabeth Jager, MA
Frank Drummond, PhD

ABSTRACT

The Impact of Placebo Lead-In

• Medications are compared to placebo in pivotal Phase III studies and have a placebo lead-in phase
  • A single-blind placebo lead-in results in improvements in virtually all measured parameters due to the regression to the mean and the placebo effect
  • Baseline data are recorded at time of randomization
  • Changes from baseline are credited to the drug or placebo
  • Device trials are compared to sham but have no "sham lead-in period"
  • The baseline data equal the screening data
  • The change from baseline = screening are credited to the device intervention
  • This results in a greater improvement due to the placebo effect
**MEDICAL VERSUS DEVICE TRIAL**

The Impact of Placebo Lead-In

<table>
<thead>
<tr>
<th>Screen</th>
<th>Bl</th>
<th>Midpoint</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plac</td>
<td>20.8</td>
<td>16.9</td>
<td>15</td>
</tr>
<tr>
<td>Act</td>
<td>21.2</td>
<td>17.6</td>
<td>12.8</td>
</tr>
<tr>
<td>Device</td>
<td>21.1</td>
<td>20.9</td>
<td>13</td>
</tr>
</tbody>
</table>

**Common Concerns**

- Impact of trial design on efficacy data
- Quality control of data
- Mean/median changes hide individual results
- Early positive data from single centers vs multi-center trial results
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- Overstated claims
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**Quality Control of Data**

- Differences between pharmaceutical industries and device manufacturers
- Number of patients enrolled in clinical trials
- Resource availability for independent CRO to monitor trial conduct, data integrity and analysis
- Scrutiny at level of FDA (different branches regulate drugs vs devices)

**Transurethral Water Induced Thermotherapy (WIT) for BPH**

Muschter et al J Urol 165:1565, 2000

- A total of 125 patients with lower urinary tract symptoms due to BPH were enrolled at 8 study centers.
- Pretreatment evaluation included determination of International Prostate Symptom Score (I-PSS), peak urinary flow rate and quality of life score.
- Patients were evaluated 3, 6 and 12 months after water-induced thermotherapy.

**Table 2. Outcome at 12 months**

<table>
<thead>
<tr>
<th>Peak Urine Flow Rate (ml/sec)</th>
<th>Quality of Life Score</th>
<th>Post Void Residual (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>15.3</td>
<td>4.4</td>
</tr>
<tr>
<td>SD</td>
<td>6.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Range</td>
<td>2.5-21.3</td>
<td>1-12</td>
</tr>
<tr>
<td>Median</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>SD</td>
<td>5.9</td>
<td>1</td>
</tr>
<tr>
<td>Range</td>
<td>2.3-15.4</td>
<td>1-4</td>
</tr>
</tbody>
</table>

| % Change                     | -9%                   | -9%                    | -9%                     |

* Based on mean values at baseline and 12 months.
Editorial Comment to Muschter et al J Urol 165:1565, 2000

- The editorial comment was written by the Editor of the J Urology, Dr. Jay Gillenwater
- Dr. Gillenwater was also investigator of the ArgoMed WIT technology in the US
- He was listed as consultant on the website at the time of the publication

Background

- The trial was done at 13 centers, but data from only 8 sites were analyzed and published!
  - The so-called center effect is tested for in pharmaceutical trials to assure that the results from one center are applicable in others as well
- In two sites, all patients underwent a TURP. When I called the PIs they told me that “the treatment did not work and all pts required a TURP” and “I thought that this was just a feasibility study and after the treatment they all should get a TURP as they were on the [UK] waiting list”
- The raw data were given to the AUA guideline committee for analyses
Background

- In the submitted dataset several patients had a posttreatment Qmax of > 70 ml/sec which seemed to have gone unnoticed!
- After my inquiries no original tracings (source documents) were found.
- Eventually I was told that the error was a decimal point (i.e., instead of 74 it was 7.4 ml/sec etc).
- When eliminating these patients the improvement in Qmax dropped from 16.4 at 24 mo to 12.7 ml/sec!

Transurethral Water Induced Thermotherapy (WIT) for BPH
Muschter et al J Urol 165:1565, 2000

After being bought by ACMI ArgoMed went out of business.
WIT was offered under the name of Aquatherm by ACMI.
It appears that it is not heavily promoted or used at the present time.

Common Concerns

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### UROWAVE TUMT VS SHAM TRIAL

#### PEAK URINARY FLOW RATE MEAN ± 99%CI ALL UROWAVE CHANGES FROM BASELINE < 0.001

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>147</td>
<td>153</td>
<td>141</td>
<td>143</td>
<td>119</td>
<td>123</td>
</tr>
<tr>
<td>Peak Flow Rate (ml/sec)</td>
<td>12.0</td>
<td>11.0</td>
<td>9.5</td>
<td>8.5</td>
<td>9.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

At 6 mo 10% of patients worsening, at 12 mo 20%

20% of patients have no noticeable improvement (less than 3 points IPSS)

### UROWAVE TUMT VS SHAM TRIAL

#### AUA SI: CUMULATIVE PERCENT OF PTS. WITH THRESHOLD CHANGES AT 6 AND 12 MONTHS

<table>
<thead>
<tr>
<th>Change from Baseline</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
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<tr>
<td>90</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
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<tr>
<td>70</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
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<tr>
<td>50</td>
<td>0</td>
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<td>20</td>
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<td>40</td>
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<td>70</td>
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<tr>
<td>40</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
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<td>70</td>
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<tr>
<td>30</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
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<td>70</td>
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<tr>
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<td>0</td>
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<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

### UROWAVE TUMT VS SHAM TRIAL

#### QMAX: CUMULATIVE PERCENT OF PTS. WITH THRESHOLD CHANGES AT 6 AND 12 MONTHS

<table>
<thead>
<tr>
<th>Change in Peak Flow Rate (ml/sec)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Percentage</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

20% of patients experience worsening of their flowrate
Common Concerns

- Impact of trial design on efficacy data
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- Early positive data from single centers vs multi-center trial results
- Sham results bias effect on symptoms
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FRENCH HYPERTHERMIA BPH TRIAL
Abbou et al, PCBR Vol 386:449, 1994

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>3</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia</td>
<td>11.3</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Sham</td>
<td>12.3</td>
<td>8.8</td>
<td>8.5</td>
<td>8</td>
</tr>
</tbody>
</table>

Symptom Score

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia</td>
<td>10</td>
<td>10.8</td>
<td>10.5</td>
<td>10.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>9.4</td>
<td>9.9</td>
<td>9.9</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Peak Flow Rate

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia</td>
<td>10.1</td>
<td>10.8</td>
<td>10.5</td>
<td>10.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>9.4</td>
<td>9.9</td>
<td>9.9</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UROWAVE TUMT VS SHAM TRIAL
AUA SI (0-35): MEAN ± 99%CI
ALL UROWAVE CHANGES FROM BASELINE < 0.001

N      147            145            142           143          120            122
 N 73              71              72             70

UROWAVE TUMT VS SHAM TRIAL
PEAK URINARY FLOW RATE MEAN ± 99%CI
ALL UROWAVE CHANGES FROM BASELINE < 0.001

N      147            138            141           143          119            123
 N 73              68              71             68

UROWAVE SHAM AND CROSS-OVER
AUA SI (0-35): MEAN ± 99%CI
Changes from Sham BL different at S3, S6, C3, C6 (p<0.001)
Changes from Sham 6 different at C3, C6 (p<0.001)

N         73              71              69              47               44

UROWAVE TUMT VS SHAM TRIAL
PEAK URINARY FLOW RATE MEAN ± 99%CI
Changes from Sham BL different at S3, S6, C3, C6 (p<0.001)
Changes from Sham 6 not significantly different at C3, C6
Common Concerns

- Impact of trial design on efficacy data
- Quality control of data
- Mean/median changes hide individual results
- Early positive data from single centers vs multi-center trial results
- Sham versus true effect on symptoms
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The scientific manuscript as one version of the truth

- Recently I was asked to assign reviewers for a manuscript using the Prolieve/Celsion Thermodilation device
- The manuscript purportedly reported on a multi-center randomized controlled clinical trials
- Insider knowledge suggested otherwise…

Objectives

Compare the safety and efficacy of Prosee® to Prolieve Thermodilation® System, which treats symptoms of benign prostatic hyperplasia (BPH) by employing simultaneous transurethral microwave therapy (TUMT) and helium dilatation.

Methods

A multi-center, randomized, open-labeled pivotal trial enrolled men >50 years old with symptomatic BPH and AUA symptom score ≥8. 120 patients were randomized and treated with the Prolieve System, and 66 to Prosee® (0:6 ratio). Prosee patients meeting specific eligibility criteria could elect Prosee after 6 months. Primary endpoint was AUA Symptom Index score change after 6 months. Secondary effectiveness measures included changes in PFR, QoL, and sexual function. Treatment durability was assessed to 2 years for Prosee patients.
Components of Prolieve™ Thermodilatation System

Among Cross-Over patients, the results of treatment with the Prolieve System were consistent at similar time points with those observed in the population originally randomized and treated with the Prolieve System. At 12 months post-treatment with the Prolieve System, patients’ (n = 14) AUA scores had improved 34% over baseline (p = 0.0058), and PFR had improved 34% over baseline (p = 0.047). The AUA responder rate (≥ 38%) among cross-over patients with available data at baseline and 12 months was 57% (8/14), while the PFR responder rate (≥ 20%) was 64% (9/14).

Components of Prolieve™ Thermodilatation System

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean AUA Score (Std. Dev.)</th>
<th>Change from Baseline</th>
<th>% Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>N</td>
<td>Visit</td>
<td>Dev.</td>
</tr>
<tr>
<td>120</td>
<td>110</td>
<td>Baseline 21.9 (4.85)</td>
<td>6.2±</td>
</tr>
<tr>
<td>115</td>
<td>106</td>
<td>Week 2 15.4 (8.09)</td>
<td>9.2±</td>
</tr>
<tr>
<td>114</td>
<td>104</td>
<td>Month 1 12.6 (7.14)</td>
<td>10.1±</td>
</tr>
<tr>
<td>114</td>
<td>103</td>
<td>Month 3 11.7 (7.27)</td>
<td>9.7±</td>
</tr>
<tr>
<td>105</td>
<td>101</td>
<td>Month 6 12.3 (7.39)</td>
<td>10.1±</td>
</tr>
<tr>
<td>92</td>
<td>94</td>
<td>Month 12 11.5 (6.61)</td>
<td>9.7±</td>
</tr>
</tbody>
</table>

PMA Prolieve, Celsion Corporation
PO 30006, Feb 2004

Accountability
A total of 190 patients were randomized in the study, 142 to Prolieve™ and 48 to Proscar®. Before the initiation of treatment, 24 patients chose to withdraw from the study prior to any attempt at treatment (17 Prolieve™ / 7 Proscar®). Therefore, while still maintaining the 3:1 ratio, a total of 125 patients in the Prolieve™ arm and 41 patients in the Proscar® arm were included in the statistical analysis and comprise the intent-to-treat population (Table 1). At the time the database was closed for analysis 92/125 (74%) of the patients in the treatment arm completed their 12-month follow-up. There were 20 patients treated with Prolieve™ following their participation in the pivotal trial in the Proscar® arm. The information for these 20 patients is included in the safety summary with the 125 patients originally randomized to Prolieve™. Five of the patients in the Prolieve™ intent-to-treat population went for treatment but treatment was canceled during the preparatory steps and these five patients are not included in the safety presentation for the post-treatment period.
### Table 1: Inclusion of Total Patients by Treatment Arm and Study Center

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Number of Patients Treated or Attempted to Treat</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Antonio Research</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>San Antonio, Texas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional Urology</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>Michigan, Cincinnati</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Great Lakes Urology</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>North Carolina Urology</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Austin Urology</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>San Francisco, California</td>
<td>12</td>
<td>12</td>
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<tr>
<td>Seattle Urology</td>
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<td>5</td>
</tr>
<tr>
<td>Jacksonville, Florida</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>New York, New York</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>University of Maryland, Maryland</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>University of Maryland, Georgia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Northwestern University, Chicago</td>
<td>2</td>
<td>2</td>
</tr>
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<td>University of Chicago, Illinois</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>University of North Carolina</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Johns Hopkins, Baltimore</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>University of Southern California</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>University of Colorado, Denver</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>University of Michigan, Ann Arbor</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total Patients</td>
<td>166</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Repeated Measures Analysis

<table>
<thead>
<tr>
<th>Visit</th>
<th>Treatment Arm</th>
<th>Absolute Mean Improvement (95% CI)</th>
<th>Percent Improvement (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(Visit - Baseline)</td>
<td></td>
</tr>
<tr>
<td>2-week</td>
<td>Proscar®</td>
<td>-3.5 (-6.3, -0.7)</td>
<td>18% (3, 35)</td>
</tr>
<tr>
<td>1-month</td>
<td>Proscar®</td>
<td>-3.5 (-6.3, -0.7)</td>
<td>18% (3, 35)</td>
</tr>
<tr>
<td>3-month</td>
<td>Proscar®</td>
<td>-3.5 (-6.3, -0.7)</td>
<td>18% (3, 35)</td>
</tr>
<tr>
<td>6-month</td>
<td>Proscar®</td>
<td>-3.5 (-6.3, -0.7)</td>
<td>18% (3, 35)</td>
</tr>
<tr>
<td>12+ month</td>
<td>Proscar®</td>
<td>-3.5 (-6.3, -0.7)</td>
<td>18% (3, 35)</td>
</tr>
</tbody>
</table>

*Note: the data above is based on the Proscar® group, N=41.
**CoreTherm – Microwave treatment for BPH**

**Effectiveness Results on Evaluable Patients (Prolieve™ Patients Only)**

*AUA Responder Rate for Treated Patients:* All patients having a 30% or greater improvement in AUA total score from baseline during the follow-up evaluation were considered responders. Only patients treated with Prolieve™ who were present at the visit were included in the analysis, i.e., evaluable patients. The percent of treated patients present at the 3-month visit with an improvement in AUA total score of 30% or greater was 69% (79/114). This response was maintained out to the 12-month visit where 74% (68/92) of the treated patients had a 30% or greater improvement in AUA total score (Table 3) where up to 23% (28/120) of the patients were not available for a 12-month follow-up but 18/28 were later found to have received alternative treatment.

**Prostate weight and response rates:** A comparison in response rates based on AUA total score and prostate weight was made for the patients treated with Prolieve™. Those patients with prostate weights of ≤40 grams were included in one group while patients with prostate weights >40 grams were placed in the other group. At the 6-month visit the patients in the ≤40 gram group had a 71% (51/72) AUA responder rate (percent improvement of 30% or greater compared to baseline) compared to 34% (18/53) for the patients in the >40 gram group (95% CI, 20.4, 53.4). These results demonstrated that patients with prostates >40 grams did not demonstrate as significant a response as patients with prostates of ≤40 grams.

**INDICATIONS FOR USE**

Prolieve™ is a transurethral microwave therapy device that provides a non-surgical, minimally invasive procedure for the treatment of symptomatic Benign Prostate Hyperplasia (BPH) in men with prostate sizes of 20 to 80 grams, a prostate length between 1.2 cm and 5.5 cm and in whom drug therapy (e.g., Finasteride (Proscar®)) is typically indicated.

**Catheterizations associated with treatment:** Sixteen percent (22/140) of the patients were catheterized due to urinary retention post treatment. Sixty-four percent (14/22) of these catheterizations were for three days or less. All but one patient was catheterized for less than one week. There were 2 patients who were catheterized for reasons other than urinary retention. One patient experienced bladder spasms requiring catheterization and a second patient had the catheter replaced during treatment due to a leak. The third patient had a repeat procedure.

The pivotal study of the Prolieve Thermilization™ System supports a clinical option for successful microwave therapy treatment with decreased morbidity and enhanced convenience.

Treatment with the Prolieve System is a well-tolerated, single-session, out-patient procedure that requires only intracuteral lidocaine and does not typically require post-treatment catheterization; the adverse event frequency is low and treatment effectiveness is durable to at least 2-years post-treatment.
Three-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study
Wagrell et al, Urology 64:698–702, 2004

Common Concerns

- Impact of trial design on efficacy data
- Quality control of data
- Mean/median changes hide individual results
- Early positive data from single centers vs multi-center trial results
- Sham versus true effect on symptoms
- Chosen direct comparator
- Overstated claims
- Technology changes occur faster than clinical experience can be accumulated
- In general no demonstration of effect on prostate volume and PSA to substantiate ablative claim
- Relatively high or not reported retreatment rates
- Inability to predict patients more likely to benefit from therapy
- Differing patient population between controlled trials vs clinical practice

TherMatrx DOT

- “This therapy is different from other clinical studies which have looked at surrogate markers such as gadolinium defects on an MRI scan. When we do our treatments, we're looking to...achieve symptom improvement in patients with the greatest amount of safety.”
  David Albala, MD

“In its pre-PMA dose-response study, TherMatrx found a thermotherapy dose that causes necrosis without sloughing.”

Lingeman, White Paper
Permanent tissue necrosis. Tissue from a prostate treated with TherMatrx Dose Optimized Thermotherapy clearly demonstrates permanent tissue necrosis.

1. The promotional literature states that the TMx-2000 provides “A-Plus Years Durability” and “proven 5-year durability.” Our review of P000943 is based on 1-year data. We have not reviewed data establishing that treatment with the TMX-2000 system is effective for 4 to 5 years. As a result, it appears that your claim may be false or misleading. If you have data demonstrating that the claim is not false or misleading, please submit it with your response to this letter.

2. The promotional literature claims the TMx-2000 “Causes Permanent Tissue Necrosis.” While all thermotherapy catheters result in necrosis, this does not stop BPH tissue from forming again. To the extent that a claim of “permanent tissue necrosis” implies Thermatrx will provide a permanent cure of the patient’s BPH, it is misleading. Please clarify the meaning of your claim of “permanent tissue necrosis.”

3. The promotional literature claims “Superior Peak Flow Rate Improvement” for the TMx-2000. This claim also may be false and misleading since we are not aware of data establishing a statistically significant improvement over other therapies. If you have data that establishes the truthfulness of your claim of superiority, please submit it with your response to this letter.

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- Relatively high or not reported retreatment rates
- Inability to predict patient outcome
- Patient population between controlled trials vs clinical practice

**Promotion of New Intended Uses**

From a review of the promotional material for this product, we have identified the following instances of promotion of the device for a new intended use:

1. The promotional material states that the TMx-2000 “Treats Enlarged Median Lobe.” Your FMD submission does not contain clinical data to support the use of your device to treat median lobe enlargement of the prostate. This claim is considered a significant modification to the intended use of the TherMatrx BPH Thermotherapy System, TMX-2000, requiring submission of a PMA supplement. 21 CFR § 814.39(a)(1).

2. We also note your literature states that treating physicians can “see other patients during treatment” with the TMx-2000.

This directly conflicts with the precautions in the approved TMx-2000 labeling: “Attention by a qualified physician is required during the use of the TMx-2000 system. The control unit display must be monitored and controlled during the course of therapy sessions to make sure that the RX-200 Applicator and rectal temperature are within prescribed treatment parameters. Failure to monitor and deliver the TMx-2000 System procedure per recommendations by TherMatrx, Inc. may lead to decreased patient safety and reduced clinical effectiveness.”

Because you do not have FDA approval for these new indications for use, marketing your product may be a violation of the law. In legal terms, the product is adulterated under section 501(a)(5) of the Act.
The Original TUNA Device
VidaMed

Software and Catheter Escalation

• Prostatron [EDAP to Urologix]
  – Software from 1.0 to 2.0 to 2.5 to 3.0 to 3.5....
• Targis [Urologix]
  – Original treatment catheter
    • 60 min treatment time
  – Expedius Treatment
    • 28 min treatment time
• CTC (Cooled Thermo Catheter)
  • 28 min treatment time

Changes in Design...

Common Concerns

• Impact of trial design on efficacy data
• Quality control of data
• Mean/median changes hide individual results
• Early positive data from single centers vs multi-center trials
• Sham versus true effect on symptoms
• Chosen direct comparator
• Overstated claims
• Technology changes occur faster than clinical experience can be documented
• In general no demonstration of effect on prostate volume and PSA to substantiate ablative claim
• Relatively high or not reported retreatment rates
• Inability to predict patients more likely to benefit from therapy
• Differing patient population between controlled trials vs clinical practice
**Differences**

**Surgery**
- Removes Tissue

**Office**
- Treats Tissue

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**Common Concerns**

- Impact of trial design on efficacy data
- Quality control of data
- Mean/median changes hide individual results
- Early positive data from single centers vs multi-center trial results
- Sham versus true effect on symptoms
- Chosen direct comparator
- Overstated claims
- Technology changes occur faster than clinical experience can be accumulated
- In general no demonstration of effect on prostate volume and PSA to substantiate ablative claim
- Relatively high or not reported retreatment rates
- Inability to identify patients more likely to benefit from therapy
- Differing patient population between controlled trials vs clinical practice
Common Concerns

- Impact of trial design on efficacy data
- Quality control of data
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PREDICTORS OF GOOD/INTERMEDIATE SYMPTOM OUTCOMES AFTER TUMT (2.5)
D’Ancona et al., Urology 53:111, 1999
Def: IPSS from >19 to <8 or Change > 3 points
Common Concerns

- Impact of trial design on efficacy data
- Quality control of data
- Mean/median changes hide individual results
- Early positive data from single center vs multi-center trial
- Bias versus true effect on symptoms
- Chosen direct comparison
- Overlapped claims
- Technology changes occur faster than clinical experience can be documented
- In general no demonstration of effect on prostate volume and PSA to substantiate positive claim
- Relatively high or not reported retreatment rates
- Inability to predict patients more likely to benefit from therapy
- Differing patient population between controlled trials vs clinical practice

Selection Bias

- Age: 0 40 50 60 70 80 90 100
- IPSS: 0 5 10 15 20 25 30 35
- Qmax: 0 5 10 15 20 25 30 35 40 45 50
- TRUS: 0 10 20 30 40 50 60 80 100
- PSA: 0 1 2 3 4 5 6 7 8 9 10 15
- Rx: WaWa Phyto Rx Medical Rx MIST Surgery

High energy transurethral microwave thermotherapy in the treatment of benign prostatic hyperplasia: criteria to predict treatment outcome

D'Ancona et al., Urology 53:111, 1999

Def: Qmax from < 10 to > 15 or Change > 3 ml/sec
**Selection Bias**

**Controlled Trial: MIST Intervention**

- **Age**: 0, 40, 50, 60, 70, 80, 90, 100
- **IPSS**: 0, 5, 10, 15, 20, 25, 30, 35
- **Qmax**: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50
- **TRUS**: 0, 10, 20, 30, 40, 50, 60, 80, 100, 150
- **PSA**: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15
- **Rx**: WaWa, Phyto Rx, Medical Rx, MIST, Surgery

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**Impact of Inclusion and Exclusion Criteria in Clinical Trials vs Clinical Practice**

- In controlled clinical, patient enrollment is often controlled by strict inclusion and exclusion criteria.
- The results obtained are only applicable to the tested population – strictly speaking.
- By treating patients in practice outside of such criteria, the results will not necessarily be the same leading to dissatisfied consumers and disappointed health care providers.

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**Thermotherapies to be considered**

- Water Induced Thermotherapy (WIT)
- Transurethral Needle Ablation (TUNA)
- Interstitial Laser Coagulation (ILC)
- Transurethral Microwave Thermotherapy (TUMT)
  - TherMatrx™ (TherMatrx/AMS)
    - Low energy (7 Watts), no water cooling
  - Prolieve™ (Celsion/Boston Scientific, Natick, MA)
    - 50 Watts energy, water temperature 34°C, 46 Fr balloon dilation, 45 min
  - CoreTherm™ (Prostalund, Lund, Sweden)
    - High energy (> 60 Watts), no water cooling, intraprostatic needle for temperature feedback
  - Prostatron® (Urologix, Minneapolis, MN)
    - High Energy (> 60 Watts) with water cooling
  - Targis® (Urologix, Minneapolis, MN)
    - High energy (> 60 Watts) with water cooling, 28 min
Interstitial Temp Mapping

Interstitial Temperature Mapping

Heat Sensitivity of Human Prostatic Tissue: Implications for Thermal Therapy

J.C. Bischof, P. Bhowmick, J.E. Coad, S. Bhowmick, J. Pryor, T. Larson, J. de la Rosette

The time-temperature relationship for 90% destruction of human BPH. Temperature vs. time plot.

Endorectal coil MRI
Gadolinium
7 days after Targis TUMT

Horseshoe shaped area of necrosis in TZ surrounding viable urethra, PZ intact

Data courtesy of Dr. Thayne Larson, Scottsdale AZ
Percent Necrosis Following TUMT (TUMT followed by Prostatectomy)

Data courtesy of Dr. Thayne Larson, Scottsdale AZ

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Comments
- Each health care provider has to make decisions based on
  - Unsatisfactory data in the literature
  - Sales representatives with not always truthful information
  - Recommendations from “experts” and colleagues
  - Own experience
  - Common sense
- Of the stakeholders, the AUA, NIDDK, FDA, CMS or managed care organizations should demand better information on behalf of our patients

Comments
- The field of MIST interventions is ideally suited for standardized technology assessment, best supported by government or other 3rd party sources (remember the French government!)
- A consortium of centers could conduct randomized direct comparator trials with the different devices (5 devices, 10 centers, 2 devices at each center, each device placed and tested at 4 centers)
- A independently sponsored registry of treatment and outcome data would also help understand differences between the devices