

Protocol Title: Extracorporeal shock wave therapy (ESWT) for the treatment of detrusor underactivity/ underactive bladder (DU/UAB) — a single center, randomized, double-blind, placebo-controlled, prospective study

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1. STUDY DESIGN

In this study we will evaluate the application of ESWT for patients with DU/UAB. ESWT with 2500 shocks, frequency of 4 pulses per second and maximum total energy flow density 0.25 mJ/mm² or placebo (Shock Wave setting without shock wave energy transmission) will be applied to the suprapubic bladder region once a week for 6 weeks. Treatment parameters were modified from different urologic and nonurologic case studies and publications. The device used for the study was a standard electromagnetic shock wave unit with a focused shock wave source (LITEMED LM-ESWT-mini system, Taiwan). The focus zone penetration depth was in the range of 30–90 mm. This study was designed in a single center, randomized, double-blind, placebo-controlled trial to test the actual therapeutic effects of ESWT on DU/UAB. The results of this study may provide clinical evidence for an alternative therapeutic regimen in the treatment of DU/UAB.

2. OBJECTIVE AND ENDPOINTS

The objective of this study is to evaluate the efficacy and safety of ESWT for the treatment of DU/UAB.

The primary and secondary endpoints are described as shown below:

(1) Primary End-point (1 month)

The efficacy of LESW will be evaluated for:

Net changes of the mean post void residual (PVR) volume (mL) from baseline to 1 month after the treatment day.

(2) Secondary end-points

Efficacy

The efficacy of ESWT will be evaluated for:

- (1) Net changes of the following parameters from baseline to 1 month after the treatment day: functional bladder capacity (FBC), voiding frequency at daytime and voiding frequency at night time, incontinence, as record 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 last treatment day. An improvement of GRA by 2 scales at 1 months is considered effective.
- (3) Net changes of the maximum flow rate, voided volume, Pdet@Qmax, and postvoid residual volume from baseline to 1 month after the treatment day.

(4) Changes of Underactive Bladder Questionnaire (UAB-Q) score.

(5) Changes of urinary nerve growth factor and cytokines level from baseline to 1 month after treatment day.

Safety

(1) Local adverse event incidences (hematuria, miction pain, UTI, urinary retention). The severity of adverse event is categorized as indicated below:

<i>Severity of AE</i>	<i>Description</i>
Mild	Transient and easily tolerable, not affecting usual daily activities
Moderate	Causes patient's discomfort, interrupting usual daily activities
Severe	Causes considerable interference with daily activities and may be incapacitating or life-threatening

(2) Systemic Adverse Events:

Any systemic adverse event occurring after ESWT will be asked to report and patients will be properly investigated and treated. The cause for systemic adverse event may be not related with ESWT.

(3) Changes in physical examinations.

(4) Changes in blood pressure and other laboratory test results will be examined if patients have severe adverse events or physical examinations reveal abnormalities.

(3) Follow-up (3 months)

Efficacy

The efficacy of ESWT will be evaluated for:

- (1) Net changes of the following parameters from baseline to 3 month after the treatment day: functional bladder capacity (FBC), voiding frequency at daytime and voiding frequency at night time, incontinence, 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 3 month after the last treatment day. An improvement of GRA by 2 scales at 3 months is considered effective.
- (3) Net changes of the maximum flow rate, voided volume, Pdet@Qmax, and postvoid residual volume from baseline to 3 months after the treatment day.
- (4) Changes of Underactive Bladder Questionnaire (UAB-Q) score.
- (5) Changes of urinary nerve growth factor and cytokines level from baseline to 3 months after treatment day.

Patients who are not effective to the treatment at 3 months will receive repeated ESWT treatment.

Safety

- (1) Local adverse event incidences (hematuria, miction pain, UTI, urinary retention) are reported.
- (2) Any systemic adverse event occurring after ESWT will be asked to report and patients will be properly investigated and treated. The cause for systemic adverse event may be not related with ESWT treatment.

3. SHOCK WAVE MACHINE AND PROCEDURES

The shock wave applicator, FS-I (“LITEMED” LM-ESWT-mini system, Taiwan), will be gently placed on the skin area over the bladder dome, right upper lateral wall, right lower lateral wall, left upper lateral wall, and left lower lateral wall during once a week for 6 weeks, with 2500 shocks, frequency of 4 pulses per second, and maximum total energy flow density 0.25 mJ/mm². The current shock wave intensity and number used was followed from reference [1].

Eligible patients will be assigned a randomization number in sequential order and each of the randomization will determine the allocation of one of the two treatment groups (ESWT and Placebo) in 1: 1 ratio as shown below. The ESWT and placebo will be controlled by a research assistance who will not evaluate the therapeutic outcome to ensure the double-blind method.

Vital signs (body temperature, blood pressure, heart rate and respiration rate) will be recorded at pre-treatment and 30 minutes following treatment.

The treatment will be carried out in the out-patient clinic. Patient will be stayed in a treatment room and accompanied by a research assistant.

3.1. Randomization

Permuted block randomization method will be applied to generate randomization codes. Each randomization number will be assigned to individual patient according to the time-sequence for screened patient become eligible.

3.2. Blinding

The blinding of the study is double blind to the investigator and patients. The placebo treatment was performed with the same therapy head, which was also fitted with a placebo stand-off. This stand-off contained shock wave-absorbing material, a layer of air, and air-filled microspheres.

Performance of the placebo stand-off was validated by measuring the output pressure in a laboratory setup. The setting was identical to the verum treatment. The blinding included the specification that neither the patient nor the investigator/follow-up observer was aware of placebo or verum assignment.

4. SUBJECTS

4.1. Number and Source

Approximately 60 patients will be enrolled and a total of 48 evaluable patients will be completed within the three-year study period.

4.2. Inclusion Criteria

Patients must meet all the following criteria to be eligible to enter the trial:

- 4.2.1. Adult male or female, at least 20 years of age.
- 4.2.2. History of UAB (defined as bothersome chronic incomplete bladder emptying) for at least 3 months documented in the medical record with recurring UAB symptoms.
- 4.2.3. No UAB symptom relief (unresponsiveness) with previous used medications and/or other treatments.
- 4.2.4. Voiding difficulty (complains of difficulty emptying the bladder).
- 4.2.5. UAB consistent with diabetes, MS, Parkinson's disease, or aging idiopathic.
- 4.2.6. Post void residual ≥ 100 mL.
- 4.2.7. Bladder capacity > 200 mL and < 800 mL.
- 4.2.8. Pressure flow Urodynamic testing demonstrating impaired detrusor contractility or areflexia without evidence of BOO, with maximum detrusor pressure Pdet at Qmax (Pdet@Qmax) of < 20 cmH₂O and Maximum flow rate (Qmax) < 15 mL/sec for female and BCI <100 and BOOI < 40 for male [2, 3].
- 4.2.9. Total UAB Questionnaire Score ≥ 3 .
- 4.2.10. Females of child-bearing potential agree to use reliable birth control for the entire study duration.
- 4.2.11. Willing and capable of understanding and complying with all requirements of the protocol, including proper completion of the voiding diaries and self-administered questionnaires.
- 4.2.12. Free of active urinary tract infection.
- 4.2.13. Free of bladder outlet obstruction on enrollment.
- 4.2.14. Patient or his/her legally acceptable representative has signed the written informed consent form.
- 4.2.15. Subject on clean intermittent catheterization (CIC) should have been on CIC for at least 1 month and should be able to void spontaneously and not be completely dependent on CIC.

4.3.Exclusion Criteria

- 4.3.1. Female patients who is pregnant, lactating, plans to become pregnant, or with child-bearing potential without contraception.
- 4.3.2. Simultaneously participating in another investigational drug or device study or use of any investigational drug(s) or therapeutic device(s) within 3 months preceding enrollment.
- 4.3.3. Has been treated with an investigational device, drug, or procedure for UAB within the last 3 months.
- 4.3.4. History of cancer in pelvic organs, ureters, or kidneys or any cancer that has undergone treatment within the past 12 months.
- 4.3.5. Medical condition or disorder that may limit life expectancy or that may cause protocol deviations (e.g. unable to perform self-evaluations/accurately report medical history, and/or urinary symptoms).
- 4.3.6. History of spinal cord injury affecting urinary function.
- 4.3.7. Patients with uncontrolled acute urinary tract infection. An active urinary tract infection as evidenced by positive urine culture at the time of baseline assessment.
If a UTI is confirmed in the baseline sample (e.g., positive urine culture containing > 100,000 cfu/mL in midstream urine), the run-in period should be stopped. After successful treatment of the UTI, the patient can be rescreened and if eligible enroll in the study. If the patient has asymptomatic bacteriuria (i.e., a positive urine culture without clinical signs and symptoms of a UTI), the patient should not be excluded [3].
- 4.3.8. Currently taking medication(s) that may affect urination, including prescription drugs (i.e. anticholinergics, tricyclic antidepressants, bethanechol), over the counter drugs, dietary and/or herbal supplements. Alpha adrenergic blockers are allowed to use in a stable condition (longer than 1 month and keeping use during the study period).
- 4.3.9. Pelvic organ prolapses beyond the introitus (e.g., cystocele, rectocele).

- 4.3.10. Prior mesh surgery for stress urinary incontinence or pelvic prolapse.
- 4.3.11. Any other condition which per investigators' judgement, may affect the patient's safety (e.g. significant cardiovascular disease, asthma or other breathing disorders).
- 4.3.12. Patients with bladder outlet obstruction on enrollment.
- 4.3.13. Patients with any contraindication to be urethral catheterization during diagnostic test or treatment or follow-up period.
- 4.3.14. Patients have laboratory abnormalities at screening including:
ALT > 3 x upper limit of normal range
AST > 3 x upper limit of normal range
Serum creatinine level > 2 x upper limit of normal range.
- 4.3.15. Patients with any other serious disease considered by the investigator not in the condition to enter the trial.
- 4.3.16. Patients with cortisone treatment 6 week before first LESW therapy

Other single item of Lab examination also can be retested per Investigator's discretion if abnormality. Patient will be rescreened and randomized into the study once confirmed eligible.

5. STUDY PROCEDURE

5.1. General Study Design

This study is designed as a double-blind, randomized, paralleled, controlled trial. The DU/UAB confirmed patients will be randomly assigned to receive (1) ESWT or (2) placebo control group. The treatments will be evaluated at baseline screening and at least 2 study required visits (treatment visit and primary end-point evaluation visit) will be performed for PVR, symptom score recording, urodynamic studies, adverse event recording and global satisfaction assessments. Urine samples (30 ml) will also be collected at each visit for analysis of the urinary NGF and cytokines levels.

Procedures of LESW

Studied patients are requested to void completely before treatment. Urine samples (30 ml) will be collected for analysis of the urinary NGF and cytokines levels. The patients are placed in supine position in an examination room at out-patient clinic.

The shock wave applicator, FS-I (“LITEMED” LM-ESWT-mini system, Taiwan), will be gently placed on the skin area over the bladder dome, right upper lateral wall, right lower lateral wall, left upper lateral wall, and left lower lateral wall during once a week for 6 weeks, with 2500 shocks, frequency of 4 pulses per second, and maximum total energy flow density 0.25 mJ/mm². The current shock wave intensity and number used was followed from reference [1].

Patients will be asked about any painful sensation that they experience during the treatment. Vital signs (body temperature, blood pressure, heart rate and respiration rate) will be recorded at pre-treatment, and 30 mins following treatment. During the treatment, patient will be stayed in a treatment room and accompanied by a research assistant.

5.2. Study Visits and Evaluations

5.2.1. Screening Visit (V0, 2 weeks before the treatment day)

- 5.2.1.1. Explain the nature of the study and have patients to read and sign an Informed Consent Form.
- 5.2.1.2. Screen patients for inclusion/exclusion criteria (section 4.2 and 4.3).
- 5.2.1.3. Medical History of DU/UAB and previous treatment modalities.
- 5.2.1.4. Vital signs monitoring and general physical examinations of all systems, EKG examination to rule out abnormal cardiac diseases, and biochemistry examinations including CBC, PT, APTT, ALT, AST and Cr.
- 5.2.1.5. Check Uroflowmetry and record, urodynamic study and PVR volume.
- 5.2.1.6. Urinalysis for WBC, RBC, pH, Protein, Glucose and Bacteria if patient has symptoms suggestive of urinary tract infection.

5.2.1.7. Physical assessments to exclude bladder outlet obstruction or bladder pathology.

5.2.1.8. Record concomitant medication.

5.2.1.9. Dispense three-day voiding diary to record for 3 days before the treatment day.

5.2.1.10. Record UAB symptom score.

5.2.1.11. Discontinue all previous UAB-related medication.

5.2.2. Randomization and Treatment Visit (V1, Week 0)

5.2.2.1 A randomization number is given to eligible patient.

5.2.2.2 Inform patient of the possible adverse events

5.2.2.3 Review three-day voiding diary.

5.2.2.4 Collect 30 ml urine for analysis of the urinary NGF and cytokines levels.

5.2.2.5 ESWT given.

5.2.3. Treatment Visit (V2, Week 1, 1 week \pm 3 days after the V1 treatment day)

5.2.3.1 Vital signs monitoring, and confirm eligibility of patients.

5.2.3.2 ESWT given.

5.2.4. Treatment Visit (V3, Week 2, 1 week \pm 3 days after the V2 treatment day)

5.2.4.1 Vital signs monitoring, and confirm eligibility of patients.

5.2.4.2 ESWT given.

5.2.5. Treatment Visit (V4, Week 3, 1 week \pm 3 days after the V3 treatment day)

5.2.5.1 Vital signs monitoring, and confirm eligibility of patients.

5.2.5.2 ESWT given.

5.2.6. Treatment Visit (V5, Week 4, 1 week \pm 3 days after the V4 treatment day)

5.2.6.1 Vital signs monitoring, and confirm eligibility of patients.

5.2.6.2 ESWT given.

5.2.7. Treatment Visit (V6, Week 5, 1 week \pm 3 days after the V5 treatment day)

5.2.7.1 Vital signs monitoring, and confirm eligibility of patients.

5.2.7.2 ESWT given.

5.2.7.3 Dispense three-day voiding diary to record for 3 days before the next visit day.

5.2.8 Evaluation Visit I (Primary end-point, V7, 4 weeks \pm 3 days after the V6 treatment day)

5.2.8.1 Review patients voiding diary for urinary frequency, functional bladder capacity, and record reported UAB symptom score, and GRA.

5.2.8.2 Vital signs monitoring and record adverse events.

5.2.8.3 Check urinalysis for urinary tract infection if patient has symptoms.

5.2.8.4 Check uroflowmetry for maximum flow rate, voided volume, and PVR volume.

5.2.8.5 Appointment for the next visit at 12 weeks \pm 3 days after the V6.

5.2.8.6 Dispense three-day voiding diary to record for 3 days before the next visit day.

5.2.8.7 Collect 30 ml urine for analysis of the urinary NGF and cytokines levels.

5.2.9 Evaluation Visit II (V8, 12 week \pm 7 days after the V6)

5.2.9.1 Review patients voiding diary for urinary frequency, functional bladder capacity, and record reported UAB symptom score, and GRA.

5.2.9.2 Vital signs monitoring and record adverse events.

5.2.9.3 Check urinalysis for urinary tract infection if patient has symptoms suggestive of urinary tract infection.

5.2.9.4 Perform Uroflowmetry study for maximum flow rate, urodynamic study and PVR volume.

5.2.9.5 Collect 30 ml urine for analysis of the urinary NGF and cytokines levels.

5.3. Withdrawal Criteria

Patients with any of the following conditions may be withdrawn from the trial:

5.3.1. Patients decide to withdraw their consent at any time-point.

5.3.2. Patients indicate the status of lack of efficacy which is of clinical significance judged by the investigators that may lead to permanent damage to the patients.

5.3.3. Investigators consider that there is of safety concerns for the patients to remain in the trial (such as development severe medical disease).

5.3.4. Lost of follow-up or death.

5.4. Concomitant Treatments

Investigator will try to minimize the concomitant medications for the patients during the trial duration.

Currently taking medication(s) that may affect urination, including prescription drugs (i.e. anticholinergics, tricyclic antidepressants, bethanechol), over the counter drugs, dietary and/or herbal supplements, adrenergic antagonists. Alpha adrenergic blockers are allowed to use in a stable condition (longer than 1 month and keeping use during the study period).

6. ADVERSE EVENTS

6.1. Introduction

An adverse event is defined as a new medical condition or worsening of the existing condition following or during the trial medicinal exposure (including placebo). However, a deterioration of medical condition can be in doubt of either an adverse event or being due to the lack of efficacy of the treatment. Situations as such should be considered as a lack of efficacy unless the sponsor or the investigators or the regulatory authorities state to the contrary.

All adverse events occurring during the study should be documented on Adverse Event Forms. One Adverse Event Form should be filled out for each adverse event. All items on the form should be completed and feedback to National Reporting System of Adverse Drug Reaction in Taiwan (ADR) as soon as possible. For serious adverse events, a preliminary Adverse Event Form must be returned to the ADR immediately (within 24 hours), with complete and/or new information submitted to the ADR as soon as it becomes known.

6.2. Nonserious Adverse Event

A nonserious adverse event is defined as a change in a patient's medical health which does not fulfill the definition of Serious Adverse Event. Nonserious AEs should be reported to ADR by use of an Adverse Event Form.

6.3. Serious Adverse Event

Serious adverse events are defined as any finding which suggests a significant hazard, contraindication, side effect, or precaution.

Additionally, any adverse event which the consequence is:

- Fatal

- Life threatening

- Permanently disability or incapacity

- Requiring hospitalization or prolonging a current hospitalization

- A congenital abnormality

Serious, alarming and/or unusual adverse events must be reported to the following individual within 24 hours of the investigator's knowledge of the event.

An Adverse Event Form should be completed for all serious adverse events and forwarded to the ADR within 24 hours. When new significant information is obtained as well as when outcome of an event is known, the investigator should inform the ADR. In applicable cases, ADR may request a letter from the investigator summarizing events related to the case. Investigators should follow patients as far as possible until an outcome to the events is known.

The investigator is responsible to communicate details of medical emergencies in trial patients to the ethics Committee.

REFERENCES

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3. Astellas Pharma Inc (Astellas Pharma Europe B.V.). A Study of ASP8302 in Participants With Underactive Bladder. ClinicalTrials.gov Identifier: NCT03702777. <https://clinicaltrials.gov/ct2/show/NCT03702777?term=NCT03702777&draw=2&rank=1>