Universitätsspital Basel

# Synopsis of study protocol

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| **Sponsor / Sponsor-Investigator** | PD Dr. Jan Ebbing, MD |
| **Study Title:** | SteamOne - Prospective Registry Database for Rezum water vapor therapy of the prostate |
| **Short Title / Study ID:** | SteamOne |
| **Protocol Version and Date:** | Version 1.3, 10.02.2023 |
| **Trial registration:** | www.clinicaltrial.gov, ID: NCT05495633<br>www.drks.de, ID: DRKS00029915 |
| **Study category and Rationale** | Risk category A acc. to ordinance HRO Art.7 |
| **Clinical Phase:** | NA |
| **Background and Rationale:** | Benign prostate obstruction (BPO) affects many men over 50 years of age. It is associated with a number of lower urinary tract symptoms (LUTS), like increased urinary urgency, increased frequency of micturition, weakened urine stream, residual urine sensation or nocturia. In addition to drug treatments for BPO-related LUTS, there are several surgical treatment options for BPO. Due to its minimally invasive character, the approved Rezum - water vapor therapy of the prostate for the treatment of LUTS associated with BPO is attracting increasing attention from both the urological experts and from patients. Data on efficacy, durability of efficacy, safety/complications and groups of indications are still limited and refer to relatively small numbers of cases in cohort studies and one sham comparison study (1–5). In addition, data on quality of life, recovery from anesthesia and pressure-flow studies (urodynamic investigations) associated with a Rezum treatment, as well as data on patients´ preferences, motivations and expectations for Rezum treatment are not available at all. The European Association of Urology (EAU) mentions Rezum under alternative ablative techniques under investigation without giving any recommendations in the use of Rezum in its current guideline "Management of Non-neurogenic Male LUTS" (6). The guideline panel gives practical considerations and demands randomised controlled trials against a reference technique to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety of water vapor energy treatment. However, randomised controlled trials often examine idealized patients, which may make it difficult to draw conclusions for other patient groups or for patients in routine practice. Thus, “real life” data are just as important to determine the role of Rezum water vapor therapy in the treatment of BPO and male LUTS. |
| **Objective(s):** | a) To assess the available promising clinical data of Rezum – water vapor therapy in patients with BPO and male LUTS in terms of efficacy, durability and safety in a large, prospective, multi-center cohort consisting of 1000 “real-life” patients with a follow-up of 5 years.<br>b) To answer endpoints/questions of special interest in the context of a Rezum treatment. |

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| **Outcome(s):** | Primary Endpoint<br>Efficacy of the Rezum intervention to improve micturition through a 25% (minimal clinical difference of 5.2 points) improvement in International Prostate Symptom Score (IPSS) (7) five years after treatment with Rezum.<br><br>**Secondary endpoints**<br>**Efficacy of Rezum to improve micturition**<br>• Improvement of maximum urinary flow rate (Qmax)<br>• Decrease of post voiding residual volume (PVR)<br>• Decrease of prostate size<br>• Retreatment rate (medical (drugs), bladder catheter and surgical)<br>• Improvement of International Consultation on Incontinence Questionnaire for male lower urinary tract symptoms (ICIQ-MLUTS) (8)<br><br>**Efficacy of Rezum to preserve sexual function (erection, ejaculation, orgasm, sexual satisfaction)**<br>• Changes of Male Sexual Health Questionnaire (MSHQ) (9)<br>• Changes of International Consultation on Incontinence Questionnaire Male Sexual Matters Associated with Lower Urinary Tract Symptoms Module (ICIQ-MLUTSsex) (10)<br><br>**Surgical safety and side effects of Rezum**<br>• Intraoperative complications classified by ClassIntra (11)<br>• 30-days postoperative complications classified by Clavien-Dindo classification (12)<br>• Typical side effects of Rezum like hematopsermia, dysuria and hematuria are investigated by a self-designed patient questionnaire<br><br>**Antimicrobial prophylaxis**<br>• Effectiveness of the chosen antimicrobial prophylaxis by analysing the rate of postoperative symptomatic urinary tract infections (UTI) within the first 30 days after surgery as part of the Clavien-Dindo classification<br><br>**Patients with pressure-flow studies (urodynamic investigations)**<br>• Changes of bladder outlet obstruction index (BOOI), bladder contractility index (BCI) and detrusor (bladder muscle) overactivity (DO) associated with Rezum (13)<br><br>**Patients with MRI investigations**<br>• Changes of prostate size, ablative lesions (lesions caused by Rezum) PI-RADS (prostate imaging-reporting and data system) lesions associated with Rezum (14,15)<br><br>**Patients with prostate cancer**<br>• Rate of patients under active surveillance with prostate cancer that get Rezum treatment<br>• Rate of prostate cancer detected by positive prostate biopsy in the 5 years of follow-up after treatment with Rezum<br><br>**Anesthesia**<br>• Type of anesthesia (general anesthesia, spinal anesthesia, local anesthesia, analgosedation) incl. reason for chosen type of anesthesia |

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| | • Postoperative recovery from surgery/anesthesia using the Quality-of-Recovery-15 (QoR-15GE) questionnaire (16)<br>**Quality of Life (QoL)**<br>• Investigation of QoL changes associated with the Rezum treatment using the PROMIS Global Health 10 questionnaire (17)<br>**Patient's perception of pain during and after Rezum treatment**<br>• Changes of Numeric pain Rating Scale 0-10 (NRS)<br>**Patients´ satisfaction with clinic treatment**<br>• The ICIQ-S assesses aspects of experience, expectations, and outcomes to evaluate satisfaction after urological surgery. The questionnaire is answered by patients 2 weeks, 6 weeks, 3 months, 6 months, 12 months and annually after surgery. This endpoint has never been investigated in a study related to Rezum.<br>**Patients´ preferences, motivations and expectations for Rezum treatment**<br>• Investigation of patients' reasons for preference/choice of Rezum and associated expectations using self-designed questionnaires<br>**Doctors´ preferences, motivations and reasons to use Rezum**<br>• Investigation of doctors´ reasons for preference/choice of using Rezum in a patient using self-designed questions<br>**Influence of steam injection number and injection points**<br>• Investigation of influence of steam injection number and Injection points arrangement on outcome parameters, (micturition parameters (IPSS, ICIQ-MLUTS), sexual function (MSHQ, ICIQ-MLUTSsex) prostate size, side-effects, and complications) |
| **Study design:** | This is a prospective, multicentre observational study following up patients with BPO-related LUTS treated with Rezum over a period of 5 years. |

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| **Inclusion / Exclusion criteria:** | **Inclusion criteria:**<br>- All male patients who are treated with Rezum due to prostate obstruction and LUTS in the participating study centers can be included if certain inclusion criteria are met and some exclusion criteria are not present.<br>- The indication to perform Rezum needs to be made independently from the study. The decision for Rezum treatment is the responsibility of each individual practitioner and patient.<br>- Age ≥ 18 years<br>- Operated or supervision of surgery by a certified urologist<br>- Subgroups of special interest are e.g. catheter-dependent patients, patients with oral anticoagulation, patients with preoperative urodynamic pressure-flow investigation (not older than 6 months) or patients with prostates bigger than 80 ml<br><br>**Exclusion criteria:**<br>- Missing informed consent<br>- Lack of ability to answer questionnaires in German language or mentally by oneself (e.g. in dementia, mental disability).<br>- Patient does not have a personal email address available and the survey cannot be completed via a relative's email address and the patient is not willing to complete the survey on the tablet at the clinic.<br>- Known or suspected neurogenic bladder dysfunction in e.g. Parkinson's disease, multiple sclerosis or other neurological diseases with possible effects on bladder function<br>- History of malignant bladder tumor in the last two years (including CIS) or currently present malignant bladder tumor at time of Rezum treatment (including CIS)<br>- Previous operation(s) on the prostate, except prostate biopsy, if this was performed more than 4 weeks ago at time of Rezum treatment<br>- Previous operation(s) on the bladder neck<br>- Presence of bladder neck stenosis requiring treatment at time of Rezum treatment<br>- Planned combination of Rezum treatment concurrently with another urologic * or non-urologic procedure.<br><br>** also the combination with a planned transurethral procedure is not allowed except for bladder stone removal* |

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| **Measurements and procedures:** | The study uses a web-based German-language registry database called heartbeat ONE marketed by heartbeat medical solutions (Greifswalder Straße 212, 10405 Berlin, Germany) which provides both clinical (CROMs) and patient reported outcome measures (PROMs).<br>PROMS are investigated by validated questionnaires, self-designed questionnaires and by home urine flow measurement.<br>Validated patient questionnaires used in the study:<br>• IPSS/QoL<br>• ICIQ-MLUTS<br>• ICIQ-S<br>• MSHQ<br>• ICIQ-MLUTSsex<br>• QoR-15GE<br>• PROMIS Global Health 10<br><br>Self-designed patient questionnaires used in the study:<br>• Patients´ preferences and expectations for Rezum treatment<br>• Patients´ satisfaction with the clinic treatment<br>• Side effects of the Rezum treatment and pain medication<br>• (Re)medication to treat BPO and LUTS<br>• Reoperations after Rezum treatment<br><br>Home urine flow measurement:<br>• Patients will use an approved and certified home uroflowmetry medical device called iUFlow marketed by Kesem Health Pty Ltd, 5A Hartnett Cl, Mulgrave VIC 3170, Australia.<br><br>The patients will fill in the questionnaires and will use the iUFlow device as outlined in the table below. Patient questionnaires can be answered by patients via e-mail link, using either their personal e-mail address or a relative's e-mail address. Alternatively patient questionnaires can be answered on a tablet during a routine visit in the clinic/medical department.. iUFlow data are transferred via a device specific smartphone app into the study database. Clinical data (CROMs) will be assessed at routine visits, as scheduled by the treating physician. If patients don't use a smartphone uroflowmetry will be performed during routine clinical follow up visits. |
| **Study Product / Intervention:** | There is no study-specific intervention in the study. Patients who receive Rezum therapy as part of their routine treatment will be observed for 5 years. |
| **Control Intervention (if applicable):** | NA |

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| **Number of Participants with Rationale:** | One of the motivations behind recruiting a large cohort is the ability to conduct subgroup analyses. Given that 15% of patients are expected to drop out each year, 920 patients should be recruited into the study in order to have 408 patients left after five years. The Clinical Trial Init (CTU) of the Department of Clinical Research (DKF) of the University Hospital Basel (USB) recommend to round this number to 1000 due to uncertainty in the assumptions made and because adding “center” as a random effect into the model could further reduce the power. |
| **Study Duration:** | Estimated duration for the main investigational plan (e.g. from start of screening of first participant to last participant processed and finishing the study) is 90 months (7,5 years). |
| **Study Schedule:** | Month/Year of First-Participant-In: December 2022<br>Month/Year of Last-Participant-Out (planned): December 2029 |
| **Investigator(s):** | PD Dr. Jan Ebbing, MD<br>University Hospital Basel<br>Department of Urology<br>Spitalstrasse 21<br>CH-4031 Basel<br>Switzerland<br>Tel. 0041 61 32 85659<br>Mail: jan.ebbing@usb.ch |
| **Study Centre(s):** | This is a multicenter observational study with a maximum of 20 sites in Switzerland, Germany and Austria. Clinics qualify as study sites if they have already performed more than 50 Rezum procedures and see potential to recruit 50 patients within a 12–18-months period. |

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| **Statistical Considerations:** | The primary endpoint of the study is symptom reduction from baseline to five-year follow-up as measured by the international prostate symptom score (IPSS). The IPSS is scored on a 0 to 35 scale with higher scores indicating greater frequency of BPH symptoms.<br>The mean difference between IPSS at five years follow-up and at baseline will be assessed using a linear mixed effects model with IPSS score as the outcome. The measurement time point will be measured as a fixed effect, and patient ID (possibly nested within center ID) will be included as a random effect. For the subgroup analyses, the group membership will be included as an interaction with measurement time point.<br>We will use both statistical models and descriptive statistics to answer our questions.<br>We will summarise the parameters for each time point to allow us to explore changes over time. In relation to the subgroup analyses, we will identify factors that influence the endpoints.<br>The endpoints described above will be assessed using the same mixed models framework that will be used for assessing the primary outcome. We will use linear mixed models for the continuous outcomes and mixed logistic regression models for the binary outcomes. The rationale for sample size calculation is outlined under “Number of Participants with Rationale”.<br>The statistical analysis plan will be finalized before database closure and will be under version control at the CTU of the DKF. |
| **GCP Statement:** | This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements. |

**Explanation for the Inclusion of vulnerable Subjects (if applicable):**

NA

**Recruitment Procedure (if applicable: Advice/Flyer have to be submitted ; if applicable, please indicate the Localisation / Medium (which Newspaper)**

Once Rezum treatment has been determined for a patient, this patient will be approached by his treating physician. If all inclusion and exclusion criteria are met, the patient will be asked if he is interested in participating in the study. Since Rezum is a highly elective surgery and will be performed on a scheduled basis, the patient has ample time to read the informed consent letter and ask questions, as is customary for any elective surgery informed consent.

**Study Procedure/Flowchart with Timelines: Study specific Examinations have to be clearly identified**

Patients are asked to fill in questionnaires at the time points indicated in the table below. In addition, clinical parameters will be assessed during routine visits at the clinic, 3, 6 and 12 months postoperative and then annually for a total of 5 years.

| | **Before Rezum** | **After Rezum** | | | | | | | | | |
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| | | *1 day* | *2 weeks* | *6 weeks* | *3 months* | *6 months* | *1 year* | *2 years* | *3 years* | *4 years* | *5 years* |
| **Questionnaires** | | | | | | | | | | | |

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| IPSS/QoL | x | | | x | x | x | x | x | x | x | x |
| ICIQ-MLUTS | x | | | x | x | x | x | x | x | x | x |
| MSHQ | x | | | x | x | x | x | x | x | x | x |
| ICIQ-MLUTSsex | x | | | x | x | x | x | x | x | x | x |
| QoR-15 | x | x | x | | | | | | | | |
| PROMIS Global Health 10 * | x | | x | x | x | x | x | x | x | x | x |
| Numerical pain rating scale (NRS) ** | x | x | | | | | | | | | |
| Satisfaction with treatment (ICIQ-S) *** | | | x | x | x | x | x | x | x | x | x |
| Side effects of Rezum treatment and pain medication. | | | x | x | x | | | | | | |
| Patients´ preferences and expectations for Rezum treatment | x | | | | x | x | x | x | x | x | x |
| BPH/LUTS medication | | | x | x | x | x | x | x | x | x | x |
| Re-operations | | | | | x | x | x | x | x | x | x |
| Bladder catheter | | | | | x | x | x | x | x | x | x |
| Completion time in minutes | 31 | 3 | 16 | 25 | 31 | 28 | 28 | 28 | 28 | 28 | 28 |
| | | **Home urine flow measurement** | | | | | | | | | |
| iUFlow | x | | x | x | x | x | x | x | x | x | x |
| Completion time in minutes | 15 Min. | | 5 Min. | 5 Min. | 5 Min. | 5 Min. | 5 Min. | 5 Min. | 5 Min. | 5 Min. | 5 Min. |

* contains a Numeric Pain Rating Scale (NRS); ** same NRS like in PROMIS Global Health 10; *** full questionnaire until 3 months; 6 months, 12 months and year 1-5 only questions 1-6

**Risks/ Inconveniences, which are Study specific:**

In general, there are no risks involved in participation in this study. Study-related activities are restricted to filling in questionnaires, which are used via secured, well-established platforms, which have been widely used in clinical trials. Filling in questionnaires can be time consuming, what can be perceived as a burden. Furthermore, the uroflowmetry measurements (iUFlow) are also approved for usage by patients at home and bear no risks. All other data collected within this study are part of routine Rezum treatment and follow-up of patient with BPO related LUTS. Patients with existing pressure-flow study (urodynamic investigation) before the Rezum treatment may be asked if they would allow a control pressure-flow study on a purely voluntary basis.

**Coverage of Damages:** Insurance: yes

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO). For sites outside of Switzerland, local regulations apply.

**Storage of Data-and Samples for Future Research Aims:** yes
If yes, please indicate in which documents (for ex. study protocol, informed consent) and on which pages you have described this topic).

No biological samples will be collected and stored for further use. Further use of data is described in the patient informed consent form on page 6 ff. and in the application for ethical approval on pages 33 ff.

**Ethical Considerations:**

As described above, participation in this study does not involve any risks that would not be in line with routine clinical practice. Individual patients may not necessarily have a benefit in participating. However, since the patients have a continuous and standardized self-assessment of their health status and of the function of their urinary tract with the help of the questionnaires and the home uroflowmetry device, they have a valid self-monitoring of the Rezum effects over time.
In addition, by participating, patients will help to further investigate the benefits of Rezum treatment, potential risks and side effects, and the effect on sexual function and quality of life for different groups of males. By doing so, study participants will give future patients the chance to be better advised by physicians regarding Rezum treatment with the data obtained from this study.

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