CLINICAL INVESTIGATIONAL PLAN

OVERACTIVE BLADDER STIMULATION SYSTEM (OASIS)

Document ID: G02-CLP-0002_US

Date: 27July 2021

Confidentiality Statement

Revision History

Version #	Name	Date	Modification Description
1	Karin Aharonson-Raz	01-July-2018	First issue
2	Karin Aharonson-Raz	07-Jan-2019	1. Rationale for the study was added to section 4.2 2. Results of Extended Pilot study were added to section 6.2 3. Addition of blood test at baseline, 6 and 12 months follow up post activation 4. Addition of other endpoints 5. Concurrent medication section 9.4 was added 6. General update of statistical section 7. administrative changes throughout the document; formatting and wording. 8. Update of administrative sections 9-22 9. Addition of coordinating investigators 10. Including GDPR as a requirement
3* was not submitted	Amit Korner	03-June-2019	1. Updating synopsis visit 3 to align with protocol requirements 2. Update wording on intended use and indication for use 3. Change of wording to secondary endpoint 4. Update of sample size to include screen failures 5. Update of definition of FAS 6. Update to inclusion criteria #2 – age 21 for US sites 7. Update to inclusion criterial # 4 - with at least one episode per day for 5 days 8. Update to exclusion criterial # 24 - Knowledge of planned MRIs 9. Re-wording of exclusion criteria #25 10. Addition of exclusion criterial #30 – history of drug or alcohol abuse 11. Section 7: reference to the IB for information regarding pre-clinical and clinical studies

			12. Section 8 – updated of anticipated AE's 13. Addition of usability assessment 14. Section 10.4.1 – clarification of medication documentation and requirement to avoid undergoing other OAB interventions during the study 15. Section 10.6.1 – clarification that patient population should have incontinence 16. Section 11.4.2 addition of alcohol wipe after the skin scrub and addition of partial physical examination. 17. Section 11.4.2 Update of wording 18. Section 11.4.3 update of parameter setting 19. Section 11.4.5 – deleting the option to undergo second implantation in case of failure to response. 20. Section 11.4.6 Allowing out of window visits in case of UTI 21. Section 13.2.3 change of per protocol definition threshold 22. Section 13.2.4 deletion the definition of responder: will be part of the SAP 23. Section 14.2.1 updating CEC responsibilities 24. Section 18.9 update of contact person 25. Section 18.10 update severity to comply with CTCAE common terminology 26. Section 18.11 update of relationship to comply with MEDDEV 27. Section 24 update of the study schedule with usability questions 28. Update of voiding diary version 4
4	Amit Korner	21-July-2019	1. Section 11.4.2 a. addition of optional ultrasound during implantation visit b. Changing implantation visit window to (-)2 (+)3 weeks

			c. Suture removal after 14 days d. Remove option to remove suture by the GP.
5	Lori Fein Amit Korner	05-Jan-2020	1. Section 1 – update to be applicable to the US 2. Sections 1, 4, 6.1, 10.1 and 13.1 – update indication for use to female with UUI. 3. Sections 4, 5.2, 10.2.1, 10.6.2, 13.4 and 13.5.8 – update sample size 4. Section 4 and 10.2.1 – update number of sites to 35 5. Sections 4 and 10.3.1 - update primary safety endpoint to include all AE's 6. Sections 4 and 10.7 - updated inclusion/exclusion criteria 7. Section 4 and 11.4 – update time window for implantation 8. Section 4 and 13.5.4 – update hypothesis testing method to Clopper-Pearson 9. Section 5.2 – update CE approval for OAB 2000 10. Sections 10 and 14.2.2 – updated for staged enrollment provisions 11. Sections 10.4.3 and 11.4.1 – clarification of documentation of concurrent medication. 12. Section 11.4 – updated to allow phone visits and addition of device usage information 13. Section 11.4.1 update handling of UTI at baseline. 14. Section 11.4.2 update suture technique and material at implantation procedure. 15. Sections 13.3, 13.2.2. and 10.8.1- update failure definition. 16. Section 3 – adding UUI to acronym list. 17. Section 6.3 – adding reference to the software version.

			18. Section 18.9 – update adverse event reporting contact details to be applicable to the US 19. Section 24 – adding section on "Reporting Results on ClinicalTrials.gov" 20. Wording throughout the document 21. Administrative changes thought the document
06	Roni Diaz	29-Nov-2020	1. Deleted blood chemistry at 6 and 12 months follow-up 2. Added morbid obesity exclusion criteria 3. Added PVR evaluation at baseline visit 4. Removed option for paper diary 5. Updated SAE definition 6. Administrative corrections throughout
07	Roni Diaz	14-Jun-2021	1. Update to sample size 2. Update to name of EU representative after acquisition 3. Removal of FAS definition 4. Reduction of the number of sites from 35 to 30 5. Clarification of exclusion criteria 14 and 25 6. Update to patient study duration 7. Update to minimum retention period 8. Minor administrative changes
08	Roni Diaz	25-Jul-2021	1. Add 18-, 24-, 30- & 36-month visits 2. Add inclusion/exclusion criteria for long-term follow-up 3. Restate & reorder §10.3.3 4. Update Figure 1 and add long-term follow-up chart 5. Add §13.5.8 Interim Analysis 6. Update §14.2.1 & §14.2.2 7. Add §26 long-term follow-up schedule 8. Minor administrative changes

1. General

Protocol Number	G02-CLP-0002_US Rev. 08
Revision Date	27 July 2021
NCT #	NCT03596671
Protocol Title	A prospective study to assess the efficacy and safety of the BlueWind RENOVA iStim™ System for the treatment of patients diagnosed with overactive bladder (OASIS – OverActive bladder Stimulation System study)
Investigational Device	RENOVA iStim™
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2. Protocol Agreement

I have read the OASIS (Over Active bladder Stimulation System study) protocol G02-CLP-0002, Revision 08 from 27 July 2021 and agree to adhere to the requirements outlined within. I will provide all pertinent information regarding the protocol to the study personnel under my supervision. I will review and discuss this material with them and ensure they are fully informed of the requirements of this protocol. I will also ensure that this study is conducted in compliance with this protocol, Good Clinical Practice (GCP) E6(R2), EN ISO 14155:2011 and any applicable local and/or national regulatory agencies and their requirements.

Principal Investigator Name (Capital Letters)	*Investigational Site*
Principal Investigator Signature	*Date*

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3. Acronym List

AE	Adverse Event
BL	Baseline
BSW	Benefit, Satisfaction and willingness to Continue questionnaire
CEC	Clinical Event Committee
CIP	Clinical Investigation Plan
CP	Clinician Programmer
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety and Monitoring Board
EC	Ethic Committee
FI	Fecal Incontinence
GCP	Good Clinical Practice
HRQL	Health Related Quality of Life
IRB	Institutional Review Boards
ITT	Intend To Treat
MESA	Medical, Epidemiological, and Social Aspects of Aging
MID	Minimal Important Difference
MS	Multiple Sclerosis
OAB	Over Active Bladder
OAB-q	Over Active Bladder questionnaire
OASIS	Over Active bladder Stimulation System
PCB	Printed Circuit Board
PPIUS	Patient Perception of Intensity of Urgency Scale
PTNS	Percutaneous/Posterior Tibial Nerve Stimulation
PGI-I	Patient Global Impression of Improvement
PHQ-9 (or 15)	Patient Health Questionnaire
PVR	Post Void Residual
QoL	Quality of Life
VD	Voiding Diary
UADE	Unanticipated adverse device effect
UUI	Urinary Urge Incontinence

4. Protocol Synopsis

FULL TITLE	A prospective study to assess the efficacy and safety of the BlueWind RENOVA iStim™ System in the treatment of patients diagnosed with overactive bladder (OASIS – OverActive bladder StImulation System study).
RUNNING TITLE	BlueWind RENOVA iStim™ System for the treatment of OAB.
STUDY INTENDED USE AND INDICATION FOR USE	The BlueWind Medical System is intended for peripheral nerve stimulation. The RENOVA iStim™ System is indicated for the treatment of women with symptoms of urgency incontinence alone or in combination with urinary urgency and/or urinary frequency.
STUDY DESIGN	Prospective, interventional, multi-center, single arm, open label study.
STUDY PURPOSE	To demonstrate efficacy and safety of BlueWind RENOVA iStim™ System therapy in the treatment of UUI.
STUDY ARMS	Single arm. Device: **RENOVA iStim™ System** All subjects will receive active RENOVA iStim™ System treatment for the duration of the study.
STUDY CONDUCT	The study will consist of the following activities: Visit 1 - Screening • **Enrollment:** Potential female subjects with UUI, who fulfil basic criteria will be informed of the study and will be invited to sign an informed consent form. • Enrollment criteria will be verified against medical records and subject's interview. • **Baseline**: Study candidates will be asked to fill out a 7- consecutive day voiding diary and a MESA incontinence questionnaire to determine predominant type of incontinence and a PHQ-15 questionnaire and a quality of life questionnaire (OAB-q). The diary and questionnaires will determine eligibility criteria and will serve as baseline data. Demographic information (age, race, height and weight, leg circumference), medical and surgical history and concomitant medication information will be collected.

	• Urine sample will be collected, blood will be drawn and a full physical examination, including a PVR measurement, will be performed. • Once all eligibility criteria have been met and confirmed, implantation procedure will be scheduled. Visit 2 - Implantation • 6 ± 4 weeks after starting the diary, eligible subjects will undergo unilateral implantation with the BlueWind RENOVA iStim™ System, during which intra-operative tibial motor or sensory response test will be performed. Visit 3 - Activation • After a recovery period of 4-weeks (±2 weeks) post implantation, subjects will attend the clinic to undergo physical examination, urinalysis and parameter setting according to the individual patient sensations and will be trained on the use of the system. Therapy will be delivered for a minimum of 30 minutes and a maximum of 2 hours per day. Visits 4-8 – Treatment optimization and follow up • Follow-up visits will be performed at 1, 3, 6, 9 and 12-months post activation. • All follow-up visits will require completion of a voiding diary (a 3-day diary at 1, 3 and 9 months post activation and a 7-day diary at 6 and 12 months post activation) by the patient before coming to the visit. During the 6 and 12- months post activation follow-up visits quality of life (OAB-q), patient global impression of improvement (PGI-I) and Benefit, Satisfaction and Willingness to Continue (BSW) questionnaires will be collected. • During each visit, stimulation parameters and level of treatment will be checked and adjusted as needed. • At all follow up visits physical examination and collection of AE and concomitant medication will be performed • Urine sample will be collected at each follow up visit • Patients will be asked to complete usability questions Visits 9-12 – Long term follow-up • Long term follow-up visits will be performed at 18, 24, 30, and 36-months post activation. • If a subject already completed the 12-month follow-up visit and exited the study, she will be invited for a long-term follow-up consent visit in which, following her consent to participate, some eligibility criteria will be verified and treatment parameters setting will be performed. The subject will enter the visit schedule at the visit that aligns with her system activation date. • If the subject discontinued treating herself after completion of the 12-month visit, she will be asked to treat herself for 30 minutes, twice a day, for at least 4 weeks before arriving for her closest follow-up visit.

	During this period, she will be asked to complete modified daily diary to capture incontinence episodes, time to treatment effect, and symptom improvement questions. Subjects continuing to the long-term follow-up will be asked to treat themselves per physician discretion but not less than twice a week for 30-minutes per treatment. • All follow-up visits will require completion of 3-day voiding diary by the patient before coming to visit. • Follow-up visits 9 (18-months) and 11 (30 months) will be performed by phone. Questions on treatment satisfaction will be asked, and any lifestyle, concomitant medication or OAB related changes from previous follow-up as well as any health issues will be addressed and documented. Visits may be performed in clinic if needed (i.e. treatment parameter adjustment, AE or device malfunction, etc. In such cases, the patient will arrive to the clinic and a visit similar to the 1, 3, and 9- months post activation will be performed. • Follow-up visits 10 (24-months) and 12 (36-months) will be performed in clinic and will be similar to the 6 and 12- months follow-up visits
COMMITTEES	• Clinical Events Committee (CEC) Members will review and adjudicate safety information on an ongoing basis through the 12-month visit. • Data Safety and Monitoring Board (DSMB) will conduct periodic independent reviews of the data and the reported adverse events, in order to ensure that an ongoing acceptable safety profile is maintained. A minimum of semi-annual meetings, or after about each new 50 subjects have been recruited is planned until all patients complete the 12-month visit and then a minimum of annual meetings thereafter until study completion.
NUMBER OF PATIENTS	150 subjects will be enrolled.
NUMBER OF CLINICAL SITES	Up to 30 sites.

PRIMARY ENDPOINT	**Efficacy** • Proportion of responders at 6 months post system activation as demonstrated by ≥50% improvement in average number of urgency related incontinence episodes, measured by 7-day Patient Voiding Diary. - Overall study success criteria are defined as a lower 97.5% confidence bound for a single binomial proportion of > 50% patient success at 6 months. **Safety** • Incidence of adverse events from implantation to 12-months post-activation.
SECONDARY ENDPOINTS	• Proportion of subjects with ≥10 points (MID) improvement compared to baseline in HRQL (based on OAB-q) at 6 months post system activation • Proportion of responders at 12 months post system activation as demonstrated by ≥50% improvement in either average number of urgency related incontinence episodes or average number of "large" (severe) urgency related incontinence episodes, as measured by 7-day Patient Voiding Diary. • Proportion of responders at 6 months post system activation as demonstrated by ≥50% improvement in the average number of moderate-severe urgency episodes PPIUS degree 3,4 or <8 voids/day
OTHER ENDPOINTS	The following endpoints will be assessed as other endpoints for the 6-, 12-, 24- and 36-months post activation, without formal hypothesis testing and type I error control. • Incidence of procedure or device related adverse events from 12- to 36-months post activation. • Patient Global Impression of Improvement (PGI-I) score. • Treatment Benefit, Satisfaction, and Willingness to Continue (BSW) • Reduction in the average number of severe/large urgency related incontinence episodes. • Improvement in OAB-q (HRQL and symptoms severity). • Changes in the following OAB symptoms as measured by voiding diary compared to baseline: o Reduction in the number of micturition episodes. o Reduction in the number of urgency related incontinence episodes. o Reduction in degree of urgency prior to void on Patient Perception of Intensity of Urgency Scale (PPIUS) from 0-4. o Reduction in severity of incontinence episodes (amount leaked).

	• Proportion of dry subjects following treatment with the RENOVA iStim System as measured by 3 consecutive days of a patient voiding diary. • Assessment of fecal incontinence symptoms in patients suffering from mixed fecal and urine incontinence. • Patient compliance with treatment. • Duration from treatment initiation to symptoms improvement (in subset of patients who stopped treatment after completing the 12 month visit and started again when consented for the long term follow-up). • Assessment of treatment regimen • Device usage
ESTIMATED STUDY DURATION	Subjects will be followed for 36 months after system activation. Overall study duration will be approximately 5 years.
INCLUSION CRITERIA	1. Signed written informed consent. 2. Female aged 18 or greater (21 or greater in the US), with no plans to become pregnant during the trial; if of bearing potential, negative pregnancy test and if sexually active, using acceptable contraception. 3. Subject who is mentally competent with the ability to understand and comply with the requirements of the study. 4. Diagnosis of UUI demonstrated on 7-consecutive days voiding diary defined as a minimum of nine (9) leaking episodes associated with urgency, with at least one episode per day for 5 days 5. More than or equal to 6 months history of UUI diagnosis 6. Subject with inadequate response to any of the following conservative treatments (i.e. dietary restriction, fluid restriction, bladder training, behavioral modification, pelvic muscle training, biofeedback, etc.) and pharmacologic treatment. 7. If used, subjects should be on stable dose of antimuscarinics and/or beta-3 adrenergic agonists for at least 3 months prior to baseline and agree to remain on stable medication consumption until the 12-month follow-up visit. 8. If used, subjects should be on a stable dose of tricyclic antidepressants, Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) for at least 3 months prior to baseline. 9. Subjects with positive tibial nerve motor or sensory response tested via physical/neurological examination. 10. Subjects with normal renal function defined by GFR of 50 ml/min or more 11. Leg circumference of no less than 20 cm and no more than 30 cm at implantation site (i.e. 5cm above the medial malleolus).

	12. Subject agrees to attend all follow-up evaluations and is willing and capable to completely and accurately fill out voiding diaries and questionnaires and is willing to complete required exams and tests. The following inclusion criteria will be re-evaluated for patients who completed 12-months follow-up and exited the study: 1. Subject who is mentally competent with the ability to understand and comply with the requirements of the study.
EXCLUSION CRITERIA	1. Previous participation in another study with any investigational drug or device within the past 90 days. 2. Subjects who are unable to operate the RENOVA iStim™ System 3. Deemed unsuitable for enrollment by the investigator based on history or physical examination 4. Subjects at high surgical risk with multiple illnesses or active general infections that expose them to excessive bleeding or delayed or non-healing wounds. This includes patients who need anticoagulation therapy that cannot be temporarily stopped for the implantation procedure 5. Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints 6. Subject has morbid obesity (>50 BMI) 7. Any psychiatric or personality disorder at the discretion of the study physician 8. PHQ-15 Patient Somatization Score ≥ 20 9. Any metal or other implant in the area of BlueWind RENOVA iStim™ implantation site (20cm distance). 10. Variation in diuretics consumption within the last 6 months. 11. Subjects who have received botulinum toxin injections within the past 12 months. 12. Failure to respond to previous neuromodulation therapy for overactive bladder. 13. Subjects who have received neurostimulation in the last 3 months. 14. Previous urinary incontinence surgery or prolapse surgery using graft material within the last 12 months. 15. Any spinal or genitourinary surgery within the last 6 months. 16. Previous abdominoperineal resection of the rectum or previous radical hysterectomy. 17. Skin, peripheral edema, orthopedic or neurologic anatomical limitations that preclude implantation or/and use of the device. 18. Diagnosis of interstitial cystitis or bladder pain syndrome as defined by either American Urological Association (AUA) or European Association of Urology (EAU) guidelines.

	19. More than minimal level of suspected stress incontinence or mixed incontinence with stress component likely to confound study outcome, based on a 7-day voiding diary or medical history, or when stress incontinence score in the MESA incontinence questionnaire is higher than the urgency incontinence score. 20. Subjects with suspected urinary retention and/or PVR>150ml. 21. Any neurological disease or disorder including Alzheimer's, Parkinson, MS, stroke (CVI), neuropathy or injury resulting in neuropathy and/or suspected neurogenic bladder. 22. Current or recurrent urinary tract infection (3 or more infections in the last 6 months), or presence of urinary fistula, or urinary tract obstruction such as cancer, urethral stricture or presence of urinary stone. 23. History of chemotherapy or pelvic radiotherapy that might have affected bladder control or caused neuropathies (i.e. peripheral neuropathy).. 24. Diabetes with peripheral nerve neuropathy or severe uncontrolled diabetes (with HbA1C > 7%). Note: patients with HbA1C in the range of 7.1-7.5% may be considered eligible based on their complete medical record. 25. Uterine prolapse, cystocele, enterocele or rectocele with pelvic prolapse beyond the hymen. 26. Subjects with a documented history of allergic response to Platinum iridium, Titanium, Zirconia, Gold, Silicone or Parylene. 27. Other active implantable electronic device/s regardless of whether stimulation is ON or OFF. 28. Have a life expectancy of less than 1 year. 29. Subjects who are breastfeeding. 30. History of drug or alcohol abuse. The following exclusion criteria will be re-evaluated for patients who completed 12-months follow-up and exited the study: 1. Subject whose RENOVA iStim implant has been removed. 2. Recent participation in another study with an active treatment arm within the past 90 days. 3. Subjects who are unable to operate the RENOVA iStim™ System 4. Deemed unsuitable for enrollment by the investigator based on history or physical examination 5. Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints 6. Any psychiatric or personality disorder at the discretion of the study physician

	7. Subjects who have received botulinum toxin injections within the past 12 months. 8. Subjects who have received any neuromodulation therapy in the last 3 months or implanted with any neuromodulation device 9. Previous urinary incontinence surgery or prolapse surgery using graft material within the last 12 months. 10. Any spinal or genitourinary surgery within the last 6 months. 11. Previous abdominoperineal resection of the rectum or previous radical hysterectomy. 12. Diagnosis of interstitial cystitis or bladder pain syndrome as defined by either American Urological Association (AUA) or European Association of Urology (EAU) guidelines. 13. Subjects with suspected urinary retention and/or PVR>150ml. 14. Any neurological disease or disorder including Alzheimer's, Parkinson, MS, stroke (CVI), neuropathy or injury resulting in neuropathy and/or suspected neurogenic bladder. 15. Current or recurrent urinary tract infection (3 or more infections in the last 6 months), or presence of urinary fistula, or urinary tract obstruction such as cancer, urethral stricture or presence of urinary stone. 16. History of chemotherapy or pelvic radiotherapy that might have affected bladder control or caused neuropathies (i.e. peripheral neuropathy). 17. Uterine prolapse, cystocele, enterocele or rectocele with pelvic prolapse beyond the hymen. 18. Other active implantable electronic device/s regardless of whether stimulation is ON or OFF. 19. Have a life expectancy of less than 1 year. 20. Subjects who are breastfeeding.
SAMPLE SIZE CONSIDERATION	Sample size calculation, based on the primary endpoint, yields a sample size of 114 patients. This calculation assumes an underlying response rate of 65%, the null response rate (performance goal) of 50%, with power of 90% and one-sided significance level of 0.025. To account for up to 15% attrition, a total of 134 subjects would be required. However, the total sample size of 150 subjects is driven by an important secondary objective that is expected to be evaluable in 70% of enrolled subjects: The proportion of responders at 6 months post system activation as

	demonstrated by ≥50% improvement in the average number of moderate-severe urgency episodes PPIUS degree 3,4 or <8 voids/day. The assumed underlying response rate is 61%, with performance goal of 45%, 85% power and one-sided significance level of 0.025 yields a sample size of 89 subjects. To account for up to 15% attrition, 105 subjects are required to meet the criteria for this objective. Assuming 70% of enrolled subjects meet the criteria, a total of 150 subjects are required to be enrolled.
STATISTICAL ANALYSIS	For the primary endpoint, the lower 95% Clopper-Pearson confidence bound on the overall success rate will be calculated and compared to a pre-specified performance goal. Success on the primary analysis will be declared if the lower confidence bound is greater than the performance goal of 50%.

5. Introduction

5.1 Background

Non-neurogenic lower urinary tract dysfunction or Overactive bladder (OAB) is a common urological chronic condition that significantly impairs the quality of life of those affected, with considerable financial costs. OAB ranks among the most prevalent and challenging problems in urology [1, 2]. The International Continence Society defines OAB as a condition characterized by symptoms of urinary urgency with or without urgency incontinence, usually with urinary frequency [3]. In most patients, the etiology of these complaints remains unclear [4]. Earlier reports estimated that about one in six adults in the United States and Europe have OAB [5, 6]. The prevalence of OAB increases with age [5, 6] thus it is expected that OAB will become more common in the future as the average age of people living in the developed world is increasing.

A European study reports that the prevalence of OAB in Europe has been estimated to be 15.6% and 17.4% for men and women respectively, with an overall prevalence of 16.6% [1]. The American Urological Association reports studies showing rates as low as 7% to as high as 27% in men and rates as low as 9% to 43% in women. Urgency incontinence was reported being higher in women [7]. An estimated 455 million worldwide experienced at least one OAB symptom in 2008, with the prevalence expected to increase to 500 million in 2013 and 546 million in 2018 [8].

The etiology of non-neurogenic OAB has not been identified, with physiologic abnormalities ruled out by diagnostic evaluation. Conservative treatment options for OAB consist of behavioral techniques with or without biofeedback, bladder re-education, pelvic muscle exercises or pharmacotherapy [9]. However, for a significant proportion of patients, response to treatment is poor and/or may be compromised by troublesome or severe side effects [10]. Therefore, other treatment modalities, such as neuromodulation are needed to treat refractory OAB.

Neuromodulation is a physiological process, which influences the activity in one neural pathway and modulates the preexisting activity in another by synaptic interactions [11]. To modulate bladder dysfunction, the stimulator signals must be delivered to the neural tissue affecting bladder activity. Different neuromodulative therapies, such as stimulation of the pudendal nerve, sacral nerve, and tibial nerve stimulation have been developed with varying success rates [12, 13].

BlueWind Medical has developed a minimally invasive implantable wireless tibial nerve stimulator for use in the treatment of overactive bladder, as described in detail, below.

5.2 Study Rationale

BlueWind obtained CE mark for OAB1000 9 June 2016, certificate 390128DE02. The CE certificate was granted among others based on the results from our pilot study described in this protocol. This product is not available on the market in Europe or elsewhere. The Investigational Device proposed for this trial is the next generation of the system with improvements for increasing patients' and physicians' experience in device usability; in addition, this

system was designed to improve manufacturability. This model (OAB2000) obtained CE mark approval on 13 Dec 2019.

The RENOVA iStim™ is composed of an active implantable unit and an external wearable unit which transmits energy via magnetic coupling to the implant, which consequently generates the electrical pulse. It should be noted that the sensory reaction associated with the treatment and the intra-operative test performed to ensure proper placement of the implant, do not permit blinding of the patients.

Due to the challenges of maintaining a blinded control arm with the RENOVA iStim™, a "true" RCT using a sham control design is not possible, nor is a surgical procedure on a control arm ethical. Taking this into consideration and based on prior feedback during the pre-submission process with the FDA, a single arm study design is proposed. Each patient serves as her own control and since only refractory OAB patients are included in this study there are no expectations that the condition would improve with time without any treatment. The primary and secondary endpoints follow-up periods are 6 and 12 months, respectively, to minimize the potential impact of the placebo effect and to enable demonstration of durable device effectiveness.

The proposed OASIS pivotal trial is different from the pilot and the extended studies described in this protocol in that, as opposed to the pilot study which was safety oriented, an efficacy primary endpoint was added. Such an efficacy-oriented study is essential to gain further medical technology assessment information and hence higher scientific value. Several recent studies have raised the awareness to the importance of combining objective and subjective results when determining short and long-term efficacy of treatment. Hence, in order to better answer a primary efficacy endpoint several validated questionnaires were added and the patient voiding diary was modified to allow more accurate capturing of the patients' reported outcomes.

An efficacy based single arm study design commonly involves a hypothesis based primary endpoint that includes a performance goal. Based on extensive literature review and the pilot and extended follow-up studies' results, a clinically meaningful performance goal was determined which, together is a hypothesis based secondary endpoint, result in sample size calculation of 150 patients (see sample size in the statistical section).

6. BlueWind RENOVA iStim™ System Description

6.1 Study Intended Use and Indication for Use

Intended use: peripheral nerve stimulation.

Indication for use: treatment of women with symptoms of urgency incontinence alone or in combination with urinary urgency and/or urinary frequency.

6.2 System Description

The BlueWind RENOVA iStim™ System has an implantable wireless neurostimulation component which is intended to be placed in the vicinity of the tibial neurovascular bundle.

The RENOVA iStim™ Implant has no battery; the Wearable Unit transmits energy to the Implant, which sends electrical pulses to the tibial nerve. These electrical pulses stimulate the nerve along the leg, reaching the sacral plexus - which also contains nerves innervating the bladder, urinary sphincter and pelvic floor. This stimulation has the power to modulate the function of these nerves, calming the over-active bladder and relieving OAB symptoms.

The RENOVA iStim™ Wearable Unit is programmed with individual customized Stimulation parameter settings, set by the clinician at an initial Treatment Setup visit, having been determined according to the patient's tolerability, sensations and motor thresholds. The patient then receives the personalized Wearable Unit and continues Treatment Sessions at home, returning to the clinician periodically for follow-up visits.

The RENOVA iStim™ System is comprised of the following components:

- One implantable component - the RENOVA iStim™ Implant
- Two non-implantable components:
  - RENOVA iStim™ Wearable Unit (with battery charger)
  - RENOVA iStim™ Clinician Programmer (CP) (with battery charger)

6.2.1 Implant

The RENOVA iStim™ Implant provides the stimulation current to peripheral nerves in vicinity of the Implant.

The Implant consists of an electronic assembly within a hermetically sealed encapsulation that is suitable for permanent implantation. On the outer surface of the encapsulation there are two ring electrodes which through them the stimulation current is delivered to the tissue.

The Implant is covered by a silicone membrane with suture holes, allowing the surgeon to anchor the Implant to the fascia by suturing.

The implant contains no battery, it is powered and controlled by an external Wearable Unit. Having an external power source (see RENOVA iStim™ Wearable Unit, below) increases the implant life time and output capability while allowing for a smaller implant size.

6.2.2 Wearable Unit

The Wearable Unit wirelessly powers the implant and controls stimulation parameters.

The RENOVA iStim™ Wearable Unit is designed for two purposes:

1. Use by the Surgeon — for verifying the Implant's functionality and correct placement in vicinity to the nerve.
2. Use by the Patient — for delivering routine treatments.

The Wearable Device contains an electrical circuit board (which includes the user controls and indications), a rechargeable battery and a flexible antenna.

The Wearable Device communicates with the Clinician Programmer (CP) via Bluetooth Low Energy (BLE). This enables the CP to program the Wearable Device and to download the patient's usage logs.

The Wearable Unit is paired to a specific Implant and can only communicate (through magnetic coupling) with the Implant it is paired with.

The Wearable Device is supplied with a dedicated charger.

6.2.3 Clinician Programmer (CP)

The Clinician Programmer (CP) is the system's interface for treatment control, status evaluation, parameter programming and data acquisition.

The Clinician Programmer which is capable of transferring data to and from the Wearable Unit via a wireless connection (via Bluetooth low energy) is designed for two purposes:

1. During the surgical procedure - when the surgeon wishes to verify the implant position in vicinity to the nerve, the CP may be used to monitor the stimulation.
2. For optimization of therapy for each patient - enables the clinician to set or adjust the stimulation parameters of the system as well as to receive treatment logs from the Wearable Unit and present them as usage reports. The technician can download this data from the CP to a computer for backup.

The RENOVA iStim™ Clinician Programmer is comprised of proprietary software that is embedded into a commercially available tablet in a single app mode i.e., the tablet can only run the RENOVA iStim™ software. Access to the Clinician Programmer is password protected to allow access only to authorized users, namely the healthcare professional and the manufacturer. All data transfer does not include any identifying patient information.

6.3 System Technical Information

Traceability of clinical investigational systems will be attained during and after the clinical study by assignment of serial numbers to each of the system components. The system technical information is specified in the RENOVA iStim™ Therapy Clinician User Manual and the components are listed in table 1 below. Software version is specified in the Investigator Brochure (G02-CLT-0002).

Table 1 - BlueWind RENOVA System Components

Quantity	Description
1/patient	Implant package

Quantity	Description
	Implant in sterile pouch; Implant IFU; Patient ID card; Patient leaflet;
1/patient	Wearable Unit kit
	Wearable Unit with leg band with charger; Patient therapy guide
1/site (additional back up systems can be provided to site)	Clinician kit
	Clinician Programmer with charger; Wearable Device with charger; Clinician manual; Surgical technique guide

7. Pre-Clinical and Clinical Experience with RENOVA iStim™ System[1]

7.1 Pre-Clinical experience with BlueWind RENOVA iStim™ System

The safety and performance of the system, including assessment of the implant position and technical performance, have been examined in an animal trial performed on ovine adult sheep. Eighteen (18) devices were implanted in nine (9) animals in the proximity of either the Tibial or Vagal nerves for 2, 30, 90 or 180 days of stimulation in order to provide both acute and long-term evidence to the procedure safety and the device performance. Stimulation sessions were conducted 5 days a week and up to 3 hours per system per day. Varying frequencies, pulse widths, and current amplitudes were used depending on the sheep tolerance.

The study demonstrated that the RENOVA iStim™ system, including all associated procedures, were found to be safe with no effect on animal's vital signs, well-being and neurological conditions. Minimal adverse events were noted following surgery and all were resolved shortly after their identification. Gross pathology as well as histopathology revealed no adverse tissue reaction presenting safety concerns. In addition, the implant's integrity was not compromised over time and the implant did not migrate and demonstrated electrical stability.

7.2 Clinical experience with BlueWind RENOVA™ System

The company performed a pilot study to evaluate the use of the BlueWind System in the treatment of patients with overactive bladder with or without urgency urinary incontinence. The study was conducted in four European sites; two in the Netherlands and two in the UK. A total of 36 patients were sub-grouped as followed:

[1] Previous pre-clinical and clinical testing were performed on the first generation of the device. More detailed information is provided in the IB

- Patients with no previous treatment with percutaneous tibial nerve stimulation (PTNS) [de novo patient group] and
- Patients with a documented success on PTNS therapy [prior-PTNS group]

Each subject served as his or her own control and evaluations were performed after 3 and 6-months of stimulations, compared to baseline.

The primary endpoint was safety and the secondary endpoints assessed the performance of the system using parameters collected from 3-day voiding diary and a quality of life questionnaire (OAB-q) and were defined as follows:

Primary Endpoints

The incidence of serious adverse events (system and/or procedure related)

Secondary Endpoints

- Six-month clinical improvement compared to baseline was measured by the effect of BlueWind Medical's therapy on the treatment of the following symptoms:
    - Number of voids/day
    - Volume voided/void
    - Number of urgency leaks per day
    - Degree of urgency prior to void

  In the presence of urgency incontinence, the following evaluations were performed:
    - Leaking episodes/day
    - Severity of leaking episodes (scale of 0-3; 0-no leak; 1-drops; 2-small amount; 3-large amount)
    - Absorbent pads used due to leaking/day
- Quality of Life Questionnaire – OAB-q

An analysis of 6-months clinical performance success was based on voiding diary parameters, where success was defined as a decrease of ≥50% in urgency frequency (UF) and urgency urinary incontinence (UUI) symptoms (voids/day or number of episodes with degree of urgency >2 from baseline; or a return to normal voiding frequency i.e. <8 voids/day for the UF group; and leaks/day for the UI group). As commonly defined in the literature, for the UUI population, dry subjects (no episodes of leakage) were considered as 100% clinical improvement.

Study Procedure

Subjects were asked to complete voiding diaries and only patients who demonstrated an average urinary frequency of at least 8 times/24 hours, and/or patients with urinary urgency leaks of at least 2 leaks on a 3-day voiding diary, were eligible to continue to the next enrollment step. Subjects meeting these criteria were tested for compatibility with the stimulator system where surface electrodes were placed over the tibial nerve and stimulation applied in order to determine whether they experienced a sensory and/or motor response.

Subjects who met all enrollment criteria were implanted with the stimulator and returned to the clinic after 2-4 weeks for activation of the stimulator and parameter setting**.** Each patient was treated with two different regimens employing different stimulation frequencies (6 treatments/week following by 3 treatments/week), with each regimen lasting for 3 months. The stimulation parameters for each patient in each treatment regimen were customized per patient to ensure a sensory or motor response to the stimulation. Patients were evaluated post activation of the stimulation at 1 month, 3 months (end of treatment regimen 1), and 6 months (end of treatment regimen 2). All subjects achieving 6-months follow-up remained implanted, without additional follow-ups.

Safety assessments were based on changes from baseline of clinical signs and symptoms reported by the subject or observed by the Investigator. Performance of the device was assessed using a voiding diary, quality of life questionnaire (OAB-q), as well as sensory/motor threshold assessments.

Subject Demographics

A total of 36 subjects were implanted with the BlueWind RENOVA™ System where 21 were enrolled into the de novo treatment group and 15 subjects in the prior-PTNS treatment group. Thirty-one (31) out of 36 subjects had UI at baseline. Twenty-one (21) out of 36 implantation procedures were performed under local anesthesia and 15 under general anesthesia. The mean surgical operation time was less than 35 minutes.

Out of the 36 implanted subjects, one subject withdrew from the study due to personal reasons and one device was explanted 2 weeks after implantation due to suspected infection, as described further below. Both of the aforementioned subjects exited the study prior to their activation visit. Thus, the safety analysis was performed for 36 subjects and performance analysis for 34 subjects (ca. 95% of the population).

Study Outcomes:

Safety

There was a single (1/36, <3%) serious adverse event over the course of the study. The patient was re-admitted approximately 2 weeks' post implantation due to suspected infected implantation site with local pain, skin redness, bleeding and fluid discharge from the implanted area. The implant was explanted and the patient was discharged from hospital at the following day with a course of antibiotics. The event was resolved without further sequelae and culture turned out to be negative. The physician described the SAE as device-related and probably related to the procedure.

Overall 44% of subjects (16/36) experienced adverse events during the study. Surgical procedure-related events occurred in approximately 33% of subjects. Device-related adverse event occurred in 36% (13/36) of subjects. The most common device-related adverse events were infection (19%; 7/36), implant site pain (14%; 5/36), and procedural complications (~8%; 3/36).

Performance

Out of 34 subjects in the performance set (one device was explanted due to the SAE and one patient withdrew from the study), 70.6% of subjects experienced ≥50% clinical improvement in OAB symptoms at 6-months. In subjects suffering from urgency incontinence (UI) at baseline, all UI symptoms (leaks/day, leaks severity and pads

change/day) decreased significantly over time. Out of 29 UI subjects, 27.6% became 'dry' (100% improvement) after 6-months of treatment. For subjects suffering from urgency frequency (UF), all UF symptoms (void/day, volume/void, pads changed) significantly improved during treatment as compared to baseline. The clinical improvement was also supported by an improvement in the quality of life of patients, demonstrated by significant improvement in the health-related quality of life and symptoms severity scores following 1,3, and 6-months of treatment with the BlueWind Medical system, as well as an increase of all HRQL subscales above the minimal important difference (MID) that is considered clinically meaningful. The PTNS group showed similar results as the De-novo group. The intensity level during sensation assessments (minimal sensation level and maximal tolerable level) did not change significantly at all follow-up visits compared to baseline.

Extended follow-up study:

Twenty OAB patients, who were previously implanted with the RENOVA iStim system for the 6-month follow-up pilot study, were re-enrolled for an extended, 3-year, follow-up study. No SAEs were reported during the extended follow-up. In both the per-protocol analysis as well as the intent to treat analysis (ITT) 75% of the patients demonstrated clinical success in OAB symptoms (defined as: ≥50% reduction in urgent voids or leaks or normalization of voids) during the long term, 3-year, follow-up. In addition, in the per-protocol population 58% and 75% of the wet OAB patients showed >50% reduction in the average number of leaks and large leaks at 3 years, respectively, and in the ITT population 50% and 80% of the wet OAB patients showed >50% reduction in the average number of leaks and large leaks, respectively. This was supported by statistically significant long-term sustainable improvement in the overall Health Related Quality of Life (HRQL) score as well as in all subscales (coping, sleeping, concern, social) and in the symptoms severity score, with 70% of the patients showing >10 points improvement (meaningful important difference) in HRQL.

Hence, BlueWind Medical RENOVA iStim system demonstrates long term safety and efficacy. The long-term success rate is comparable with the 6 months success rate.

8. Risks and Benefits

RENOVA iStim™ therapy has been tested in a clinical trial on patients suffering from OAB who did not respond to other treatments - such as, a change in diet, biofeedback and medication.

For 70% of these patients, the therapy succeeded in producing a clinical improvement in their OAB symptoms (≥50% reduction in urgency urinary incontinence or voiding episodes or normalization of voids or ≥50% reduction in moderate-severe urgency related voids).

In 51% of patients suffering from urinary urgency leaking episodes, RENOVA iStim™ therapy succeeded in producing a ≥50% reduction in this symptom, while almost 30% experienced complete alleviation of this symptom.

Clinical improvement was also supported by significant improvements in all aspects of Quality-of-Life (concern, coping, sleep, and social) and a significant decrease in symptom severity.

The potential risks related to this study are the known risks of surgical procedures and electrical stimulation. The sponsor and the investigators have determined that this study is justified because of the potential benefit to patient's symptoms relief as a result of the BlueWind RENOVA iStim™ System treatment effect.

Anticipated adverse events involved with the surgery include: bleeding, pain at stimulator site, ankle discomfort, implant site infection, skin irritation, skin erosion, seroma, formation of thrombosis and pulmonary embolism, potential temporary or permanent mobility impairment and nerve injury.

Anticipated adverse events involved with the stimulation include: undesirable changes in stimulation such as sensation of transient electric "shock"/sudden radiating sensation/sporadic sensory response, uncomfortable heating effects, discomfort, or burn.

Transient unpleasant sensations noted by subjects which may occur during a programming optimization session are not considered adverse events. Stimulation related side effects that persist beyond the programming session should be reported as adverse events.

Anticipated adverse events involved with the treatment include: adverse change in voiding/bowel function, transient nausea.

Anticipated adverse events involved with the device include: spontaneous sensory response (not in association with stimulation), implant migration or displacement, allergic reaction and technical device problems.

Many of the anticipated risks are considered minor, reversible and well tolerated (per studies performed with the BlueWind system).

Risk mitigation will include the selection of experienced, qualified investigators, and their training on proper performance of the surgical procedure, as well as on-site attendance by sponsor qualified representatives and ongoing safety monitoring by the trial DSMB and CEC.

When considering the totality of the data, including all risks identified in the risk analysis as well as all AE reported in the pilot study and comparing it to the reported benefits for OAB patients, it is apparent that overall the potential benefits are higher than the overall risks associated with the implantation procedure and treatment.

In summary, when considering carefully the risk-benefit ratio for this patient population, the following support the further evaluation of the BlueWind RENOVA iStim™ System in a pivotal trial:

- The magnitude of healthcare problem attributed to overactive bladder
- The low risk associated with tibial nerve stimulation in this and other applications
- Population had failed conservative treatments, without many further options left
- The positive results of the pilot study

9. Traceability

Complete traceability records will be kept of all investigational devices and accessory equipment used during the study.

10. Protocol Design

10.1 Study Objectives

- To demonstrate efficacy of BlueWind RENOVA iStim™ System therapy in females with UUI
- To demonstrate the safety of BlueWind RENOVA iStim™ System therapy in females with UUI

10.2 Study Design

10.2.1 Study Scope

This study is designed as a prospective, interventional, multi-center, single arm, open label study.

It is expected that 150 evaluable subjects (attempted implanted with the device) overall will be enrolled in the study in up to 30 sites. To ensure patient safety, a full report of safety data for up to 30 subjects who undergo an implantation of the RENOVA iStim will be reviewed by the DSMB. Screening activities will continue during the review of this data; however, no implantations will occur until the DSMB recommends to continue.

10.3 Study Endpoints

10.3.1 Primary Endpoint

Efficacy

- Proportion of responders at 6 months post system activation as demonstrated by ≥50% improvement in average number of urgency related incontinence episodes, measured by 7-day Patient Voiding Diary.
  - Overall study success criteria is defined as a lower 97.5% confidence bound for a single binomial proportion of >50% patient success at 6 months

Safety

- Incidence of adverse events from implantation to 12-months post-activation.

10.3.2 Secondary Endpoints

Bluewind will test three secondary endpoints. In order to control type I error of the family of secondary objectives at 5%, secondary objective hypothesis testing will only occur upon rejection of the primary objective null hypothesis.

- Proportion of subjects with ≥10 points (MID) improvement in HRQL (based on OAB-q) at 6 months post system activation
- Proportion of responders at 12 months post system activation as demonstrated by ≥50% improvement in either average number of urgency related incontinence episodes or average number of severe/large urgency related incontinence episodes, as measured by 7-day Patient Voiding Diary.

- Proportion of responders at 6 months post system activation as demonstrated by ≥50% improvement in the average number of moderate-severe urgency episodes PPIUS degree 3,4 or <8 voids/day

10.3.3 Other Endpoints

The following endpoints will be assessed as other endpoints for the 6-, 12-, 24- and 36-months post activation, without formal hypothesis testing and type I error control.

- Incidence of procedure or device related adverse events from 12- to 36-months post activation
- Patient Global Impression of Improvement (PGI-I) score
- Treatment Benefit, Satisfaction, and Willingness to Continue (BSW)
- Reduction in the average number of severe/large urgency related incontinence episodes
- Improvement in OAB-q (HRQL and symptoms severity).
- Changes in the following OAB symptoms as measured by voiding diary compared to baseline:
    - Reduction in the number of micturition episodes.
    - Reduction in the number of urgency related incontinence episodes.
    - Reduction in degree of urgency prior to void on Patient Perception of Intensity of Urgency Scale (PPIUS) from 0-4.
    - Reduction in severity of incontinence episodes (amount leaked).
- Proportion of dry subjects following treatment with the RENOVA iStim System as measured by 3 consecutive days of a patient voiding diary
- Assessment of fecal incontinence symptoms in patients suffering from mixed fecal and urine incontinence
- Patient compliance with treatment
- Duration from treatment initiation to symptoms improvement (in subset of patients who stopped treatment after completing the 12-month visit and started again when consented for the long-term follow-up).
- Device usage

10.4 Medication Usage

If used, patients should be on stable dose of OAB related medication (i.e. antimuscarinics and/or beta-3 adrenergic agonists for at least 3 months prior to baseline and agree to remain on stable medication consumption until the 12-month follow-up visit.

If used, patients should be on a stable dose of tricyclic antidepressants, Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)) for at least 3 months prior to baseline.

Type and dosage of OAB related medications as well as any change in consumption during the study will be recorded in the CRF. All other medication consumption will be recorded in the CRF during the baseline visit and tracked 3 months back.

Patients should avoid any OAB intervention (such as PTNS, SNM, or other neuromodulation treatments, Botox injections, surgical procedures, etc.) that may have an effect on overall study results throughout the 36 months follow-up period.

10.4.1 Allowed/disallowed medication

Patients will be administered prophylactic antibiotic and anti-inflammatory medications peri-operative (per section 11.4.2).

10.4.2 Documentation of concomitant medication

Any of the following concomitant medication consumption and dosages will be recorded in the CRF: Antibiotics, diuretics, anti-inflammatory, psychiatric medication, medication used to treat adverse events, cardiac, renal and endocrinology medication and any other medication that might affect urine output.

If there is a medical requirement to change OAB, diuretics or antidepressant medication during the study, these changes will be recorded and the patient will continue the study as planned.

10.5 Measurements

The clinical investigation variables will be assessed at baseline and/or at follow up visits using the following instruments:

- Voiding diary (7 day or 3 day): includes measurements of frequency, urgency, number of leaking episodes, leaks severity /amount leaked, and fluid consumed
- Quality of life questionnaire (OAB-q)
- Patient Global Impression of Improvement (PGI-I)
- Treatment Benefit, Satisfaction, and Willingness to Continue (BSW) questionnaire

10.6 Study Population

10.6.1 Patient Population

Women suffering from overactive bladder (OAB), including symptoms of urinary urgency incontinence (UUI).

10.6.2 Number of Subjects

One hundred fifty (150) subjects will be enrolled into the study to test the primary objective hypothesis (taking into account for up to 15% attrition).

10.7 Eligibility Criteria

10.7.1 Inclusion Criteria

1. Signed written informed consent.

2. Female aged 18 or greater (21 or greater in the US), with no plans to become pregnant during the trial; if of bearing potential, negative pregnancy test and if sexually active, using acceptable contraception.
3. Subject who is mentally competent with the ability to understand and comply with the requirements of the study.
4. Diagnosis of UUI demonstrated on a 7-consecutive days voiding diary defined as a minimum of nine (9) leaking episodes associated with urgency, with at least one episode per day for 5 days.
5. More than or equal to 6 months history of UUI diagnosis
6. Subject with inadequate response to any of the following conservative treatments (i.e. dietary restriction, fluid restriction, bladder training, behavioral modification, pelvic muscle training, biofeedback, etc.) and pharmacologic treatment.
7. If used, subjects should be on stable dose of antimuscarinics and/or beta-3 adrenergic agonists for at least 3 months prior to baseline and agree to remain on stable medication consumption until the 12-month follow-up visit.
8. If used, subjects should be on a stable dose of tricyclic antidepressants, Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) for at least 3 months prior to baseline.
9. Subjects with positive tibial nerve motor or sensory response tested via physical/neurological examination.
10. Subjects with normal renal function defined by GFR of 50 ml/min or more
11. Leg circumference of no less than 20 cm and no more than 30 cm at implantation site (i.e. 5cm above the medial malleolus).
12. Subject agrees to attend all follow-up evaluations and is willing and capable to completely and accurately fill out voiding diaries and questionnaires and is willing to complete required exams and tests.

The following inclusion criteria will be re-evaluated for patients who completed 12-months follow-up and exited the study:

1. Subject who is mentally competent with the ability to understand and comply with the requirements of the study.

10.7.2 Exclusion Criteria

1. Previous participation in another study with any investigational drug or device within the past 90 days.
2. Subjects who are unable to operate the RENOVA iStim™ System
3. Deemed unsuitable for enrollment by the investigator based on history or physical examination
4. Subjects at high surgical risk with multiple illnesses or active general infections that expose them to excessive bleeding or delayed or non-healing wounds. This includes patients who need anticoagulation therapy that cannot be temporarily stopped for the implantation procedure

5. Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints
6. Subject has morbid obesity (>50 BMI)
7. Any psychiatric or personality disorder at the discretion of the study physician
8. PHQ-15 Patient Somatization Score ≥ 20
9. Any metal or other implant in the area of BlueWind RENOVA iStim™ implantation site (20cm distance).
10. Variation in diuretics consumption within the last 6 months.
11. Subjects who have received botulinum toxin injections within the past 12 months.
12. Failure to respond to previous neuromodulation therapy for overactive bladder.
13. Subjects who have received neurostimulation in the last 3 months.
14. Previous urinary incontinence surgery or prolapse surgery using graft material within the last 12 months.
15. Any spinal or genitourinary surgery within the last 6 months.
16. Previous abdominoperineal resection of the rectum or previous radical hysterectomy.
17. Skin, peripheral edema, orthopedic or neurologic anatomical limitations that preclude implantation or/and use of the device.
18. Diagnosis of interstitial cystitis or bladder pain syndrome as defined by either American Urological Association (AUA) or European Association of Urology (EAU) guidelines.
19. More than minimal level of suspected stress incontinence or mixed incontinence with stress component likely to confound study outcome, based on a 7-day voiding diary or medical history, or when stress incontinence score in the MESA incontinence questionnaire is higher than the urgency incontinence score
20. Subjects with suspected urinary retention and/or PVR>150ml.
21. Any neurological disease or disorder including Alzheimer's, Parkinson, MS, stroke (CVI), neuropathy or injury resulting in neuropathy and/or suspected neurogenic bladder.
22. Current or recurrent urinary tract infection (3 or more infections in the last 6 months), or presence of urinary fistula, or urinary tract obstruction such as cancer, urethral stricture or presence of urinary stone.
23. History of chemotherapy or pelvic radiotherapy that might have affected bladder control or caused neuropathies (i.e. peripheral neuropathy).
24. Diabetes with peripheral nerve neuropathy or severe uncontrolled diabetes (with HbA1C > 7%). Note: patients with HbA1C in the range of 7.1-7.5% may be considered eligible based on their complete medical record.
25. Uterine prolapse, cystocele, enterocele or rectocele with pelvic prolapse to or beyond the hymen.
26. Subjects with a documented history of allergic response to Platinum iridium, Titanium, Zirconia, Gold, Silicone or Parylene.
27. Other active implantable electronic device/s regardless of whether stimulation is ON or OFF.
28. Have a life expectancy of less than 1 year.
29. Subjects who are breastfeeding
30. History of drug or alcohol abuse.

The following exclusion criteria will be re-evaluated for patients who completed 12-months follow-up and exited the study:

1. Subject whose RENOVA iStim implant has been removed.
2. Participation in another study with an active treatment arm within the past 90 days.
3. Subjects who are unable to operate the RENOVA iStim™ System
4. Deemed unsuitable for enrollment by the investigator based on history or physical examination
5. Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints
6. Any psychiatric or personality disorder at the discretion of the study physician
7. Subjects who have received botulinum toxin injections within the past 12 months.
8. Subjects who have received any neuromodulation therapy in the last 3 months or implanted with any neuromodulation device
9. Previous urinary incontinence surgery or prolapse surgery using graft material within the last 12 months.
10. Any spinal or genitourinary surgery within the last 6 months.
11. Previous abdominoperineal resection of the rectum or previous radical hysterectomy.
12. Diagnosis of interstitial cystitis or bladder pain syndrome as defined by either American Urological Association (AUA) or European Association of Urology (EAU) guidelines.
13. Subjects with suspected urinary retention and/or PVR>150ml.
14. Any neurological disease or disorder including Alzheimer's, Parkinson, MS, stroke (CVI), neuropathy or injury resulting in neuropathy and/or suspected neurogenic bladder.
15. Current or recurrent urinary tract infection (3 or more infections in the last 6 months), or presence of urinary fistula, or urinary tract obstruction such as cancer, urethral stricture or presence of urinary stone.
16. History of chemotherapy or pelvic radiotherapy that might have affected bladder control or caused neuropathies (i.e. peripheral neuropathy).
17. Uterine prolapse, cystocele, enterocele or rectocele with pelvic prolapse beyond the hymen.
18. Other active implantable electronic device/s regardless of whether stimulation is ON or OFF.
19. Have a life expectancy of less than 1 year.
20. Subjects who are breastfeeding.

10.8 Patient Withdrawal and Lost to Follow Up

10.8.1 Discontinuation of Subjects

Each subject who is enrolled and treated should remain in the clinical trial until completion of the required follow-up period. However, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without prejudice. Should this occur, the reason for withdrawal must be documented in the subject medical record. A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

It is recommended not to explant the device unless there is a specific medical need or otherwise deemed necessary by the treating physician.

Anticipated reasons for discontinuation may include, but are not limited to the following:

Subject Withdrawal:	Subject participation in a clinical trial is voluntary and the subject may discontinue participation (refuse all subsequent testing/ follow-up) at any time without loss of benefits they would be otherwise entitled to.
Investigator Termination:	Investigator may terminate the subject´s participation without the subject´s consent if the Investigator believes it´s medically necessary.
Lost to Follow-up:	Subject does not complete the scheduled follow-up visits but has not "officially withdrawn" from the trial (this does not apply to missed visits).
Failure (lack of effect):	Subject leaves the study due to related AE, device explant, lack of effect that results in significant increase of UUI medication and the need for other 3rd line therapies for the management of UUI.

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

10.8.2 Lost-to-Follow-up

Site personnel should make all reasonable efforts to locate and communicate with subjects at each contact time point. If there is difficulty contacting the subject, a minimum of two attempts to contact the subject should be documented. If the subject misses two consecutive scheduled study visit time points and the above-mentioned attempts at communicating with the subject are unsuccessful, and the subject is known to be alive the subject will be considered as "consent withdrawal". If the patient's vital status cannot be confirmed the subject will be considered "lost-to-follow-up". If the reason for discontinuation from the study was made clear by the patient, then it should be documented in the CRF accordingly.

10.8.3 Study Discontinuation

The Study Completion/Discontinuation Form must be completed for all patients and should specify the reason for discontinuation or the completion of the study.

The Sponsor shall be notified of the reason for subject discontinuation. The site will provide this information on the Study Completion/Discontinuation Form (CRF/e-CRF) and on source documents. Investigators must also report this to their EC if defined by their institution's procedure.

In case where an implant removal is required in any stage of the clinical study or afterwards, the sponsor will bear the costs of having it removed.

10.9 Study Duration

Overall study duration is estimated to be 5 years including about 18 months for enrollment. The study duration per patient is 38-42 months and includes; baseline assessments, followed by implantation, activation and treatment initiation one-month post implantation and 36 months of follow-up period post system activation.

11. Conduct of the Study

11.1 General

The study will be conducted according to ISO 14155:2020, Good Clinical Practice guideline E6(R2) form November 2016, the Declaration of Helsinki (2013), Protection of Human Volunteers (21 CFR 50), Financial Disclosure by Investigators (21 CFR Part 54), Electronic Records and Electronic Signatures (21 CFR Part 11), Investigational Device Exemption (21 CFR Part 812) and in accordance with local laws and regulations in each of the countries participating. All data and information concerning subjects and their participation in this trial are considered confidential by the sponsor and its designees. Only authorized investigators and Sponsor or designated personnel will have access to confidential records. The EC and other regulatory authorities also have the right to inspect and copy records pertinent to the trial. All public reporting of the results of the trial will eliminate identifiable references to the subjects. Patients will be identified by a unique ID number. The patient's name and other identifying information will be removed from any study document to maintain confidentiality.

The Ethics Committee approval for the trial is required prior to the beginning of the trial.

11.1.1 Investigator and Site Qualification

Urologists and Urogynecologists who have surgical skills applicable for BlueWind system implantation and an adequate volume of OAB patients being seen in their clinics will be enrolled as investigators for the trial.

A pre-study visit (site selection and qualification visit) will take place in order to assess the site’s ability to participate in the study.

11.2 Physician Training

Prior to study initiation, the BlueWind Medical team will familiarize the physician (and his/her study staff) on the system and the conduct of the study. BlueWind Medical specialists will train the physician on the surgical technique as well as the system activation and data collection. Only surgeons trained and qualified by BlueWind will be allowed to implant the device during the course of this study.

Training on the surgical procedure may include a session by a proctor and in some cases, when applicable, by a cadaver lab. During the first implantation/s in each site, a proctor may be present in the procedure, and a trained BlueWind representative for technical support will accompany all of the implantations. In an event that a new

issue related to the use of the system and/or the surgical procedure will be raised in the course of the study, the sponsor will perform periodic advanced training sessions, as applicable (for full training instructions, please refer to G02-CLI-0002 Rev. 02).

11.3 Baseline Evaluation

Potential female subjects with UUI, who fulfil basic criteria will be informed of the study and will be invited to sign an informed consent form. Prior to participating in the study, the investigator will inform the patient orally and in writing about the scope, purpose, rights, duties and possible risks of participating in the study. The patient has to confirm her consent in writing. Subjects are considered as eligible to undergo device implantation upon signing an informed consent, baseline evaluations are successfully completed, and all eligibility criteria are met.

11.4 Study Visits

This study is designed as a single arm interventional study. It consists of baseline assessments, implantation of the BlueWind RENOVA iStim™ System, treatment activation and 12 months of follow-up period post activation of the device.

The study will consist of the following activities (see flow chart on Figure 1):

- **Enrollment and screening**: Potential study candidates will sign an informed consent form, complete a 7-day voiding diary, MESA incontinence questionnaire, PHQ-15 questionnaire and quality of life questionnaire (OAB-q) and will undergo a PVR measurement. Data collected will serve for establishing eligibility for the study and as a baseline data for purposes of evaluating efficacy. Subjects fulfilling all inclusion and none of the exclusion criteria will be enrolled to the trial.
    - If a subject already completed the 12-month follow-up visit and exited the study, she will be invited for a long-term follow-up consent visit in which, following her consent to participate, some eligibility criteria will be verified and treatment parameters setting will be performed.
- **Implantation** – At 6 ± 4 weeks after screening visit, eligible subjects will undergo unilateral implantation with the BlueWind RENOVA iStim™ System.
- **Activation and Treatment**: 4 weeks +/- 2 weeks post implantation, subjects will undergo parameter setting, and will be trained for system home use treatment. Therapy will be delivered daily for a minimum of 30 mins per day and maximum of 2 hours per day.
- **Follow-ups visits (clinic)**: will be performed at 1 month ± 2 weeks, 3 months ± 2 weeks, 6 months ± 4 weeks, 9 months ± 4 weeks,12 months ± 4 weeks, 24 months ± 6 weeks, and 36 months ± 6 weeks post system activation. During the follow-up visits a voiding diary will be collected. During the 6,12, 24 and 36 months follow-up visits quality of life (OAB-q), PGI-I, and BSW questionnaires will be collected. Stimulation parameters and level of treatment will be checked and adjusted as needed.
- **Follow-ups visits (calls)**: will be performed at 18 months ± 6 weeks and 30 months ± 6 weeks post system activation. During the follow-up visits a 3-day voiding diary will be collected.

- NOTE: Follow-up visits may be performed in clinic if needed (ie. Treatment parameter adjustment, AE or device malfunction, etc.

Prior to each visit, sites will attempt to call the patients to remind them to comply with their treatment regimen and complete their voiding diaries.

Under certain circumstances (e.g. patient is unable to arrive to clinic, device replacement), home visits or limited phone visits will be arranged. Personnel involved in such visits will be those involved in the regular sites' visits.

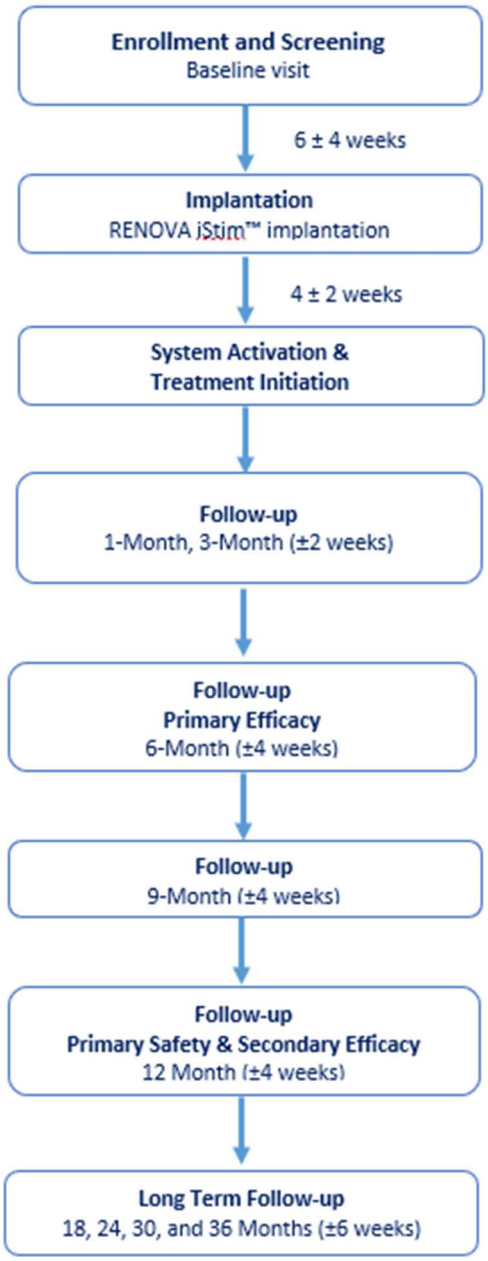
Since patients may not be able to come to the investigational site for follow-up visits, alternative methods such as phone contact or a virtual visit will be performed when feasible. NOTE: Baseline, Implantation, and Activation cannot be performed.

- If a phone or virtual visit is performed, it may not be possible to collect the following study data: urinalysis, parameter settings, and leg circumference measurements. The evaluation of these assessments is not necessary to ensure patient safety but will result in missing data or will be completed when on-sites visits will be allowed.
- If a phone or virtual visit is not possible, the visit will be performed out of window or considered a missed visit.

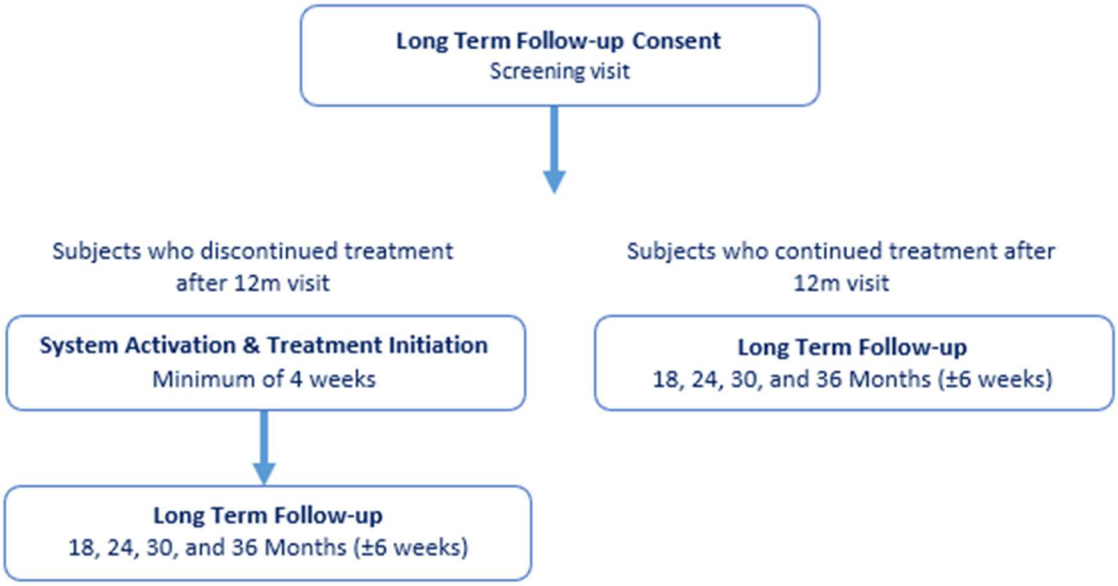
Missed visits, visits performed out of window, or missing data resulting from disruption of the clinical trial during the COVID-19 pandemic will be reported as protocol deviations. A listing of all impacted patients and a description of how their participation was altered will be described in the clinical study report.

A full study schedule chart is available in Section 25.

Figure 1 -The BlueWind RENOVA iStim™ system Study Design Flowchart



Subjects who completed the study and are re-entering for long term follow-up:



11.4.1 Patient Enrollment (Baseline) – Visit 1

Potential female subjects with wet OAB, who fulfil basic criteria will be informed of the study and will be invited to sign an informed consent form. Screening will include the following:

- Patient demographics (age, race, height, weight and leg circumference), and medical and surgical history review including duration of OAB, type of incontinence (i.e. based on the MESA incontinence questions, voiding diary and medical history) and severity of OAB, as well as information on existence of mixed fecal and urine incontinence and severity of the fecal incontinence, will be collected
- Medication use review (listing of type and doses): Patient who is eligible to enroll, will be asked to agree to remain on stable OAB medications until the 12-months follow-up visit. If there is a medical requirement to change medication during the study, these changes will be recorded and the patient will remain in the study as planned.
- Physical examination including abdominal and pelvic examination and neurological exam. Pelvic examination will include examination for vaginal abnormalities and pelvic muscles strength. As part of the physical/neurological examination, tibial nerve integrity will be verified by assessing sensory and motor response associated with this nerve per physician discretion. The motor function of the tibial nerve can be evaluated by testing the strength of the toe flexors. The gastrocnemius and abductor hallucis muscles can also be evaluated for the presence of atrophy. The sensory function of the tibial nerve can be evaluated by testing touch, pinprick and temperature sensation in the plantar aspect of the foot.

- Urinalysis and urine culture – if urinalysis or urine culture suggest the presence of urinary tract infection, patient should be treated and should start completing the baseline diary after treatment has been completed and urinalysis and culture are negative.
- Urine/blood pregnancy test (if bearing potential).
- Blood test for Creatinine levels (GFR) and HbA1C will be performed.
- A PVR measurement will be performed.
- Quality of life questionnaire (OAB-q).
- PHQ-15 questionnaire.
- Patients will receive a 7-day consecutive voiding diary and will be instructed to begin completing the diary immediately after the visit to record, among other things, instances of urgency urinary incontinence, number of voids per day, degree of urgency prior to voiding/leaking, severity of leaking episodes and number of stress related incontinence episodes per day. Results will be sent to the clinic to complete the eligibility criteria.
    - Patients who fail to complete the diaries or fail the inclusion/exclusion criteria, will not be enrolled in the study.

All of the above data collected will serve as baseline.

Subjects who already completed the 12-month follow-up visit and exited the study prior to the addition of the long-term study visits will be invited for a consent visit in which, following her consent to participate, some eligibility criteria will be verified. Screening will include the following:

- New medical and surgical history review since the 12-month visit
- Medication use review (listing of type and doses)
- Physical and neurological examination and urinalysis will be performed. If the urinalysis suggests urinary tract infection, urine sample will be sent for culture and sensitivity.
- Urine or blood pregnancy test (if bearing potential).
- Subjects will receive a 3-day consecutive voiding diary and will be instructed to begin completing the diary immediately after the visit to record, among other things, instances of urgency urinary incontinence, number of voids per day, degree of urgency prior to voiding/leaking, severity of leaking episodes and number of stress related incontinence episodes per day.
    - If the subject discontinued treating herself after completion of the 12-month visit, she will be asked to complete a modified daily diary to capture incontinence episodes, time to treatment effect, and symptom improvement questions.
- Subjects will undergo parameters' setting, and will be re-trained for system home use. Device activation, as well as parameter setting will be performed using the Clinician Programmer according to the BlueWind Clinician Manual.

11.4.2 BlueWind RENOVA iStim™ Implantation – Visit 2

The implantation of the device is carried out once the patient passed all inclusion/exclusion criteria and at 6 ± 4 weeks from the first day of the baseline diary. In the case of a patient who has to repeat the baseline diary, the window will be 6 ± 4 weeks from the first date of the final baseline diary. The investigator will perform a partial physical examination and confirm that there has not been any change to the medical condition of the patient that may necessitate excluding such patient from the study as well as record any changes to concomitant medication consumption. The procedure is performed under local anesthesia. If during the procedure, general anesthesia is warranted, the physician may decide to do so per his discretion and CRF should be filled out accordingly. In order to minimize the risk of post-operative infections several steps should be taken:

- In the evening before the surgery and the morning of the surgery patients will be asked to perform a scrub of the surgical site with antiseptic soap at home.
- Prophylactic analgesia and intravenous antibiotic (i.e. Cefazolin and/or Clindamycin) should be administered 15-60 minutes before the beginning of the procedure to ensure sufficient tissue level.
- A thorough 10-minute skin scrub with antiseptic preparation (i.e. chlorhexidine) must be performed followed by alcohol wipe, appropriate draping of the incision area and strict antiseptic technique throughout the procedure.

BlueWind RENOVA iStim™ System implantation will be conducted according to BlueWind Medical Surgical Technique Guide and the training and qualification program. Ultrasound may be used as part of the surgical preparations for training purposes or per physician discretion to better understand the anatomy. In principal, after a 5cm long incision at the appropriate location is made and the crural fascia is exposed and dissected, the posterior tibial neurovascular bundle is identified and the site is thoroughly irrigated. The implant is placed over the bundle in the appropriate orientation, while ensuring that the implant is parallel to the skin, not deeper than 3 cm below the skin, and not more than 10 mm from the nerve. The implant is then partially sutured to the fascia using non-absorbable suture material. An intra-operative sensory/motor test will be performed to verify proper implant location. An optimal result is paresthesia and/or motor response achieved at a low or moderate level of stimulation (≤ 5 mA). If results are non-satisfactory, the Implant may need to be re-positioned closer to the tibial nerve and the test repeated. The test stimulation shall be repeated after implant is completely secured to the fascia. In rare events that the neurovascular bundle is not identified or intra-operative stimulation was not successful in provoking a response, the contralateral leg may be attempted per physician's discretion. For subcutaneous tissue closure an absorbable poly-filament suture (such as 4-0 Vicryl) should be used and for the skin outer layer, either an interrupted pattern using non-absorbable mono-filament (such as 3-0 nylon) or a continuous intradermal pattern using an absorbable monofilament (such as 4-0 Monocryl), should be used. Intra-operative test will be performed for the last time. Antibiotic (Cephalexin or Clindamycin) and analgesics should be administered for the first 24 hours and may be dispensed longer according to the clinician discretion. Around 14 days following the implantation procedure, the patient will be instructed to attend the clinic for sutures removal. Patients will be instructed regarding the healing process of the wound, how to treat the wound and what to avoid during the two weeks following the procedure (i.e., elevate the operated leg above level of waist when

sitting or lying as much as possible during the first 72 hours post operation, avoid rigorous activity, keep the area dry and undisturbed).

Typical symptoms of discomfort related to the surgical procedure (such as incision pain and/or swelling, etc.) are expected in this kind of surgical procedure, and may take up to 5 days post procedure for complete resolution. Therefore, these symptoms are not considered as adverse events and thus should not be reported unless they are clearly related to RENOVA iStim™ system.

Wound healing in the distal leg region typically takes more time than in wound located more proximal or in the trunk, it is therefore normal to see some degree of redness and edema at the time of suture removal and complete healing duration of 2-4 weeks post-op.

Giving antibiotics as a precaution in cases as described above should not warrant automatically classifying them as an infection. Implant site infection should be reported when physical evidence of an infection are identified (such as described in table 2: Incisional wound classification).

11.4.3 BlueWind RENOVA iStim™ System Activation - Visit 3

After a recovery period of 4-weeks ±2 weeks post implantation, system activation based on sensation and motor assessment will be conducted as well as surgical wound inspection, in the outpatient clinic. Subjects will undergo an acute stimulation session of the tibial nerve to evaluate their sensory/motor reaction to stimulation. Thereafter, subjects will undergo parameters' setting, and will be trained for system home use. Device activation, as well as parameter setting will be performed using the Clinician Programmer according to the BlueWind Clinician Manual.

Parameter setting will be individually set for each patient, with stimulation parameters of:

- Frequency of up to 30Hz
- Peak current of up to 14mA
- Pulse width of up to 790µsec

Sensory and motor thresholds will be assessed and recorded. Tailored patient therapy parameters will be adjusted based upon patient tolerability, patient sensation and motor threshold. Stimulation parameters will be modified for each patient in a stepwise process, until a sensory response (tingling sensation in the ankle, foot, toes and sometimes a radiation sensation in the leg and/or genital area) or a sensory response in combination with a motor response (flexion of the big toe, fanning out of digits 2-5, extension of the foot) is elicited. The optimal stimulation parameters selected will be comfortable and under the maximal tolerability intensity level.

Physical and neurological examination and urinalysis, will be performed. If the urinalysis suggests urinary tract infection, urine sample will be sent for culture and sensitivity.

Concomitant medication and AEs will be documented.

11.4.4 BlueWind RENOVA iStim™ System Treatment

Treatment will include a daily stimulation of a minimum of 30 minutes and a maximum of 2 hours, per physician discretion.

Subject therapy parameters (frequency, pulse width and current) will be adjusted according to the individual patient sensations and according to the above specified range. Treatment parameters set at each visit will be recorded in the CRF.

11.4.5 BlueWind RENOVA iStim™ System Follow Up Visits – Visits 4-8

Patients will attend the clinic at 1-, 3-, 6-, 9- and 12-months post system activation. Patients will be asked to fill in an electronic voiding diary (a 3-day diary at the 1-, 3- and 9-months post activation visits and a 7-day diary at the 6- and 12-months visits), immediately prior to every follow-up visit. Only after electronic diary information is entered to the EDC the tentatively scheduled visit will be confirmed.

Patients may receive several treatment programs to choose from based on treatment effect and comfort and accordingly may be asked to fill a voiding diary after each change.

During these visits, patients will be asked about their urinary symptoms, discomforts that might have been felt or other physiological or technical problems that might have arisen. Physical examination will be performed and patients will be asked to submit a sample of urine for urinalysis at each follow-up visit. If the urinalysis or the patient's symptoms suggest urinary tract infection, urine sample will be sent for culture and sensitivity. If culture results suggest urine tract infection, follow-up visit will be re-scheduled for after treatment.

Adverse events will be recorded in the patient's CRF, according to specific categories, as defined in section 18 of the protocol.

The device will be inspected, stimulation parameters setting will be re-evaluated and system performance parameters and usage information will be recorded in the CRF. Any change in OAB related medications or dosage will be recorded in the patient's CRF. During the 6- and 12- months follow-up visits quality of life (OAB-q) PGI-I and BSW questionnaires will be collected, as well as information on existence of mixed fecal and urine incontinence and severity of the fecal incontinence will be collected.

Sensory and motor thresholds will be assessed and recorded during each follow-up visit and leg circumference will be measured and recorded.

Specific activities and questionnaires associated with each follow-up visit is outlined on section 24; Study Schedule.

At the last visit, 12 months post activation, optimal treatment parameters and treatment regimen will be determined and adjusted on the device.

11.4.6 BlueWind RENOVA iStim™ System Long-Term Follow Up (LTF) Visits – Visits 9-12

Long term follow-up visits will be performed at 18, 24, 30, 36-months post activation.

If a subject already completed the 12-months follow-up and exited the study, she will be invited for a Long-Term Follow-Up Consent Visit in which, following her consent to participate in the long-term follow-up study, some eligibility criteria will be verified and treatment parameters setting will be performed. Subjects will enter the visit schedule using their original system activation date. Any visit that has already passed will not be counted as a missed visit.

If the subject discontinued treating herself when she exited the study and is activated again she will be asked to treat herself for 30 minutes, twice a day, for at least 4 weeks prior to completing the first LTF visit. During this period, she will be asked to complete a modified daily diary to capture incontinence episodes, time to treatment effect, and symptom improvement questions.

Subjects continuing to the long-term follow-up will be asked to treat themselves per physician discretion but not less than two 30-minute treatment per week.

All follow-up visits will require completion of 3-day voiding diary by the patient before coming to visit.

Follow-up visits 10 (24-months) and 12 (36-months) will be performed in clinic and will be similar to the 6 and 12-months follow-up visits

Follow-up visits 9 and 11 will be performed over a phone call unless the treatment is not effective enough or treatment parameters are not optimal or patient is experiencing an AE or device malfunction. In such cases the patient will arrive to the clinic and a visit similar to the 1, 3, and 9- months post activation will be performed.

11.4.7 Unscheduled Visit

An unscheduled visit will be any visit to the clinical site other than the visits specified in the protocol. Unscheduled follow-up visits will be allowed as needed to adjust stimulation settings to optimize therapy. The Investigator or trained and qualified investigational staff will perform all procedures necessary to evaluate the study participant at these visits, and record the visit in the patient's CRFs. The investigational site Principal Investigator must be notified by the patient immediately of any unscheduled visits to any medical facility during the study period.

At certain circumstances (e.g. UTI) the subject will be requested to attend an additional visit, after the circumstance has been resolved. The relevant data will be collected again during this additional visit and used for analysis. This additional visit will be considered the formal visit for which the data will be used to evaluate study endpoint. At such circumstances the additional visit will be allowed to occur out of the window range.

12. Monitoring Procedures

12.1 Monitoring Procedures and Responsibilities

Monitoring visits will be conducted at the start, during, and at the closure of the clinical study in accordance with study Monitoring Plan and in compliance with recognized Good Clinical Practices, FDA's IDE guidance document, as outlined in 21CFR§812.43(d) and 21CFR§812.46 and ISO 14155:2011 and per company's (or company designee) standard operating procedure. The Monitoring Plan will be included in a separate document and maintained by the study manager or designee. The Monitoring Plan will include detailed descriptions for each type of visit to be made during the study, including pre-study visits, site initiation visits, interim monitoring visits and close-out visits.

It is the responsibility of the study sponsor to ensure that proper monitoring of the investigation is conducted. This includes ensuring subject and investigator compliance to the protocol and study agreements, adherence to regulations, and accuracy of study data.

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the principal investigator and/or sub-investigator(s) and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the principal investigator and staff.

All aspects of the study will be carefully monitored for compliance with applicable government regulations, with respect to current ISO 14155:2011 and Declaration of Helsinki regulations, and current SOPs.

The following factors will be taken into account when determining the frequency of monitoring visits at each center: implantation rate, total number of subjects enrolled, study phase (e.g., screening, treatment, long-term follow-up), center compliance, and monitoring findings from previous visits. The frequency of interim monitoring visits will be documented in the monitoring plan and approval from sponsor prior to each interim monitoring visit is required.

13. Statistical Considerations

This section describes the statistical methods that will be applied to the study's main endpoints. A detailed statistical analysis plan (SAP) will be written and finalized prior to trial initiation.

13.1 Introduction

This is a prospective, single arm, multi-center, open label study whose primary objective is to assess the safety and efficacy of the BlueWind RENOVA iStim™ system for the treatment of UUI. The trial's secondary objectives are to evaluate device performance, durability of effect and patient reported outcomes (PROs) such as quality of life (QoL).

The trial will be conducted in up to 30 centers.

13.2 Analysis Sets

13.2.1 Safety and Efficacy Analysis Population – Intent To Treat (ITT)

The safety and effectiveness endpoints will be evaluated under principles of Intent to Treat (ITT). The analysis set will consist of all subjects for whom the implantation of the BlueWind RENOVA iStim™ system was attempted. Specifically, the analysis set will consist of all subjects for whom skin incision time was not missing.

Treatment of missing values:

- Subjects missing data "not in random" will be imputed "failure" on dichotomous endpoints
- "Failures" (not MAR) include:
    - Subject leaves the study due to related AE
    - Device explant
    - Lack of effect that results in significant increase of UUI medication
    - Need for other 3rd line therapies for the management of UUI
- Baseline values will not be imputed
- Missing values in ITT not due to "failure" will be imputed using multiple imputation (MI).

Because MI assumes missing at random (MAR), sensitivity analyses will, as described below, be conducted to test the effects of other patterns of missingness. See Section 13.3 below for further discussing of how missing data will be handled in the efficacy analysis.

13.2.2 Per Protocol analysis set

The per protocol analysis set (PP) will be a subset of ITT population without major protocol violations, where "major" is defined has having the potential to meaningfully affect outcome. Also excluded will be subjects who received treatment on fewer than 50% of days during which they were eligible for therapy delivery.

Only observed values will be used in the endpoint analyses for the PP. Thus, the primary endpoint will be analyzed only on those subjects with an observed primary endpoint. Similarly, a subject will be included in the analysis of a secondary endpoint only if she has an observed value on that endpoint.

13.2.3 One-month Responders

The one-month responder analysis set will be a subset of ITT of subjects who are classified responders at one month.

All endpoints will also be assessed for this cohort of subjects for qualitative comparisons to treatments utilizing a trial period prior to permanent implant.

13.3 Treatment of Missing Data for Efficacy Analyses

Frequency of missing data and the reasons for the missing data will be presented in the final report. For ITT effectiveness endpoints, a multiple imputation procedure will be used to impute missing endpoint data. Any patients missing endpoint data due to ”failure” will be considered as a failure for the effectiveness analysis. Further sensitivity analyses will include, but may not be limited to, a tipping-point analysis for handling missing data.

Baseline variables included in the multiple imputation procedure may consist of:

- Age
- Number of UUI episodes per day
- OAB duration
- Number of prior attempted OAB treatments

13.4 Sample Size Considerations

The sample size was calculated using PASS 2015 software by a one-sided exact test for a single binomial population, under the following assumptions:

- Significance level = 0.025 (one-sided)
- Power ≥ 90%
- Assumed treatment success rate = 65%
- Prespecified performance goal = 50%.

Given these assumptions, 134 evaluable subjects would be required to participate in the trial, taking into account an assumed attrition rate of 15%.

The total sample size for this trial, however, is driven by an important secondary objective:

To demonstrate the proportion of responders at 6 months post system activation, defined by ≥50% improvement in the average number of moderate-severe urgency episodes PPIUS degree 3,4 or <8 voids/day, is greater than 45%. A total of 89 evaluable subjects are required. Assuming 15% attrition rate, a total of 105 subjects meeting the criteria described above is needed. With 70% of enrolled subjects meeting the analysis criteria, 150 total sample size is sufficient to evaluate the secondary endpoint.

13.5 Statistical Analyses

13.5.1 Overview

Analysis of subject disposition and of safety will be done on the ITT population. The primary efficacy analysis and analyses of additional endpoints will be done on ITT. Supportive efficacy analyses will be done for the primary efficacy endpoint on the PP population and for other efficacy endpoints in both ITT and PP population.

The data will be summarized in tables listing the mean, standard deviation median, minimum, maximum and number of subjects for continuous data, or in tables listing count and percentage for categorical data where appropriate. Descriptive statistics will be provided by time point both numerically and graphically as appropriate. Data listing by subject will be provided.

All statistical analyses will be performed, and data appendices will be created using the SAS® system. The effects of noncompliance, dropouts, and possible covariates such as Age will be assessed to determine the impact on the general applicability of results from this study.

13.5.2 Subject Disposition

Subject disposition will be tabulated; the number of enrolled, exposed, prematurely terminated and completed subjects will be summarized.

A list of dropouts will be prepared including reason for discontinuation, and time of discontinuation.

13.5.3 Safety

The safety analyses will be descriptive and narrative in nature, with AEs, including serious AEs (SAEs), coded and tabulated by body system, preferred term, group, severity and relation to device or procedure. Descriptive statistics and shift analysis tables will be provided as appropriate.

13.5.4 Primary Efficacy

For the primary analysis, the null hypothesis is that the response probability is less than or equal to 50%. We are interested in the alternative hypothesis that patients receiving the treatment have above 50% probability to achieve clinical improvement:

$$\mathbf{H_0: \pi_{Renova} \leq \pi_{PG}}$$
$$\mathbf{H_1: \pi_{Renova} > \pi_{PG},}$$

where π_{Renova} is the proportion of subjects meeting the pre-defined success criterion with RENOVA therapy (≥ 50% improvement in average number of urge related incontinence episodes), and π_{PG} is the prespecified performance goal (PG) of 50%.

Though sample size was conservatively calculated under an Exact Binomial test, the hypothesis testing will be conducted by constructing a two-sided, 95% Clopper-Pearson confidence interval. We will have succeeded in the trial if the lower bound of this confidence interval is above 50%.

13.5.5 Secondary Efficacy Endpoints

The following will be assessed as formal secondary efficacy endpoints:

- Proportion of subjects with ≥ 10 points (MID) improvement compared to baseline in HRQL (measured by the OAB-q) at 6 months post system activation

- Proportion of responders at 12 months post system activation, defined as ≥ 50% improvement in either average number of urgency related incontinence episodes or average number of large (severe) urgency related incontinence episodes, as measured by 7-day Patient Voiding Diary.
- Proportion of responders at 6 months post system activation as demonstrated by ≥ 50% improvement in the average number of moderate-severe urgency episodes (PPIUS degree 3,4) or < 8 voids/day

Durability of effect will be based on 12-month follow-up data and all secondary efficacy endpoints will be analyzed in the three efficacy analysis sets—ITT, PP and OR1.

13.5.6 Additional Efficacy Endpoints

The following endpoints will be assessed as other endpoints for the 6-, 12-, 24- and 36-months post activation, without formal hypothesis testing and type I error control.

- Incidence of procedure or device related adverse events from 12- to 36-months post activation.
- Patient Global Impression of Improvement (PGI-I) score.
- Treatment Benefit, Satisfaction, and Willingness to Continue (BSW).
- Reduction in the average number of severe/large urgency related incontinence episodes.
- Improvement in OAB-q (HRQL and symptoms severity) at 6- and 12- months post system activation.
- Changes in the following OAB symptoms as measured by voiding diary compared to baseline:
  - Reduction in the number of micturition episodes.
  - Reduction in the number of urgency related incontinence episodes.
  - Reduction in degree of urgency prior to void on Patient Perception of Intensity of Urgency Scale (PPIUS) from 0-4.
  - Reduction in severity of incontinence episodes (amount leaked).
- Proportion of dry subjects following treatment with the RENOVA iStim System as measured by 3 consecutive days of a patient voiding diary.
- Assessment of fecal incontinence symptoms in patients suffering from mixed fecal and urine incontinence.
- Patient compliance with treatment.
- Duration from treatment initiation to symptoms improvement (in subset of patients who stopped treatment after completing the 12 month visit and started again when consented for the long term follow-up
- Assessment of treatment regimen

- Device usage

All additional efficacy endpoints will be analyzed in all three efficacy analysis sets—ITT, PP and OR1.

13.5.7 Covariate Analyses

Covariate analyses will be done by comparing each endpoint between groups defined by the levels of the covariate at baseline, where continuous variables will be coded into two levels by median split. Analyses will be done by logistic regression. Covariates will include, but are not limited to:

- Age
- BMI
- OAB duration at baseline

Additionally, formal subgroup analyses will be conducted to assess the effects on the primary endpoint of antidepressant medications, and also to assess the potential impact of COVID-19 on the study outcomes. Details of these analyses are outlined in the SAP.

Finally, a test of homogeneity of effect across investigational center will be conducted. Descriptive statistics (e.g. success rate) will be reported for every participating center. Any center enrolling fewer than five subjects will be excluded from the formal test of homogeneity. To acknowledge that this test of homogeneity is fundamentally underpowered, a significance level of 0.15 will be used to determine whether a potential differential effect across centers exists and to trigger additional, exploratory analysis to better understand the nature of the difference.

13.5.8 Interim Analysis

An administrative interim analysis is will be performed at the time one-month post activation data is available on 50 implanted subjects. This analysis is intended to support necessary company financing activities, and visibility of the results will be restricted to only those involved in those activities. Importantly, no person – BlueWind employee or consultant – who has interaction with investigational sites will have visibility to interim results. The interim analysis does not require subsequent adjustment of the overall trial significance level (0.025) to account for type I error inflation because:

- it is administrative in nature only, with limited distribution of the results
- it is looking primarily at 1-month data, which may not be reflective of the primary endpoint at 6 months
- the interim analysis is at the time 1/4 to 1/3 of the total number of enrolled subjects is 1/6 of way (1 month follow-up) toward the primary effectiveness endpoint (at 6 months follow-up). This represents 1/18th to 1/24th of the total trial information. Under an O'Brien-Fleming alpha spending function, virtually zero alpha would be allocated to the interim analysis
- there is no opportunity to terminate the trial early for effectiveness.

Only data from the first 50 subjects with one-month post activation data will be reviewed. Data from enrolled subjects that do not yet have 1-month data available will be excluded from the analysis. All data from the 50 subjects will be included in the review (i.e. data from follow-up visits subsequent to the 1-month visit will also be summarized, if available).

The analysis will involve, in summary form, results on:

- Device and procedure-related adverse events
- Percent improvement in the average number of urgency-related incontinence episodes, as compared to baseline.
- Proportion of subjects with ≥10 points (MID) improvement compared to baseline in HRQL (based on OAB-q) at each follow-up post system activation
- Proportion of responders at each follow-up visit post system activation, as demonstrated by ≥50% improvement in the average number of moderate-severe urgency episodes PPIUS degree 3,4 or <8 voids/day

Other data summaries, such as questionnaires (e.g., PGI-I, BSW), demographics, the proportion of dry subjects, and outcomes of interest may also be summarized

14. Data Management

Data management services will be provided by TechnoSTAT Ltd. Electronic Data Capture and adverse events coding will be performed by Axiom Real-Time Metrics. It is the responsibility of the study sponsor to ensure that the investigation is conducted and the data is generated, documented (recorded), and reported in compliance to the investigational plan and study agreements, adherence to regulations, and accuracy of study data.

14.1 Electronic Case Report Form (eCRF)

The Investigator must maintain required records on all study patients. Data for this study will be recorded in the patient's medical records and on eCRFs provided by the Sponsor. The Investigator is responsible for ensuring that study data is completely and accurately recorded, including all pertinent study related information. The eCRFs will be completed by the authorized study site personnel. The Sponsor's study monitors or designees will review the eCRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

All the source documents and forms used for the trial will be kept in the patient binders and will remain on site or will be inserted into the patient's medical chart as authorized by the local medical facility procedures.

14.2 Safety Monitoring of the Study and Quality Control

14.2.1 CEC

Clinical Events Committee is an independent committee with a documented CEC Charter. The Clinical Event Committee will adjudicate adverse events in regards to their severity and relationship to the procedure or device. Adverse events adjudicated will include: all serious adverse events, and adverse events. The committee will include independent physicians, blinded to clinical site, who will adjudicate AEs, UADEs and SAEs.

All roles and responsibilities and working guidelines of the CEC will be detailed in the CEC charter prior to beginning of the adjudication process. CEC will discontinue adjudicating AEs when all patients reach 12 months post system activation.

14.2.2 DSMB

Data and Safety Monitoring Board is an independent committee with a documented DSMB Charter. Members are independent from the sponsor and are not investigators in the study. Its role is to monitor the safety of the study and it can recommend to the sponsor to continue or suspend the study due to significant safety or efficacy issues. The DSMB receives data directly from the independent statistician or/or sponsor designated study medical monitors. The DSMB will conduct independent reviews of the data and the adverse events observed. The actual number of DSMB meetings will be finalized in consultation with the committee itself. The DSMB will review the safety data of up to 30 patients. Thereafter, the DSMB will convene semi-annually, or every 50 subjects have been implanted. Once all patients reach 12-months post system activation, DSMB will continue to convene annually until the end of the long-term follow-up (i.e. last patient reaches 36-month follow-up visit).

14.3 Data Collection and Monitoring

Completed e-CRFs will be verified against source data and checked by the study monitor for completeness, consistency, and legibility.

The Research Coordinator will collect and document data in hospital and clinic charts and on source document forms prepared for the study. Data will be entered with no identifying information, using patient ID only into the secure password protected database. Passwords will not be issued by the Sponsor until Site Initiation and database training has been conducted for all personnel to whom Investigator has delegated data entry responsibilities. Completed final eCRFs in final form may be printed and filed in hardcopy for archiving if required by local governing authority.

The Sponsor will designate and train monitors to review eCRF data against source documents for completeness and accuracy. Discrepant data will be queried; the electronic database will maintain audit trails of all queried and corrected data. The Investigator is responsible for data integrity at the site and will review and electronically sign it to confirm integrity of the data.

14.4 Data Quality Control and Quality Assurance

All requested information must be entered in the eCRF. If an item is not available or not applicable this fact should be indicated.

Data will be entered into a computer database developed specifically for this trial. A system of computerized data validation checks will be implemented and applied to the database on a regular basis. During the course of the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. All queries will be entered, tracked, and resolved through the eCRF system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

14.5 Data Retention

The investigator, or an individual designated by the investigator, is responsible for retention of all study related documents, including:

- All correspondence which pertains to the investigation; e.g. Ethic committee's approvals, device information, protocol and subsequent versions, CRFs, financial disclosures, delegation logs, monitoring site visit logs, training records, CVs, etc.
- Documentation of the dates and reasons for any deviation from protocol

Records are subject to inspection by regulatory authorities and must be retained as required by the applicable regulatory requirements or for a period of at least 2 years after a marketing application is approved or from the date on which the investigation is terminated or completed and the regulatory authorities have been notified.

15. Deviations from Protocol

The investigator is not allowed to deviate from the clinical protocol, except if;

- Sponsor and EC approval and reports of deviations have been obtained for cases in which the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation;
- Under emergency circumstances, deviations from the clinical protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

All study deviations must be recorded. A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan. Study deviations should be reported as soon as someone becomes aware of them. A waiver from certain criteria may be provided by the sponsor under such circumstances allowed by the relevant guidelines.

Study deviations may be discovered through a variety of sources, such as during the Case Report Form review, telephone conversations, and site monitoring.

16. The RENOVA iStim™ System Accountability

The system shall be used only in the clinical investigation and according to the study protocol.

Complete traceability records will be kept of all systems used during the study, including data recorded during the trial by BlueWind Medical Ltd.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational system.

17. Informed Consent Process

Written consent will be obtained from each subject to be involved in the study. Legally incompetent subjects will not be enrolled in this study, thus all regulations in relation to this population are not applicable. Potential study subjects should be given the opportunity to ask questions and time for consideration.

The investigator must inform every subject in details and plain language about the nature of the study, its purpose, the treatments, those aspects of the study that are experimental, the procedures involved including all invasive procedures and the discomfort it may entail, the possible risks, the reasonably expected benefits, the expected duration and the approximate number of subjects involved and the subject's responsibilities.

The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with ISO 14155 and 21 CFR Part 50 and/or any regional and/or national regulations.

The clinical investigation shall not begin until the required approvals/ favorable opinions from EC/IRB and/or CA/FDA have been obtained.

After the information contained in the Informed Consent document has been reviewed with each subject, the subject must sign the Informed Consent document, indicating willingness to participate in the Clinical Investigational Study. A copy of the Informed Consent document should be given to the subject.

The investigator will indicate that Informed Consent has been obtained by noting so in the appropriate section of the Case Report Form.

A copy of the informed consent form approved by the Ethics Committee / IRB must be maintained in the investigator's study file. A signed copy of the patient information and informed consent form must be given to each subject.

18. Safety

18.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

*Disease signs and symptoms that existed prior to study participation are not considered AEs unless the condition recurs after the subject has recovered from the pre-existing condition, or the condition worsens during the study.

18.2 Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition also includes any event from use error or from intentional misuse of the investigational medical device.

18.3 Serious Adverse Events

A serious adverse event (SAE) is an AE that:

a) Led to death

b) Led to serious deterioration in the health of the subject, that either results in:

1) A life-threatening illness or injury, or
2) A permanent impairment of a body structure or a body function, or
3) Hospitalization or prolonged hospitalization, or
4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
5) Chronic disease,

c) led to fetal distress, fetal death or a congenital physical or mental impairment or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.

18.4 Serious Adverse Device Effects

A serious adverse device effect (SADE) is an adverse device effect that results in any of the consequences characteristic of a serious adverse event.

18.5 Anticipated Serious Adverse Device Effects

An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

For list of anticipated AEs see section 8.

18.6 Unanticipated Serious Adverse Device Effects

An unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

18.7 Device Deficiency /Malfunction / Use Error

Device deficiency (DD) is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device malfunction is the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or CIP.

Use error is the act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

NOTE 1: Use error includes slips, lapses, and mistakes.

NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error.

Device malfunction may or may not result in the subject experiencing a harmful effect. All AEs/SAEs associated with a device failure are by definition device-related.

18.8 Adverse Events Collection and Recording

Collection of AEs will start after the time that the informed consent form is signed and continue until the subject exits the study. AEs will be monitored throughout the study. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the sponsor or its designated representative. All reported AEs will be documented on the appropriate eCRF and will include the event description (sign, symptom, and diagnosis), onset, resolution, seriousness, severity, cause and action taken. The investigator or an authorized designee must assess the causality and severity for all AEs. All AEs will be followed by the investigator until

resolution or until the termination of the subject's study participation. Any adverse events that remain unresolved at the end of the study will be explained in the final report.

Individual symptoms should not be reported as AE, alternatively a diagnosis should be made based on the symptoms and this diagnosis should be entered under the "description/type" column.

18.9 Adverse Events Reporting

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of the subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Since the safety reporting requirements and classification systems vary for each regulatory authority, requirements from all geographies are taken into account for the collection and reporting of safety information.

Subjects will be carefully monitored during the study for possible AEs. Any AE that occurs after the time of informed consent through the end of the study participation will be fully evaluated by the investigator. An appropriate treatment will be initiated and the study follow-up will continue as completely as possible.

The investigator or an authorized designee will document all observations and clinical findings of AEs, including the nature, severity and relationship, on the appropriate eCRFs.

The investigator is required to report all SAEs and ASADEs/USADEs to the Sponsor within 24 hours after first learning of the event. Initial reporting may be done by completing the applicable eCRF form or via phone, fax or email in case the eCRF is inactive, with as much information as available at that time. In case of urgent questions regarding safety reporting, the investigator can contact BlueWind Medical, clinical affairs. Contact details for clinical affairs are as follows:

Europe:

oasis-group.medtech@iqvia.com

32.3290.0307

US:

Roni.diaz@bluewindmedical.com

469-423-2015

Furthermore, the investigator must follow their local IRB/EC policy for SAE/ASADE/USADE reporting. If required by national regulations or IRB/EC policy, DDs that could lead to a SADE should be reported to the Sponsor and IRB/EC within 24 hours of awareness of the event.

As additional information becomes available, the investigator will record all adverse events (serious or non-serious), adverse device effects (anticipated and unanticipated) and device deficiencies on the appropriate eCRFs.

The sponsor, Bluewind Medical Ltd., will ensure to perform expedited SAE reporting to all regulatory authorities involved in this study in line with the local reporting requirements.

In case of SAEs, copies of source documentation which contain significant information related to the event such as discharge letters, surgery reports, consultation letters, ECGs, laboratory results etc. are required for evaluation

of the event. Copies of such documentation shall be obtained from the investigator, blinded or de-identified as to the subjects' identity, and provided to the Sponsor or designee.

In case an incisional wound AE is suspected a photograph of the wound should be sent to the chief medical officer (see contact above) who will aid in the classification of the adverse event as per table 3 below.

Table 2: Incisional wound classification

AE type – description column (*CTCAE)	Individual symptom - comment column		Reporting
Wound complication	Localized inflammation (pain or tenderness, induration, erythema, local warmth of the wound).	Mild, <4 weeks	normal
		Moderate, <5 days	normal
		all other	define as AE
Wound infection (surgical site infection)	Localized inflammation (pain or tenderness, induration, erythema, local warmth of the wound)* **together with purulent discharge or positive culture**		define as AE
Wound infection with systemic symptoms	Localized inflammation (pain or tenderness, induration, erythema, local warmth of the wound)* **together with purulent discharge or positive culture and the addition of either fever or lymphangitis**		define as AE
Wound Dehiscence	Incisional separation with device exposure		define as AE
	Incisional separation with signs of reaction to suture material		define as AE

18.9.1 Periodic Safety Report

In addition to the expedited reporting of SAEs, the sponsor will submit, at a minimum of once a year throughout the clinical study, an annual safety report to the involved ethical committees and regulatory authorities of the concerned countries. This periodic safety report can be combined with the annual study report.

18.10 Severity

The investigator will use the following definitions to determine the severity of an AE:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Activities of Daily Living (ADL) *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

18.11 Relationship

The investigator will use the following definitions to assess the relationship to the device (MEDDEV 2.7/3):

- **Not related:** relationship to the device or procedures can be excluded when:
    - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has no temporal relationship with the use of the investigational device or the procedures;
    - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
    - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
    - the event involves a body-site or an organ not expected to be affected by the device or procedure;
    - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
    - the event does not depend on a false result given by the investigational device used for diagnosis 17, when applicable;
    - harms to the subject are not clearly due to use error;

  In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible:** the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition

or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

- **Probable:** the relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
- **Causal relationship:** the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
    - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has a temporal relationship with investigational device use/application or procedures;
    - the event involves a body-site or organ that:
        - the investigational device or procedures are applied to;
        - the investigational device or procedures have an effect on;
    - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
    - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
    - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
    - harm to the subject is due to error in use;
    - the event depends on a false result given by the investigational device used for diagnosis, when applicable;

  In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

19. Protocol Amendments

An amendment to the protocol may be proposed by an investigator. The amendment will be prepared and approved by BlueWind according to the company's Standard Operating Procedures. The amendment must be submitted to the relevant Ethics committee. When applicable, the amendment's implementation will take place only once approved by the committee.

20. Subject Confidentiality

The Investigator and institution involved in this study will only provide direct access to source data and documents to the Sponsor and/or designee, and to appropriate authorities for the purposes of monitoring, audit, EC review or regulatory inspection. Each subject taking part in the study will have agreed explicitly to such access in writing. All subject data will always be treated with strict adherence to professional standards of confidentiality and

according to EU GDPR guidelines effective as of 25- May- 2018. All reports and communications relating to subjects in the study will identify the subjects by their subject ID number only.

21. Termination of the Clinical Study

The sponsor will notify the involved ethics committees and the competent authorities of the end of the study within a period of 90 days or per the EC requirements, whichever is sooner. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the responsible ECs and the competent authorities within 15 days, including the reasons for the premature termination.

At the completion of the last follow-up visit, patient will exit the study. However, the implant will not be explanted and the patient will be clinically followed up per physician discretion. System support will be provided by BlueWind Medical for 3 years post activation.

22. Insurance

Study subject insurance coverage will be provided according to the laws of the country where the study will be conducted.

In Europe, the insurance company is Newline Syndicate 1218 at Lloyd's and in the US, the insurance company is Medmarc Insurance Group.

23. Publication Policy

It is BlueWind Medical's policy to publish the results of its Clinical Trials.

The publication of the common database will be under the direction of the study manager. Publication of the complete data set will not be allowed unless approved by the study manager.

Individual investigators may publish their own data based on the terms and conditions specified in the clinical trial agreement.

All publications will be reviewed by BlueWind Medical in order to assure that no confidential information is disclosed. Such confidential information is not allowed for publishing.

A final study report will be submitted, including any publications/abstracts of the study, to the accredited EC/IRB and the Competent Authority within one year after the end of the study.

24. Reporting Results on ClinicalTrials.gov

The clinical investigation will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical investigation completion, as required by section 801 of the Food and Drug Administration (FDA)

Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

25. Study Schedule

#	Section name	Enrollment and Screening	Implantation (6 ± 4 weeks)	Activation (4 ± 2 weeks)	FU 1m (±2 weeks)	FU 3m (±2 weeks)	FU 6m (±4 weeks)	FU 9m (±4 weeks)	FU 12m (±4 weeks)
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1.	Informed consent form	X							
2.	Patient Demographics	X							
3.	Inc/Exc criteria	X							
4.	Medical History	X							
5.	Physical & Neurological Exam (including vital signs) *partial physical examination	X	X*	X*	X*	X*	X*	X*	X
6.	Urinalysis	X		X	X	X	X	X	X
7.	Urine culture (at baseline, *and then pending urinalysis results)	X		*	*	*	*	*	*
8.	Urine/blood pregnancy test (if bearing potential)	X							
9.	Blood – chemistry (Creatinine levels; GFR, and HbA1C)	X							
10.	PVR	X							
11.	Medications	X	X	X	X	X	X	X	X
12.	Quality of Life Questionnaire	X					X		X
13.	MESA incontinence questionnaire	X							
14.	PHQ-15	X							
15.	PGI-I						X		X
16.	BSW						X		X
17.	Usage information collection				X	X	X	X	X
18.	Voiding Diary	X (7-days)			X (3-days)	X (3-days)	X (7-days)	X (3-days)	X (7-days)
19.	Usability/patient satisfaction questions		X	X	X	X			
20.	Parameter Setting			X	X	X	X	X	X
21.	Leg circumference measurements	X	X	X	X	X	X	X	X
22.	Patient Training on wearable unit			X					
23.	Adverse Event		X	X	X	X	X	X	X
24.	Study completion/discontinuation form								X

26. Study Schedule – Long-Term Follow-Up

#	Section name	Long Term FU Consent Visit	FU 18m (±6 weeks)	FU 24m (±6 weeks)	FU 30m (±6 weeks)	FU 36m (±6 weeks)
	Visit		**9**	**10**	**11**	**12**
25.	Informed consent form	X				
26.	Inc/Exc criteria (verify new criteria – if exited study at 12m FU)	X				
27.	New medical history since 12m FU visit	X				
28.	Physical & Neurological Exam (including vital signs) *partial physical examination †if in clinic	X	X*†	X*	X*†	X*
29.	Urinalysis †if in clinic	X	X†	X	X†	X
30.	Urine culture *pending urinalysis results †if in clinic	X*	X*†	X*	X*†	X*
31.	Urine/blood pregnancy test (if bearing potential)	X				
32.	Medications	X	X	X	X	X
33.	Quality of Life Questionnaire			X		X
34.	PGI-I			X		X
35.	BSW			X		X
36.	Usage information collection	X	X	X	X	X
37.	Voiding Diary (3-days)	X	X	X	X	X
38.	Voiding Diary (UUI for ~4 weeks) *only for applicable subjects	X*				
39.	Usability/patient satisfaction questions		X		X	
40.	Parameter Setting †if in clinic		X†	X	X†	X
41.	Leg circumference measurements	X				
42.	Patient Training on wearable unit	X				
43.	Adverse Event	X	X	X	X	X
44.	Study completion/discontinuation form					X

Appendix 1 - BSW questionnaire

Benefit, Satisfaction, and Willingness to Continue (BSW) Questions

The following questions are administered by the physician:

BENEFIT: Please ask the patient the following question:

1. Have you had any benefit from your treatment? ☐ (0) No ☐ (1) Yes

If **YES**, please ask the patient the following question:

Have you had little benefit from your treatment or much benefit?
☐ (1) Little benefit
☐ (2) Much benefit

SATISFACTION: Please ask the patient the following question:

2. Taking all things into account, are you satisfied with your treatment?

☐ (1) Yes If **YES**, please ask the patient the following question:

Are you a little satisfied with your treatment or very satisfied with your treatment?
☐ (1) A little satisfied
☐ (2) Very satisfied

☐ (0) No If **NO**, please ask the patient the following question:

Are you a little dissatisfied with your treatment or very dissatisfied with your treatment?
☐ (1) A little dissatisfied
☐ (2) Very dissatisfied

WILLINGNESS TO CONTINUE

3. Would you be willing to continue treatment with this medication?

☐ (1) Yes If **YES**, please ask the patient the following question:

Would you be a little bit willing to continue treatment with this medication or very willing to continue treatment with this medication?
☐ (1) A little bit willing
☐ (2) Very willing

☐ (0) No If **NO**, please ask the patient the following question:

Would you be a little bit unwilling to continue treatment with this medication or very unwilling to continue treatment with this medication?
☐ (1) A little unwilling
☐ (2) Very unwilling

BSW

Appendix 2 - MESA incontinence questionnaire

MESA Incontinence Questionnaire

Urge Incontinence Questions

Some people receive very little warning and suddenly find that they are losing, or about to lose, urine beyond their control. How often does this happen to you?
_____Often (3) _____Sometimes (2) _____Rarely (1)_____ Never (0)

If you can't find a toilet or find a toilet that is occupied and you have an urge to urinate, how often do you end up losing urine and wetting yourself?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Do you lose urine when you suddenly have the feeling that your bladder is full?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does washing your hands cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does cold weather cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does drinking cold beverages cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

TOTAL URGE SCORE _____
URGE SCORE RATIO _____

Stress Incontinence Questions

Does coughing gently cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does coughing hard cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does sneezing cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does lifting things cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does bending over cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does laughing cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does walking briskly cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does straining, if you are constipated, cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

Does getting up from a sitting to a standing position cause you to lose urine?
_____Often (3) _____Sometimes (2) _____Rarely (1) _____Never (0)

TOTAL STRESS SCORE _____
STRESS SCORE RATIO _____

Add the total score for each category. For urge incontinence, the maximum total score is 18 based on 6 questions, with a maximum score of 3 for each question. For stress incontinence, the maximum score is 27, based on a question with a maximum score of 3 for each question. To determine predominance of either stress or urge incontinence, the percent score is obtained (by dividing the score by the maximum total possible score, e.g., 9 urge score divided by 18 x 100 = 50% urge vs. 9 stress score divided by 27 x 100 = 33%. Urge is considered predominant when the % score of urge is greater than stress.)

Appendix 3 - OAB-q

Pt Initials:_____ Pt ID No.:_____

OAB-q

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please *check the box* that best describes the extent to which you were bothered by each symptom during the past 4 weeks. There are no right or wrong answers. Please be sure to answer every question.

During the past 4 weeks, how bothered were you by . . .	Not at all	A little bit	Some-what	Quite a bit	A great deal	A very great deal
1. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. An uncomfortable urge to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. A sudden urge to urinate with little or no warning	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. Accidental loss of small amounts of urine	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. Nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. Waking up at night because you had to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
7. An uncontrollable urge to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
8. Urine loss associated with a strong desire to urinate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

The above questions asked about your feelings about individual bladder symptoms. For the following questions, please think about your overall bladder symptoms in the past 4 weeks and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please *check the box* that best answers each question.

Pt Initials:_____ Pt ID No.:_____

During the past 4 weeks, how often have your bladder symptoms ...	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
9. Made you carefully plan your daily travelling?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Caused you to plan "escape routes" to toilets in public places?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
12. Caused you distress?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
13. Frustrated you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
14. Made you feel like there is something wrong with you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
15. Interfered with your ability to get a good night's rest?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
16. Caused you to reduce your physical activities (exercising, sports, etc.)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
17. Prevented you from feeling rested upon waking in the morning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
18. Frustrated your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
19. Caused you anxiety or worry?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
20. Caused you to stay home more often than you would prefer?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
21. Caused you to adjust your travel plans so that you are always near a toilet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
22. Made you avoid activities away from toilets (i.e., walks, running, hiking)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
23. Made you frustrated or annoyed about the amount of time you spend in the toilet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
24. Awakened you during sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
25. Made you worry about odour or hygiene?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
26. Made you uncomfortable while travelling with others because of needing to stop to go to the toilet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

UK OAB-q, ver 1.0, 2004 2

Pt Initials:_____ Pt ID No.:_____

During the past 4 weeks, how often have your bladder symptoms ...	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
27. Affected your relationships with family and friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
28. Caused you to reduce participating in social gatherings, such as parties or visits with family or friends?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
30. Interfered with getting the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
31. Caused you to have problems with your partner or spouse?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
32. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
33. Caused you to locate the closest toilet as soon as you arrive at a place you have never been?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Appendix 4 – PGI

Patient Global Impression of Improvement

Check the one number that best describes how your urinary tract condition is now compared with how it was before you started treatment with the BlueWind RENOVA iStim™ System

1	Very much better
2	Much better
3	A little better
4	No change
5	A little worse
6	Much worse
7	Very much worse

Appendix 5 – PHQ-15

PHYSICAL SYMPTOMS (PHQ-15)

During the past 4 weeks, how much have you been bothered by any of the following problems?

	Not bothered at all (0)	Bothered a little (1)	Bothered a lot (2)
a. Stomach pain	☐	☐	☐
b. Back pain	☐	☐	☐
c. Pain in your arms, legs, or joints (knees, hips, etc.)	☐	☐	☐
d. Menstrual cramps or other problems with your periods ***WOMEN ONLY***	☐	☐	☐
e. Headaches	☐	☐	☐
f. Chest pain	☐	☐	☐
g. Dizziness	☐	☐	☐
h. Fainting spells	☐	☐	☐
i. Feeling your heart pound or race	☐	☐	☐
j. Shortness of breath	☐	☐	☐
k. Pain or problems during sexual intercourse	☐	☐	☐
l. Constipation, loose bowels, or diarrhea	☐	☐	☐
m. Nausea, gas, or indigestion	☐	☐	☐
n. Feeling tired or having low energy	☐	☐	☐
o. Trouble sleeping	☐	☐	☐

(For office coding: Total Score T_____ = _____ + _____)

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix 6 – References

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