Protocol Title: Low Energy Shock Wave for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) — a randomized, double-blind, placebo-controlled, prospective study

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7. STATISTICAL ANALYSIS

7.1. Evaluability

Patients receiving baseline screening and treatment will be considered as intent-to-treat (ITT) population. The ITT population with the following conditions will be considered as per-protocol (PP) population:

1.Not taking any prohibited medications

2.Fulfilling all entry criteria

3.Have treatment visit and post-treatment evaluations on the primary endpoint

The efficacy evaluation will be performed on both the ITT and PP datasets while the safety evaluations will be performed only on the ITT datasets. The primary conclusions will be made for the primary and secondary endpoints on the ITT patients.

7.2 Analysis

The statistical objective of this study is to demonstrate that the efficacy of LESW is superior to placebo with respect to the decreases of O'Leary-Sant symptom score, VAS, increase in functional bladder capacity and improvement in GRA. The safety profile of LESW or placebo for the either group of intravesical treatment of patients with IC/BPS will also be confirmed.

Primary Efficacy Endpoint

The efficacy of LESW treatment will be evaluated for:

(1) Net change of the O'Leary-Sant symptom score from baseline to 1 month after the treatment day.

Secondary Efficacy Endpoint

The efficacy of LESW will be evaluated for:

(1)Net change of the following parameters from baseline to 1 month after the treatment day: Visual analog score (VAS) for pain (from 0 to 10), functional bladder capacity (FBC), voiding frequency at daytime and voiding frequency at night time as recorded in 3-day voiding diary.

(2) Global response assessment (GRA) of satisfaction by the patient (categorized into -3, -2, -1, 0, 1, 2, 3, indicating markedly worse to markedly improved) at 1 month after the treatment day. An improvement of GRA by 2 scales at 1 month is considered effective.

(3) Net changes of the maximum flow rate, voided volume and PVR from baseline to 1 month after the treatment day.

Voiding frequency at daytime and nighttime is measured as mean of the three-day voiding diary preceding the scheduled visit and the record days are 3 days.

Net change of each efficacy item will be analyzed by paired t-test between baseline and post-treatment in the treatment group and controlled group. The net changes of each efficacy item will be analyzed by ANOVA test to compare between treatment group and controlled groups. The global response assessment by the patients will be analyzed by Fisher exact test between the treatment and controlled groups.

All efficacy variables will be reported of respective point estimated and 95% confidence interval. Comparison tests will be reported of respective p value.

Secondary Safety Endpoints

(1)Local adverse event incidences (hematuria, micturition pain, UTI, urinary retention) will be reported by both treatment group and controlled group and by physiological systems as appropriate. Incidence of adverse events and the categories of adverse event severity between treatments will be analyzed. The coding system used will be COSTART.

(2) The abnormalities of laboratory test results will be reported by patient list in the patients who have been tested for having severe adverse event.

(3) The changes in physical examinations will be presented in the by-patient list.

(4) All statistical tests used will be two-tailed with $\alpha = 0.05$.

7.3. Estimation of Incomplete Data

Due to this relatively small scale of clinical trial, any incomplete observation will be considered as missing data with no specific estimation for the incomplete data.

7.4 Sample Size

The sample size per treatment group is arbitrarily determined to be 48 evaluable patients within the two-year study period. Approximately 96 patients are planned to be enrolled to complete the study.

The design of this study was compared between the two groups. The main evaluation index (O'Leary-Sant score) was set to 8.0 decreased in the treatment group, 5.0 decreased in the control group, SD = 1.0, $\alpha = 0.05$, power= 0.80, and the total sample size was analyzed by computer:

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + k p_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.65 * 0.35 * (1 + \frac{1}{1})} + 0.84 * \sqrt{0.8 * 0.2 + (\frac{0.5 * 0.5}{1})} \right\}^2 / 0.3^2$$

$$N_1 = 38$$

$$N_2 = K * N_1 = 38$$

p_1, p_2 = proportion (incidence) of groups #1 and #2
$\Delta = |p_2 - p_1|$ = absolute difference between two proportions
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
K = ratio of sample size for group #2 to group #1

The sample size of this study is about 38 people in each group, at least 76 people need to reach statistical significance. According to 20% of the patient's drop-out rate, the number of subjects is set to 96, and the evaluator is 76 to get enough verification power.