Statistical Analysis Plan

A Real World Study to Evaluate the Feasibility, Preliminary Safety and Performance of Rezūm System in BPH Treatment in China (Rezūm RWS study)

Study Reference: U0719

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APPROVALS (Check/Complete one below):

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Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
Version-AA	90702621 Rev/Ver AE	Initial document	NA	NA

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1 PROTOCOL SUMMARY

- **Study title:**

A real world study to evaluate the feasibility, preliminary safety and performance of Rezūm system in BPH treatment in China.

- **Study Objective(s):**

This RWS study is to evaluate the feasibility, preliminary safety and performance of Rezūm system in BPH treatment in China, to generate local real world data from a Chinese BPH population.

- **Study Design:**

This is a retrospective, single arm, RWS study, which will be performed in investigation site, Boao Yiling Life Care Center.

- **Planned Number of Subjects:**

Up to 30 subjects who were diagnosed as BPH and treated with Rezūm system will be collected to get 22 treated subjects with valid data.

- **Planned Number of Centers:**

One (1) investigation site, Boao Yiling Life Care Center

- **Indication(s) for Use:**

The Rezūm System is intended to relieve symptoms, obstructions, and reduce prostate tissue associated with BPH. It is indicated for men ≥50 years of age with a prostate volume ≥ 30cm^3 and ≤80cm^3. The Rezūm System is also indicated for treatment of prostate with hyperplasia of the central zone and/or a median lobe.

- **(Commercial) Device/System applied**

Rezūm Generator （Model #G2200-0032）
Rezūm Delivery Device Kit (Model # M006D2201-0032）

- **Method of Assigning Patients to Treatment:**

Not applicable, this is a single arm study.

- **Study Duration:**

This is a retrospective study, and it will take about 3 months to complete data collection.

- **Follow-up Schedule:**

Not applicable, this is a retrospective study with no prospective follow up visit.

- **Key Inclusion Criteria:**
    - The subjects will provide written informed consent and agree to data collection

- The subjects who were diagnosed as BPH and treated by Rezūm procedure in Hainan medical pilot zone will be enrolled in this study.

- **Key Exclusion Criteria:**

This is a retrospective study without any formal exclusion criteria.

2 INTRODUCTION

Benign prostatic hyperplasia (BPH) with associated lower urinary tract symptoms (LUTS) is a common medical condition in the aging male. Progressive prostate enlargement causes bladder outflow obstruction and lower urinary tract symptoms, which have a significant impact on patients' quality of life. For many men, medications are the most common way to control mild to moderate symptoms of BPH to reduce its major symptoms. However, BPH medications have several systemic side effects, are costly if used for long periods of time, and some subjects have difficulty with complying with medications, particularly in the older population. For severe BPH symptoms, transurethral resection of the prostate (TURP), laser vaporization, or thermal ablation are common treatments of choice.

Transurethral resection of the prostate (TURP), which is considered the gold standard intervention, have a high complication rate, such as TRUS, retrograde ejaculation, erectile dysfunction, urethral stricture; and its surgical retreatment rate was 1–2% per year. Furthermore, it requires the use of general or spinal anaesthesia, which may cause more risks for elderly.

The Rezūm System is a minimally invasive thermal ablation treatment that may mitigate the symptoms of BPH. The Rezūm System treatment is rapid, preserves the urethra, and subjects may potentially have relief from the symptoms of BPH as soon as 1 week after treatment. The Rezūm System has got CE mark and FDA approval in 2013 and 2015 respectively, and a series of clinical studies have been conducted worldwide.

In view of the aggravation of the aging process in China and the high incidence rate of male patients over 50 years old, there is a considerable socioeconomic burden to patients and society as it represents the most commonly presenting urological complaint.
This retrospective study will collect the data of treated subjects in the hospitals in BOAO medical pilot zone, to evaluate it safety and performance in Chinese patients, which will provide real world evidence for extensive use in China.

Please refer Protocol Table 9.1-1 Data collection schedule

Table 9.1-1:The data collection schedule

Procedure/Assessment	Baseline/pre-procedure	Index Procedure	Post procedure/ Prehospital Discharge	follow-up post-precedure #
Informed consent				X&
Demographics	X			
Medical history	X			
Physical examination (height, weight, etc)	X			X
Prostate volume (MRI, DUS)*	X			X
Uroflowmetry(Qmax, Urinary volume)	X			X
PVR	X			X
IPSS	X			X
QoL	X			X
IIEF	X			X
MSHQ-EjD	X			X
Procedure information		X		
Length of catheterization			X	
Surgical retreatment				X
Medication(s) used(LUTS /BPH)	X		X	X
Device Defect (if available)		X		
Adverse events assessment		X	X	X

Note: # All information of subjects available before the defined end of study will be collected in this retrospectively study, data missing will be allowed.

*Prostate volume -data form MRI and DUS are collected, MRI data will be preferred to used for statistic, DUS data will be used ONLY MRI data unavailable.

&Only written informed consent form is provided after initiation , data will be collected.

3 ENDPOINT ANALYSIS

Primary Efficacy Endpoint: IPSS change at 3-6M post Rezūm procedure.

Primary Safety Endpoint: Device Related Serious Complications at 3-6M post Rezūm procedure.

Composite device related serious complications for this endpoint are defined as:
1. Device perforation of the rectum or GI tract
2. Device related formation of fistula between the rectum and urethra
3. De novo severe urinary retention lasting more than 21 consecutive days post treatment.

3.1 Primary Effectiveness Endpoint

Primary Efficacy Endpoint is IPSS change at 3-6M post Rezūm procedure.

International prostate symptom score (IPSS) is a questionnaire used to indicate the severity of LUTS symptoms, there are 7 questions relating to different symptoms subjects be experiencing and one question relating to overall quality of life.

IPSS scores will be collected at baseline and post procedure. If several IPSS scores are collected between 90 and182 days, the last IPSS score for 3-6 months post procedure will be used to assess the primary efficacy endpoint.
Reduction in IPSS score from Baseline = IPSS score at baseline - IPSS score at 3-6M post procedure.

The improvement of IPSS score of 30% will be calculated for 3-6 months post procedure against baseline.

3.1.1 Hypotheses

H_0: $\Delta \leq 5.5$
H_1: $\Delta > 5.5$
Where Δ = reduction in IPSS score at 3-6 month compared to baseline

The mean reduction in IPSS score at 3-6 month from baseline will be calculated with its 90% confidence interval. If the lower bound of the one-sided 95% CI is greater than 5.5 then the null hypothesis will be rejected, and the primary endpoint will be met.

3.1.2 Sample Size

In Rezūm Pivotal II study, IPSS score represents a 11.2±7.6-point reduction at 3M post Rezūm procedure in treatment arm, while 4.3±6.9-point reduction in sham control. In Pivotal trial, IPSS score in treatment group decreased 25% (5.375) compared to sham control group is recognized as meaningful. For this retrospective RWS study, a performance goal (PG) of 5.5 was deemed as clinically meaningful, and the expected score reduction is assumed to be 10 at 3-6M post Rezūm procedure.

The sample size is calculated according to below formula:

$$n = \frac{(Z_\alpha + Z_\beta)^2 * \sigma^2}{\delta^2}$$

n is sample size, δ = 4.5 (since 5.5 is the performance goal and 10 is expected IPSS change), σ = 7.6, α=0.05，β=0.20（power=80%）. Considering the small sample size needs to be iterative distribution, 22 subjects will provide more than 85% power. As this is retrospective study, there are chances of missing data in the study. A sample size up to 30 are expected to yield 22 treated subjects with available data at 3-6 months post procedure.

3.1.3 Statistical Methods

Descriptive statistics will be used to summarize the study endpoints. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum, and the corresponding 95% confidence interval of the mean. Categorical variables will be tabulated with frequencies, percentages along with the 95% confidence intervals.

3.2 Primary Safety Endpoint

Primary Safety Endpoint: Device Related Serious Complications at 3-6M post Rezūm procedure.

Composite device related serious complications for this endpoint are defined as:
1. Device perforation of the rectum or GI tract
2. Device related formation of fistula between the rectum and urethra
3. De novo severe urinary retention lasting more than 21 consecutive days post treatment.

AEs will be collected and relationship to device will be assessed by investigators, it will be assessed whether meet the pre-specific device related serious complications. All serious complications in up to 6 months (i.e. 182 days) post procedure will be used for primary safety endpoint.

Frequencies and percentages will be provided for AE summary.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

The primary effectiveness and safety endpoints will be analyzed on an efficacy analysis set and on safety analysis set respectively. Baseline characteristics and other variables descriptive statistics will be presented for safety analysis set.

4.1.1 Efficacy Analysis Set

The efficacy analysis set includes subjects with IPSS scores at baseline and at 3-6 months post-procedure.

4.1.2 Safety Analysis Set

The safety analysis set includes all enrolled subjects who has been treated with Rezūm system in hospitals in Hainan BOAO medical pilot zone.

4.2 Control of Systematic Error/Bias

All subjects treated with Rezūm system in Hainan BOAO medical pilot zone will be enrolled to reduce select bias during given time. The data will be collected completely and accurately.

4.3 Number of Subjects per Investigative Site

Not Applicable as this a single center study.

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

Following are the categorical endpoints:

1. Anesthesia method
2. Surgical retreatment post Rezūm procedure (if available)
3. Medication retreatment post Rezūm procedure (if available)
4. All SAEs

Following are the Continuous endpoints:

1. Rezūm operation time
2. Qmax and Post Void Residual Urine Volume (PVR）
3. Length of Catheterization
4. Quality of Life (if available)
5. Ejective function (MSHQ-EjD and IIEF (if available))

All the above measurements data will be presented in respective exhibits.

Length of catherization = Days from insertion to the removal day

5.2 Interim Analyses

Not Applicable.

5.3 Subgroup Analyses

The endpoints which would be presented using IPSS score as subgroup factor of are (0-7) Mildly symptomatic, (8-19) moderately symptomatic and (20-35) severely symptomatic.

All subgroup analyses are exploratory.

5.4 Protocol Deviations

No protocol deviations recorded due to retrospective study design.

5.5 Device Deficiencies

Summary table will be generated based on device deficiencies with count and percent for the available parameters. The counts and percentages of serious AEs in connect to the device deficiencies will be presented. A data listing will be also provided by subject, deficiency type, and if it leads to any event and preventive action taken for that.

5.6 Justification of Pooling

This is a single site study therefore all the data collected at the site will be included in the analysis.

5.7 Multivariable Analyses

No multivariate analysis is included for the primary or other endpoints.

5.8 Other Analyses

Missing data will be excluded for primary analysis in this small sample size study.
Based on the missing data during data review, Imputation with mean or median where applicable for continuous variable, and tipping point analysis for categorical variable might be conducted for sensitivity analysis. Incorrect and unreasonable data will be clarified before database lock.

Subject disposition (e.g., number completing the study) will be summarized with frequency tables and percentages.

Non-serious AE's and SAE's will be summarized as the number of events and rate per subject by MedDRA system organ class (SOC) and preferred term.

5.9 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the primary endpoint analysis will be documented in an amended Statistical Analysis Plan approved prior to performing the analysis. Changes from the planned statistical methods after performing the analysis will be documented in the clinical study report along with a reason for the deviation.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation. The validation level R1 chosen for all primary, secondary, safety and other additional endpoints. The validation program includes checking logs and generating compare reports in comparing with main programming datasets. Statistical analyses and validation will be performed by IQVIA team.

7 PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by IQVIA™ independently.

7.1 Statistical Software

All statistical analyses will be done using The SAS System Version 9.4_M6 software or above (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.).

7.2 Format of Output

Results of analysis will be output programmatically to Microsoft Office® Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Methods for Handling Missing Data

Missing data will be excluded for primary analysis in this small sample size study.

Sensitivity Analysis will be performed by imputing missing values with Last Observation Carried Forward (LOCF) method and Worst-case scenario method using values at baseline where applicable for continuous variable.

When calculating rates of all adverse events, both device and/or procedure related with missing event date (i.e. mm/dd/yyyy), the ideal is to work with safety and/or data management representatives to query sites for missing data. However missing and partial missing dates may be handled as using the worst-case scenario as follows:

Partial Date	**Action Taken**
Entire adverse event onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

7.4 SAS Code for Descriptive Statistics

Standard BSC macros will be used for descriptive statistics for continuous /categorical endpoints.

Proc Means code for Primary efficacy analysis

```
proc means data=XYZ  LCLM MEAN SD Min MAX N MEDIAN MAXDEC=2;
var chg;
run;
```