Statistical Analysis Plan

BlueWind Medical Ltd.

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)

Date: 18 May 2022

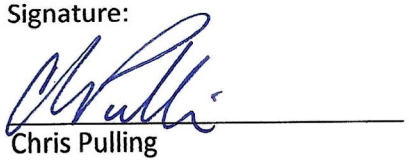
Confidentiality Statement

Signature Page

Study Name	**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 – Over Active bladder Stimulation System study)**
Sponsor	**BlueWind Medical Ltd.**
Doc ID	**G02-CLT-0009 Rev 05**
Reference Doc ID	**G02-CLP-0002 Rev 5**
SAP Date	**6 Jan 2020**

Written by:

Signature: Date:



24 May 2022

Chris Pulling
Statistician Consultant

Sponsor Signature will be provided in Sponsor electronic Document Control System

Version History

History of Revisions				
Revision	Description of Change	Revision By	Position	Date
01	Initial release	TechnoSTAT Ltd.	Consultants	2 July 2019
02 draft 1	1. Update to List of abbreviations 2. Section 1.1, 4 - Update indication for use to female with UUI 3. Section 2, 3, 11 – update to fixed sample size 4. Section 2 – update number of sites to “up to 35” 5. Section 6 – update time window for implantation 6. Section 7.2.1, 9.2 and 9.4 – delete “axiom data management” 7. Section 8.1 – update treatment of missing values 8. Section 9.1 – update safety endpoint to match the protocol 9. Section 9.3 – update baseline values for urgency frequency and urgency degree 10. Section 9.4 – adding reference to instructions for diary calculation 11. Section 10 – update data derivation and transformation 12. Section 11 – update interim analysis 13. Section 12.6.1 – updating primary efficacy analysis 14. Section 12.6.2 – updating secondary efficacy analysis 15. Section 12.7 – update subgroup analysis for antidepressants 16. Sections 15,16 – adding appendixes for rules for correction of discrepancies in paper diary and diary calculations 17. Wording throughout the text	Lori Fein	Director of Clinical Regulatory Affairs	6 Jan 2020

History of Revisions				
Revision	Description of Change	Revision By	Position	Date
03	1. Section 7 and throughout the document – FAS population was replaced with ITT (intent to treat) population 2. Section 9.3 – typo, changed to "increased" instead of "decreased" 3. Typo – "This endpoint is defined only for patients with baseline number of voids per day of at least 8 *and* baseline number of urgent episodes (PPIUS 3 or 4) of at least 9 per 7-day diary." "Or" was replaced with "and". 4. Section 9.4 – added an "additional endpoint" 5. Section 12.5 – staged enrollment for interim for interim safety report 6. Section 12.6.2 – changed to a more appropriate test (Clopper Pearson instead of Exact Binomial) and deleted the last paragraph which is elaborated on section 12.6.2.1 7. Section 12.7 – the following were added/elaborated on: • A covariate test to assess the potential impact of COVID-19 on study outcomes • A test of homogeneity of effect across investigational center, while excluding small sites from the formal homogeneity test.	Karin Aharonson - Raz	Medical Director	9 June 2020
04	1. Section 9 – revised sample size 2. Section 11 – interim analysis 3. Administrative changes	Karin Aharonson -Raz	VP Medical Affairs	30 July 2021

History of Revisions				
Revision	Description of Change	Revision By	Position	Date
05	1. Section 13 - Long-Term Follow-up 2. Section 12.6.3 - assessment of Nocturia as "additional endpoint" 3. Section 1.1 - Added clarification of the analysis and submission process of 6- and 12-months data	Karin Aharonson -Raz	VP Medical Affairs	17 November 2021
06	1. Section 12.8 – update subgroup analysis for OAB meds	Karin Aharonson -Raz	VP Medical Affairs	18 May 2022

Table of Contents

List of Abbreviations

AE	Adverse Event
BSW	Benefit, Satisfaction and willingness to Continue questionnaire
CP	Clinician Programmer
CRF	Case Report Form
CS	Clinically Significant
HRQL	Health Related Quality of Life
ITT	Intent to Treat
MAR	Missing At Random
MESA	Medical, Epidemiological, and Social Aspects of Aging
MI	Multiple Imputation
MID	Minimal Important Difference
OAB	Over Active Bladder
OABq	Over Active Bladder questionnaire
OASIS	Over Active bladder Stimulation System
OR1	One Month Responders
OUS	Outside of United States
PGI-I	Patient Global Impression of Improvement
PHQ-9 (or 15)	Patient Health Questionnaire
PP	Per Protocol
PPIUS	Patient Perception of Intensity of Urgency Scale
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUI	Stress Urinary Incontinence
UUI	Urinary Urge Incontinence

1 Introduction

1.1 General

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). This SAP is applicable to the following protocol versions:

Country	Document No.	Version/Date
Belgium	G02-CLP-002_BE	Rev. 06 / 27 Jul 2021
Netherlands	G02-CLP-002_NL	Rev. 06 / 27 Jul 2021
United Kingdom	G02-CLP-002_UK	Rev. 06 / 27 Jul 2021
United States	G02-CLP-002_US	Rev. 06 / 27 Jul 2021

Once all patients complete six months of follow-up, a complete data analysis will be performed and submitted to relevant regulatory bodies, with a 12-month update and endpoint evaluation performed and submitted at study completion.

1.2 Study Design Configuration

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

2 Centers

This study is a multi-center study. It is expected that 150 subjects will be enrolled to the study in up to 30 sites.

3 Study Objectives

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

4 Treatment Groups

This study is a single arm study. All subjects will receive active RENOVA iStim™ System treatment for the duration of the study.

5 Study Schedule

Table 1 - Study Schedule of Events

#	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.	Post Void Residual	X							
10.	Blood – chemistry (Creatinine levels; GFR, and HbA1C)	X					X		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.	Voiding Diary	X (7-days)			X (3-days)	X (3-days)	X (7-days)	X (3-days)	X (7-days)
18.	Usability/patient satisfaction questions		X	X	X	X			
19.	Parameter Setting			X	X	X	X	X	X
20.	Leg circumference measurements	X	X	X	X	X	X	X	X
21.	Patient Training on wearable unit			X					
22.	Adverse Event		X	X	X	X	X	X	X
23.	Study completion/discontinuation form								X

Table 2 - Study Schedule of Events – 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**
1.	Informed consent form	X				
2.	Inc/Exc criteria (verify new criteria – if exited study at 12m FU)	X				
3.	New medical history since 12m FU visit	X				
4.	Physical & Neurological Exam (including vital signs) *partial physical examination †if in clinic	X	X*†	X*	X*†	X*
5.	Urinalysis †if in clinic	X	X†	X	X†	X
6.	Urine culture *pending urinalysis results †if in clinic	X*	X*†	X*	X*†	X*
7.	Urine/blood pregnancy test (if bearing potential)	X				
8.	Medications	X	X	X	X	X
9.	Quality of Life Questionnaire			X		X
10.	PGI-I			X		X
11.	BSW			X		X
12.	Usage information collection	X	X	X	X	X
13.	Voiding Diary (3-days)	X	X	X	X	X
14.	Voiding Diary (UUI for ~4 weeks)					
15.	Usability/patient satisfaction questions		X		X	
16.	Parameter Setting †if in clinic		X†	X	X†	X
17.	Leg circumference measurements	X				
18.	Patient Training on wearable unit	X				
19.	Adverse Event	X	X	X	X	X
20.	Study completion/discontinuation form					X

6 Analysis Populations

6.1 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.

6.1.1 Per Protocol Population (PP)

The per protocol analysis set (PP) will be a subset of ITT subjects with observed data on the endpoint analyzed. Excluded will be subjects with major protocol violations, where "major" is defined has having the potential to meaningfully affect outcome. A list of major protocol violations, as assessed by qualified personnel who is masked to patient outcomes will be provided by the Sponsor prior to database lock. Subjects with a major protocol violation will be excluded globally in the PP population.

Also excluded from per visit analyses will be subjects with less than 50% compliance (i.e. those who received treatment on fewer than 50% of days during which they were eligible for therapy delivery) for the period prior to the visit. These will be local exclusions for the timepoint the subject is considered non-compliant.

6.1.2 One-month Responders (OR1)

The one-month responder analysis set (OR1) will be a subset of ITT of subjects who are classified responders in urinary incontinence at one month, defined as ≥ 50% reduction from baseline to one-month in average number of urgency-related leaks/day (urinary incontinence).

Percent reduction is defined as it is for the primary endpoint (see section 7.2, below) as related to the 3-day diary collected at the one-month follow-up. For the purposes of the OR1 population, all available diary data will be used (including partial data).

7 Handling of missing data

7.1 ITT population

Treatment of missing values:

- Subjects missing data "not in random" will be imputed as "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).

Multiple imputation will be applied to the primary and three secondary endpoints. The 'additional endpoint' analyses will not use multiple imputation. The imputation procedure will be performed on the continuous outcomes (e.g. number of incontinence episodes). Based on the imputed continuous outcome, the response will be defined accordingly for each endpoint.

The hypotheses will be tested by performing the logistic regression on each imputed dataset. Then SAS PROC MIANALYZE procedure will be used to calculate the combined confidence interval and the corresponding p-value. The evaluation on each endpoint will be successful if the lower limit of the confidence interval is above 50%. In addition, the primary analysis will present the observed frequency of responders and descriptive statistics of response rates over all imputed datasets.

Fifty (50) imputed datasets will be created (the seed is set to 123456).

The imputation will be done using covariates: Age, BMI, average number of urgency leaks, average number of urgent voids, HRQL score and OAB duration at baseline. This list might be reduced if the model fails to converge.

Because MI assumes missing at random (MAR), sensitivity analyses (i.e. tipping point) described below, will be conducted to test the effects of other patterns of missingness.

7.2 Per Protocol Population

Only observed values will be used in PP. Thus, the primary endpoint will be analyzed in PP 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.

7.3 OR1 Population

Missing primary endpoint data will be imputed using MI, as described above. For all other endpoints, only observed data will be used for the OR1 population.

8 Definition of Endpoints

8.1 Safety Endpoints

Following are the study's safety endpoints:

- Incidence of adverse events (AEs) including serious adverse events (SAEs) from implantation to 12-months post-activation.

8.2 Primary Efficacy Endpoints

The study's primary efficacy endpoint for each subject is response at 6 months post system activation as demonstrated by ≥50% improvement in the average number of urgency-related incontinence episodes as compared to baseline, measured by 7-day Patient Voiding Diary. Specifically, the primary endpoint will be defined as follows:

Success ("1")	If the percent change from baseline to 6 months post system activation in urgency-related incontinence episodes ≥50%
Failure ("0")	Otherwise

Where the percent change from baseline to 6 months post system activation in urgency-related incontinence episodes is calculated as follows:

$$\%\ Change_{BL\ to\ 6-months} = \frac{Episodes_{Avg.\ at\ BL} - Episodes_{Avg.\ at\ 6-months}}{Episodes_{BL}} * 100\%$$

where the average number of episodes is the average number of urgency-related leaks per day over the 7- day voiding diary. In the case that fewer than 5 days of diary data are available, then the average number of episodes for the given time point will be considered missing and, consequently, the primary endpoint will also be considered missing.

For the primary efficacy analysis, missing data will be addressed using the multiple imputation (MI) method, described above (Section 7.1).

Note: continuous score will be MI-imputed, and then the response is defined.

8.3 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 (based on OAB-q) at 6 months post system activation**

  This endpoint is defined dichotomously as follows:

  Success ("1") If the absolute improvement (increase) in HRQL from baseline is ≥10 points (MID)

  Failure ("0") Otherwise

- **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.**

  This endpoint is defined dichotomously as follows:

  Success ("1") If the percent reduction in either average number of urgency-related leaks per day ***or*** average number of large urgency-related leaks per day from baseline to 12 months follow-up is ≥50%

  Failure ("0") Otherwise

- **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**

  This endpoint is defined dichotomously as follows:

  Success ("1") If either the percent reduction in average number of moderate-severe urine

output episodes with PPIUS degree 3,4 per day (i.e. average number urine output episodes with urgency level above 2) from baseline to 6 months is ≥50% ***or*** the average number of total voids per day is less than 8 at 6 months

Failure ("0") Otherwise

This endpoint is defined only for patients with baseline number of voids per day of at least 8 and baseline number of urgent episodes (PPIUS 3 or 4) of at least 9 per 7-day diary.

Missing data for the secondary endpoints will be imputed according to Section 7.1, above.

8.4 Additional Efficacy Endpoints

The following additional efficacy endpoints will be assessed based on the data summarized in the data management reports:

- Patient Global Impression of Improvement (PGI-I) score
- Treatment Benefit, Satisfaction, and Willingness to Continue (BSW)
- Improvement in OABq (HRQL (and its subscales) and symptoms severity)
- Changes in the following OAB symptoms as measured by voiding diary 6 and 12-months post system activation compared to baseline:
    - Reduction in the average number of severe/large urgency related incontinence episodes
    - 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.
- Device usage
- Patient compliance with treatment through 6-months

Instructions for Diary calculation are as detailed in the appendix to the SAP.

9 Sample Size Considerations

The sample size for the primary endpoint 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 ≥ 80%
- Assumed treatment success rate at 6 months = 65%
- Prespecified performance goal = 50%.

Given these assumptions, 114 evaluable subjects are required. A total of 134 enrolled subjects, accounting for 15% attrition, is sufficient to evaluate the primary endpoint. However, this sample size is not adequate to evaluate all secondary objectives with sufficient power – specifically the following 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%.

This endpoint is defined only for patients with baseline number of voids per day of at least 8 and baseline number of urgent episodes (PPIUS 3 or 4) of at least 9 per 7-day diary. It is expected that 70% of enrolled subjects will meet these criteria.

Sample size requirements to evaluate this secondary endpoint are calculated in the same manner as the primary, under the following assumptions:

- Significance level = 0.025 (one-sided)
- Power ≥ 85%
- Assumed treatment success rate at 6 months = 61%
- Prespecified performance goal = 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.

The total sample size for the OASIS trial is 150 subjects.

10 Data Derivation and Transformation

Data not specifically recorded on a CRF will be derived as follows:

- Study Duration [days]= Date of Last Visit – Date of First Visit + 1.
- HbA1c values will be reported in units of mmol/mol. For cases of HbA1c reported in percentage, the following conversion formula will be used:

HbA1c (mmol/mol) = [HbA1c (%) - 2.15] x 10.929[1]

- Coding of Adverse Events will be done using the most recent MedDRA version.
- Coding of Concomitant Medication will be done using the most recent WHO Drug dictionary version.
- Baseline will be defined as the value at the "Enrollment and Screening" visit unless noted otherwise.
- OAB duration at baseline from Date of OAB Diagnosis [years] = Date of Screening – Date of OAB Diagnosis/365.25.
- Partial dates that are required for analysis will be imputed in the following fashion:
  - Dates with missing month and day will be imputed as July 1st.
  - Dates with missing day only will be imputed as the 15th of the month.
- Since querying of paper diaries is not possible at the time of completion and not feasible in an accurate manner afterwards, no query management process is used for the paper diaries. In its place a set of automatic rules will be applied to correct discrepancies in the paper diaries, as detailed in the appendix to the SAP.

11 Interim Analysis

An administrative interim analysis is required at the time one-month 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
- it is looking primarily at 1-month data, which may not be reflective of the primary endpoint at 6 months
- the interim look 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 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 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 interim analysis will be performed on the PP population, and MI will not be employed.

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, measured by 7-day Patient Voiding Diary. The percent change from baseline to each follow-up visit post system activation in urgency-related incontinence episodes is calculated as follows:

$$\%\ Change_{BL\ to\ f/u} = \frac{Episodes_{Avg.\ at\ BL} - Episodes_{Avg.\ at\ f/u}}{Episodes_{BL}} * 100\%,$$

where the average number of episodes is the average number of urgency-related leaks per day over the 7- day voiding diary.

A frequency distribution will be presented with bins defined as:

- <0.25
- ≥0.25 - <0.50
- ≥0.50 - <0.75
- ≥0.75

- Proportion of responders at each follow-up 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 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
- Subject disposition
- Demographics
- Additional Endpoints of interest

12 Statistical Analysis

The present section details the statistical analyses to be performed. 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.

12.1 Subject Disposition

The following will be provided:

- Number and percent of subjects in each of the analysis populations (ITT, PP, OR1) by center and overall
- Listing of subjects excluded from each of the analysis populations along with reason for exclusion.
- Number and percent of subjects consented to the study
- Number and percent of subjects implanted
- Subject accountability table by visit

Study termination:

- Number and percent of subjects who completed the study.

- Frequency of premature termination reasons
- Listing of all dropouts along with reason for termination and time of termination according to date of last study visit.

Protocol Deviations

- Listing of protocol deviations.

12.2 Baseline Characteristics

Baseline characteristics will be analyzed using the ITT population.

Descriptive statistics will be provided for the following:

- Demographic characteristics (age, race (if applicable), ethnicity, weight, height, BMI, Index leg circumference). Note that ethnicity will be reported only on enrolled subjects from the US.
- Overactive bladder history, including OAB medication, previous PTNS, Botulinum toxin injections
- Frequency distribution of medications for the OAB indication
- Listing of concomitant medications at time of enrollment
- Listing of general medical/surgical history
- Smoking history (Past/Current/No)
- Neurological Examination:
    - Frequency distribution of evaluation (normal/abnormal/not done) at baseline

12.3 Implantation

Evaluation of implantation parameters will be assessed using the ITT population and include descriptive statistics of the following:

- Implanted leg (Right/Left)
- Use of pre-op and post-op medications (antibiotics and anti-inflammatory/analgesics)
- Preparations performed (skin scrub and anesthesia type)
- Skin to skin time (minutes)
- Implant position depth (cm)
- Final incision size (cm)
- Intraoperative test performed (Yes/No). If testing was performed then the descriptive statistics of the following will be presented:
    - Response to test stimulation (Yes/No). For cases of response, descriptive statistics of the following will also be presented:
        - Number of implant positioning performed
        - Frequency (Hz)

- Pulse width (µsec)
- Amplitude (mAmp)
- Polarity
- Response type (Sensory/Motor/Both)

12.4 System Activation

System activation parameters will be summarized in tables containing descriptive statistics of the following using the ITT population:

- Parameters setting (, sensory response level, motor response yes/no, motor response level)
- Treatment settings
- Location and description of stimulation sensation
- Activation evaluation
- Treatment regimen: frequency and duration of treatment prescribed

12.5 Safety

A staged enrollment of the study is planned, with up to 30 patients enrolled in parallel with completion of additional toxicology testing. To support the planned IDE supplement to expand to full pivotal enrollment, an interim safety report will be generated when the first stage of enrollment is complete, with a maximum of 30 subjects. No primary endpoint data will be evaluated, and the data reported will be consistent with the safety data to be included in future IDE progress reports. Therefore, this does not constitute an interim analysis.
All safety analyses will be performed on the ITT population.
The following will be provided:

- Adverse Events:

  All Adverse Events (including serious) will be tabulated in a series of frequency tables with - number of AEs, number of subjects and percentage of subjects with AE and according to :

  - Severity
  - Relation to implantation procedure
  - Relation to medical device
  - Severity and Relation to implantation procedure
  - Severity and Relation to medical device
  - Body system and preferred term

  A single adverse event will appear in multiple tables.

- Serious Adverse Events:

  Same as the previous bullet (Adverse Events), limited to serious adverse events only.

- Vital Signs (systolic and diastolic blood pressure, temperature, pulse and index leg circumference). Note - when more than one measurement exists per visit, the average result will be used for the analysis:
    - Descriptive statistics of vital signs by visit
    - Descriptive statistics of change from activation visit to each follow-up visit
- Physical Examination by body system:
    - Frequency distribution of evaluation (normal/abnormal/not done) by visit
    - Shift table of normal/abnormal transitions from Implantation to all subsequent visits
    - Listings of abnormal physical examination results, including patient ID, visit, body system and abnormality description (CS/Not CS).
- Concomitant medications
    - By-subject listing of concomitant medication including subject ID, site, medication generic name or therapy, daily dose, units, route, start date, end date, whether ongoing, indication.

12.6 Efficacy

12.6.1 Primary Efficacy Analysis

The following primary efficacy analyses will be carried out using the ITT population with multiple imputation as described in Section 7.1. The primary efficacy analysis will test the null hypothesis that the response probability on the primary efficacy endpoint is less than or equal to 50%. The alternative hypothesis for the primary analysis is that patients receiving the treatment have above 50% probability to achieve clinical improvement, as follows:

$$H_0: \pi_{Renova} \leq \pi_{PG}$$

$$H_1: \pi_{Renova} > \pi_{PG},$$

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, measured by a 7-day Patient Voiding Diary at 6 months post system activation), and π_{PG} is the prespecified performance goal (PG) of 50%.

Although sample size was conservatively calculated under an Exact Binomial test, the hypothesis will be tested by performing the logistic regression on each imputed dataset as described in Section 7.1. Then SAS PROC MIANALYZE procedure will be used to calculate the combined confidence interval and the corresponding p-value.

We will declare success on this endpoint if the lower limit of the confidence interval is above 50%.

12.6.2 Secondary Efficacy Analysis

The following secondary efficacy analyses will be carried out using the ITT, PP and OR1 populations:

- The analysis carried out as the primary efficacy analysis will be repeated on the PP and OR1 populations.
- The secondary endpoints will be presented according to the following performance goals stated for each:
    - Proportion of subjects with ≥10 points (MID) improvement compared to baseline in HRQL (based on OAB-q) at 6 months post system activation with PG of 50%.
    - 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, with PG of 50%.
    - 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 with PG of 45%.

Hypothesis testing for the secondary endpoints will be performed in the same manner described for the primary endpoint with respect to multiple imputation. Success on each of the secondary endpoints will be declared if the lower bound of this confidence interval is above the stated performance goal.

12.6.2.1 Multiple Comparisons for Secondary Analyses

The secondary hypotheses will be tested only if the null primary is rejected.

The secondary endpoints will be tested using Hochberg step-up procedure to control the overall type I error rate.

The calculation of each comparison to performance goal will be performed separately rather than simultaneously, as done in the Hochberg procedure. In addition, each hypothesis will be tested with two- sided (unadjusted) Alpha = 0.05.

12.6.3 Additional Efficacy Analysis

The additional efficacy endpoints will be assessed descriptively on the ITT, PP and OR1 populations. Descriptive statistics will be provided for diary parameters collected within the Axiom data management report and will include the following by visit for each diary period available:

- Patient Global Impression of Improvement (PGI-I) score
- Treatment Benefit, Satisfaction, and Willingness to Continue (BSW)
- Improvement in OABq (HRQL (and its subscales) and symptoms severity)
- Changes in the following OAB symptoms as measured by voiding diary 6 and 12-months post system activation compared to baseline:
- Reduction in the average number of severe/large urgency related incontinence episodes
- Reduction in the number of micturition episodes.
- Reduction in the number of nocturia 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.
- Device usage
- Patient compliance with treatment through 6-months
- Descriptive statistics of percent compliance with treatment will be presented by center and visit.

12.7 Sensitivity Analysis

To evaluate robustness of the study's primary outcome, an alternative imputation methodology will be examined to assess sensitivity. The primary analysis will utilize multiple imputation.

Tipping Point Imputation

Different proportion of subjects with missing data will be imputed best or worst imputation progressively until the tipping point is reached; i.e. missing cases will be progressively imputed “failure” until the primary analysis is no longer significant (the tipping point).

12.8 Covariate, Subgroup, and ‘Poolability’ Analyses

Covariate analyses will be done by comparing the primary endpoint 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
- US vs. Outside of US (OUS)
- Race and ethnicity
- Baseline average urgency leaks/day
- Baseline average voids/day
- Smoking history (Past/Current/Never)
- Concomitant OAB medication at time of screening
- Ratio between average stress related leaks and average urgency related leaks at baseline.

For each of the listed above covariates descriptive statistics of the primary endpoint by covariate levels will be

presented. Continuous covariates will be divided into quartiles for this presentation. Additionally, formal subgroup analyses will be conducted to assess the effects on the primary endpoint of antidepressant medications and OAB medication, and also to assess the potential impact of COVID-19 on the study outcomes.

The analyses for antidepressant medications and OAB medications will be structurally similar. The first level of the analyses for each medication type will compare treatment effect (success rates) among those taking and not taking the respective medication at baseline. This will be performed as a logistic regression model, with baseline status as an indicator variable. If there is no difference in outcome, the second level of the analysis will be a logistic regression analysis on all subjects, with an indicator variable for changes in medication (lower, same or higher total dosage). If there is a differential effect concerning baseline status, the second level analysis will be comprised of two analyses; one only consisting of the subjects on the respective medication at baseline, with an indicator for any subsequent changes, and this will be repeated for the complementary subgroup of those subjects not on the respective medication at baseline. For each level of analysis, the success rate for each level of the subgroup will be reported for completeness. It should be noted that changes in usage of antidepressants and OAB medications will need to be defined and filtered from the concomitant medications form in exploratory fashion.

Any subjects enrolled prior to the COVID-19 outbreak may be subject to telephone follow-ups instead of on-site follow-up visits for a period of time. Interactions with affected subjects, then, would be different than for those who are routinely followed in the clinic, and only a subset of data will be able to be collected. A covariate adjusted logistic regression model, as described above, will be fit to assess the potential impact of COVID-19 on study outcomes, with an indicator variable indicating subjects enrolled prior to, and after, stay- at-home policies were enacted.

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 Long-Term Follow-Up

Upon completion of the 12-month follow-up visits, patients will enter a long-term follow-up phase. Formal study visits will occur at 24 and 36 months. Less comprehensive visits conducted via telephone will be conducted at months 18 and 30. The telephone visits will assess adverse events and subject diary data.

All primary, secondary and additional efficacy measures will be summarized using appropriate descriptive statistics - mean, median, standard deviation and 95% confidence intervals for continuous measures and frequency distributions for categorical or binary data. Adverse events, and treatment regimen data will be summarized.

14 Data Listings

Data listings will be provided for all data available from the CRF.

15 Computer Software

All statistical analyses will be carried out using SAS® Version 9.4 or higher under Windows® 2016 Terminal.

16 Appendix 1: Rules for Correction of Discrepancies in Paper Diaries

Since querying of paper diaries is not possible at the time of completion and not feasible in an accurate manner afterwards, no query management process is used for the paper diaries. In its place the following set of automatic rules will be applied to correct discrepancies in the paper diaries. The rules will be determined before database lock.

17 Appendix 2: Rules for Diary Calculations

Diary calculation will be added before database lock.