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Final 5-Year Outcomes of the Multicenter Randomized Sham-Controlled Trial of Rezūm Water Vapor Thermal Therapy for Treatment of Moderate-to-Severe Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

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**Brief title:** Minimally invasive prostate convective water vapor thermal energy ablation

**Key words:** prostate, benign prostatic hyperplasia, minimally invasive, water vapor thermal therapy

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OBJECTIVE: To present final 5-year outcomes of the multicenter randomized sham-controlled trial of Rezum water vapor therapy for treatment of moderate-to-severe LUTS due to BPH.

MATERIALS AND METHODS: Total of 197 subjects ≥ 50 years of age, with IPSS ≥ 13, maximum flow rate (Qmax) ≤15 mL/s and prostate volume 30 to 80 cc were randomized and followed for 5 years. From the 61 subject control arm, a subset of 53 subjects requalified and after 3 months, received treatment as part of the crossover group and were also followed for 5 years. The total number of vapor treatments to each lobe of the prostate was determined by length of prostatic urethra and included middle lobe treatment per physician discretion.

RESULTS: Significant improvement of LUTS was observed at ≤ 3 months post thermal therapy, remaining durable through 5 years in the treatment group (IPSS reduced 48%, QOL increased 45%, Qmax improved 44%, BPHII decreased 48%). Surgical retreatment rate was 4.4% with no reports of device or procedure related sexual dysfunction or sustained de novo erectile dysfunction. Results within the crossover group were similar through 5 years.

CONCLUSION: Minimally invasive treatment with Rezum water vapor thermal therapy provides significant and durable symptom relief as well as flow rate improvements through 5 years, with low surgical retreatment rates and without impacting sexual function. It is a versatile therapy, providing successful treatment to obstructive lateral and middle lobes.
Introduction

The prevalence of BPH rises drastically as age advances. Between 50% and 70% of men suffer from LUTS associated with BPH after the age of 50 years while evidence suggests that the prevalence of LUTS/BPH is as high as 80% by the 8th decade.[1]

The available treatment options for moderate-to-severe LUTS/BPH range from oral medications to surgical treatments.[2] Most commonly, the first line of treatment is medication, via AB and/or 5-ARI prescribed as either mono- or combination therapy. Evidence suggests however that due to AEs, poor medication adherence, and/or disease progression many men seek secondary treatment.[3] Common AEs associated with AB include abnormal ejaculation due to reduced or absent seminal fluid, dizziness and postural hypotension; with 5-ARIs, AEs include erectile dysfunction, reduced libido and less commonly ejaculation failure, retrograde ejaculation and gynaecomastia.[4] TURP has traditionally been considered the gold-standard surgical treatment option.[2] While TURP has demonstrated its efficacy in improving urinary symptoms, acute safety concerns and long-term negative impacts such as erectile and ejaculatory dysfunction, possible incontinence, as well as other associated complications have been well documented.[5]

As an alternative to TURP, MISTs have emerged as options to relieve symptoms while minimizing or eliminating hospital stays and complications.[2] Rezum water vapor thermal therapy (Rezum System, Boston Scientific, Marlborough, MA) is an innovative MIST cleared by the FDA in 2015 to reduce prostate tissue volume associated with BPH including hyperplasia of the central zone and/or a middle lobe.[6] This therapy transfers stored thermal energy (540 calories/mL H$_2$O) as vapor to the prostatic tissue. No thermal effects occur outside the targeted treatment zone,[7] thus addressing limitations of conductive heat transfer experienced with other MISTs, such as TUNA and TUMT where cell kill gradient was noted.[8]

The most unique feature of Rezum thermal therapy is that it can treat lateral and central zones without morphological limitation or learning an advanced technique. Difficult anatomic varients, such as intravesical prostatic protrusion, can be treated without effects on sexual function.[9] In the 5 years following FDA clearance, the Rezum system has been embraced by urology practices, health technology assessment bodies, and urologic societies throughout the US and Europe.[10, 11] This adoption is attributed to the evidence of its clinical advantages, including sustained relief of LUTS, enhanced quality of life, and durability of treatment response.[12-14] In this manuscript, we report final 5 year clinical results for the treatment- and crossover-arms for the multicenter, prospective, blinded, controlled trial of Rezum water vapor thermal therapy (Rezum II Study, NCT01912339).

Materials & Methods

The Rezum II pivotal study was conducted at 15 centers in the United States with a follow-up period of 5 years. In total, 384 subjects were screened and 197 subjects entered the study. All participants signed a written informed consent form prior to participation, and approval of the protocol was granted by an institutional review board for each participating investigational site. Subjects, ≥ 50 years of age, who had moderate-to-severe symptomatic BPH, were included in the study. A complete list of inclusion and exclusion criteria for this clinical trial have been previously published.[15] Key inclusion criteria included an IPSS ≥13 and prostate volume of 30 cm$^3$ to 80 cm$^3$ without restrictions on the presence of a middle
lobe. Subjects were randomized to treatment and control in a 2:1 ratio using a permuted-block randomization schedule with varying block size, stratified on center and baseline IPSS. Unblinded at the 3-month follow-up visit, 53 control subjects requalified for inclusion in the study and elected to receive Rezum thermal therapy. Crossover treatment occurred within 3 to 6 months post-enrollment date.

**Statistical Method**

The study was powered at 80% with 0.025 one-sided type I error to evaluate the hypothesis that the reduction in IPSS from baseline to 3 months for the active treatment exceeds 125% of that for the control. This hypothesis was assessed using a Student t-test on the ITT populations to compare the mean changes in treatment and control arms. For the primary efficacy endpoint, subjects who chose alternate treatments other than the assigned treatment prior to the 3-month follow up period were considered failures and their baseline value was used for the primary endpoint analysis. Summary results for quantitative variables were presented as mean ± standard deviation.

**Procedure**

The technology, device description and technical details of the procedure for Rezum water vapor thermal therapy have been published in detail in earlier reports.[12] The basic principle of the Rezum System is to apply a controlled level of RF power to an inductive coil heater in the Delivery Device through which a pre-determined amount of sterile water is delivered to selected areas of the prostate. Using a transurethral approach, the heat generated by the RF power transforms the sterile water from liquid to vapor state (stored thermal energy). The vapor is convectively delivered directly into the tissue interstices of the hyperplastic tissue in the transition zone of the prostate when treating the lateral lobes, or in the central zone of the prostate in the case of treatment for an obstructive middle lobe. Each vapor injection lasts for 9 seconds. The number of injections varies from case to case depending on the size of the prostate and whether the physician chooses to treat the median tissue. Subjects in the control arm underwent a sham procedure with 19F to 21F rigid cystoscopy.

**Study Assessment**

The efficacy endpoint comparing the treatment and sham/control arms was measured at 3 months post-procedure via IPSS. Subjects were unblinded following completion of their 3-month follow-up visit and participants in the control arm were offered the option of treatment with the Rezum System if they still met the initial study inclusion criteria. Crossover treatment occurred within 3 to 6 months post-enrollment date. Subjects in the treatment and crossover-arms were followed at 3, 6, and 12 months and then annually until 5 years. At each follow-up visit, subjects were evaluated by measuring Qmax, PVR volume, voided volume, and PSA, and by administration of the IPSS, IPSS-QOL and BPHII, surveys. Incontinence was assessed using the OAB-q SF and ICS male IS-SF; sexual function was assessed using IIEF-EF and MSHQ-EjD. The protocol pre-specified a responder endpoint defined as freedom from retreatment for BPH and 30% reduction of IPSS from baseline. AEs were captured and adjudicated by independent data monitoring and clinical events committees. To prevent lost to follow up and minimize attrition, patients were closely followed as per clinical trial protocol. Retreatment of BPH, by medical or surgical management, was recorded and follow-up of the subject discontinued.
Results

One hundred thirty six subjects were randomized to the Rezum treatment-arm and 61 subjects were randomized to the control-arm. Fifty three control subjects requalified for crossover, received treatment and participated in follow-up through 5 years. (Table-1)

All of the Rezum treatments were completed in the office or ambulatory-surgery center. Of these 188 treated subjects, 170 (90.4%) received oral pain medication, 39 (20.7%) received a prostate block/epidural and 19 (10.1%) subjects received IV sedation (one subject opted out of the study after preparation for the procedure, but prior to treatment). The mean number of vapor injections per subject was 4.5 ± 1.8 (135) and 5.1 ± 1.9 (53) across the treatment and crossover groups respectively. Middle lobe was noted and treated in 58 of 188 subjects (30.9%). These subjects received an additional mean 1.6 injections ± 0.7 to the median tissue. The average procedure time (initial insertion of device until complete removal) for subjects in the treatment-arm was 5.3 minutes ± 3.5 and 4.4 minutes ± 1.7 in the crossover-arm.

As noted in Figure-1, after 5 years, data from 77 subjects from the treatment-arm were analyzed. There were no study withdrawals attributed to any procedure or device-related AEs. Eighteen subjects were lost to follow-up while an additional 13 withdrew consent. Five subjects were censored for protocol non-compliance, and 2 were withdrawn for prostate cancer treatment. Within the crossover group, 21 subjects completed 5 years of follow-up. Ten subjects withdrew consent and an additional 5 were lost to follow-up. One subject was censored for non-compliance, 1 due to cancer diagnosis, and 1 subject died due to unrelated causes.

Device and procedure related AEs were similar between groups. A total of 151 related-AEs were reported in 53 subjects in the treatment-arm and 59 events in 23 subjects in the crossover group. As expected, the most common AEs related to the device or procedure were dysuria (16.9% and 18.9%), gross hematuria (12.5% and 11.3%), hematospermia (7.4% and 3.8%), urinary frequency (5.9% and 5.7%), AUR (4.4% and 5.7%), suspected UTI (3.7% and 7.5%) and decrease in ejaculatory volume (3.7% and 7.5%) between the treatment and crossover-arms respectively. These AEs were mild to moderate in severity and resolved either spontaneously or with routine treatment. No late related-AEs occurred from years 1 to 5. Details of all other AEs, including the SAEs were previously reported.[12-14]

Outcome measures for the original treatment-arm are as follows: IPSS decreased from 22.0 points at baseline to 10.6 at three months for a change of −11.3 ± 7.6. The primary endpoint analysis demonstrated that the IPSS reduction in the active treatment exceeded 125% of that in the control arm (P < 0.0001). IPSS score improvement remained consistent throughout the study as the mean value at 5 years showed near 48% reduction (11.1 ± 7.8) from baseline. Similarly, the improved IPSS QOL score remained consistent from baseline reducing from a mean value of 4.4 ± 1.1 to 2.3 ± 1.5 at 3 months and to 2.2 ± 1.4 or 45% reduction at 5 years. Flowrate as measured by Qmax [voided volume ≥ 125 mL] exhibited similar sustained improvement: increasing from a baseline of 9.9 ± 2.2 to 15.5 ± 6.7 at the end of year 1 and remained at 14 ± 5.4 (49%) through year 5 of follow-up. Additionally, 5-year BPHII results, which peaked at a 65% decrease 6 months post-treatment (2.2 ± 2.6), showed similarly durable improvement with a mean decline of 48% at 5 years (2.8 ± 3.2). (Figure-2) Further, 61% of subjects in the treatment-arm (82 of 135) were both free from retreatment and had a 30% or greater reduction from baseline IPSS at 5 years.
There were no reports of de novo device or procedure-related erectile dysfunction throughout the duration of the study. Five-year results corresponded well with prior time points. Mean PSA value remained stable through 5 years of follow-up. Modest changes were observed in IIEF-EF, MSHQ-Function at 5 years consistent with the aging of the treated cohort, with changes of -2.4 ± 9.2 and -2.0 ±3.9 respectively. MSHQ-EjD Bother score improvement remained consistent through the length of follow-up with a 16% improvement at 60 months (Appendix).

As displayed in Figure-3, the total surgical retreatment rate for the treatment-arm at the end of the study was 4.4%. Within that group, 83% of the surgical retreatments occurred in the first 2 years of follow-up, with no treatment-arm subjects receiving surgical retreatment after year 3. As was noted in a prior manuscript, of the 6 subjects retreated surgically, 4 of these subjects had identified obstructive median tissue that was initially left untreated. An additional 11.1% of treatment-arm subjects were retreated with BPH medication through 5 years. Four crossover-arm subjects were retreated surgically (3 for previously untreated obstructive median tissue) and 10 received BPH medication.

**Discussion**

The results of this RCT revealed that Rezum thermal therapy for BPH has clinically meaningful outcomes and proven durability. The inclusion of patients with obstructive median tissue underscores the rare versatility of water vapor thermal therapy especially among MISTs, as Rezum is capable of ablating tissue from lateral lobes as well as tissue of an enlarged central zone (i.e. middle lobe or median bar) without advanced training or learning a complex technique.

The 5-year responder analysis endpoint (30% improvement of IPSS and freedom from retreatment) is also of particular importance given the recent draft guidance proposed by FDA as the basis for minimal clinical improvement following device therapy for BPH as reported in the analysis from Roehrborn et al. Without a predefined measure for clinically significant difference, this IPSS responder analysis provides a reliable surrogate.

Other MISTs like PUL or other implantable devices, provide relief from symptoms without removing tissue. It is perhaps less surprising then that the 5-year surgical retreatment rate of 4.4% for the treatment-arm herein compares so favorably to the 13.6% reported in the 5-year LIFT study. These results also compare well to other MISTs as TUNA and TUMT where 5-year study surgical retreatment rates ranged from 14% to 51% and 8.9% to 21% respectively. This is noteworthy when considering that 7 of the 10 subjects retreated surgically in this study had identified middle lobes that were previously untreated, supporting a more durable impact on LUTS if an obstructive middle lobe is addressed when noted.

Despite the majority of subjects in this study presenting with severe LUTS at enrollment (72.5% with IPSS 19-35) outcomes measured by storage and voiding function, urinary flow rates, quality of life improved from the first visit 3 months post-procedure through the final at 60 months after a single water vapor thermal therapy treatment without negatively impacting sexual function. In order to produce outcome measures with similar results to this study, pharmacotherapy requires patients to adhere to a combination of interminable prescription regimens, which often have undesirable sexual side effects. To achieve similar results with PUL, permanent implants are required, but the retreatment rates appear much higher. The Rezum II study results aid in establishing water vapor
therapy as a first-line treatment for BPH. Patients who may be candidates for Rezum are often referred to more invasive surgical techniques such as TURP, HoLEP, or other laser treatments that can involve greater bleeding risks, longer-term recovery time, declines in measures of sexual function, and other undesirable side effects.[27]

Study limitations included participant attrition, but that is neither unique to this trial, nor studies within this disease state. As was the case with the LIFT study, a similar percentage of participants from the treatment-arm were evaluated at 5 years per protocol (62%) as this study (57%), and in each study the statistical significance of the functional results was not negatively impacted.[20] Attrition rates are also similar for prospective studies with other modalities like TURP,[23, 28] PVP,[29] TUMT,[30] and TUNA.[23] Additionally, the lack of urodynamic testing limits the opportunity to analyze bladder function, the degree of obstruction, and bladder contractility and the potential impact on these reported results.

Conclusion

Water vapor thermal therapy for BPH is a treatment that combines the properties of a MIST with the functional outcomes expected from other ablative therapies. There is a short learning curve without the need for advanced techniques to treat various zones of the prostate, including an obstructive middle lobe. The positive safety profile, long term durability, and maintenance of sexual function make water vapor thermal therapy an optimal treatment choice for patients with moderate-to-severe LUTS.

Acknowledgements

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References:

24. Gupta, N., Rogers, T., Holland, B. et al.: Three-Year Treatment Outcomes of Water Vapor Thermal Therapy Compared to Doxazosin, Finasteride and Combination Drug Therapy in Men with Benign Prostatic Hyperplasia: Cohort Data from the MTOPS Trial. J Urol, 200: 405, 2018
Table 1. Baseline Characteristics of Treatment and Crossover Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment (n=135*)</th>
<th>Crossover (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening, years</td>
<td>63.0 ± 7.1</td>
<td>62.9 ± 7.0</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
<td>2.1 ± 1.5</td>
<td>2.1 ± 1.6</td>
</tr>
<tr>
<td>IPSS</td>
<td>22.0 ± 4.8</td>
<td>20.0 ± 6.6</td>
</tr>
<tr>
<td>IPSS QoL</td>
<td>4.4 ± 1.1</td>
<td>3.9 ± 1.4</td>
</tr>
<tr>
<td>Prostate Volume, cm$^3$</td>
<td>45.9 ± 12.9</td>
<td>44.5 ± 13.3</td>
</tr>
<tr>
<td>$Q_{\text{max}}$, mL</td>
<td>9.9 ± 2.2</td>
<td>10.1 ± 3.7</td>
</tr>
<tr>
<td>PVR, mL</td>
<td>82.4 ± 51.5</td>
<td>93.9 ± 77.2</td>
</tr>
</tbody>
</table>

PSA: Prostate Specific Antigen, IPSS: International Prostate Symptom Score, QoL: Quality of Life, $Q_{\text{max}}$: Peak Flow Rate, PVR: Post Void Residual

*One subject from the treatment cohort opted out immediately from the study without being treated with the Rezum procedure, and consequently, that subject was not considered while calculating the average baseline values.
Figure-1. CONSORT (Consolidated Standards of Reporting Trials) diagram of subject disposition in Rezum water vapor thermal therapy study including the thermal therapy, control and crossover (C) groups.

*Subjects retreated with Rezum procedures were excluded from analysis. ITT, intent to treat analysis; PP, per protocol analysis; TURP, transurethral resection of prostate. (Color version available online.)
Figure 2. Graphical representation of the outcomes at the end of the 5 year study for Rezum water vapor thermal therapy, showing the results of both treatment and crossover arm. IPSS (A), IPSS Qol (B), Qmax (C), BPHII(D). Values are means and error bars represent 95% CI.
Figure 3.

Treatment Arm Retreatment Rates through 5 Years

<table>
<thead>
<tr>
<th>Time</th>
<th>Medication</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>12M</td>
<td>0.8%</td>
<td>2.2%</td>
</tr>
<tr>
<td>24M</td>
<td>2.2%</td>
<td>3.7%</td>
</tr>
<tr>
<td>36M</td>
<td>3.7%</td>
<td>4.4%</td>
</tr>
<tr>
<td>48M</td>
<td>5.2%</td>
<td>4.4%</td>
</tr>
<tr>
<td>60M</td>
<td>11.1%</td>
<td>4.4%</td>
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