STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 1 Multicenter Study Evaluating the Safety and Potential Activity of Two Escalating Doses of *h*Maxi-K Gene Transfer by Direct Injection into the Bladder Wall in Female Participants with Idiopathic (Non-Neurogenic) Overactive Bladder Syndrome and Detrusor Overactivity: Double Blind, Imbalanced Placebo Controlled Design Within 2 Sequential Active Treatment Groups
SAP Version:	1.0
SAP Date:	12 JAN 2017
Study Drug:	*h*Maxi-K
Phase of Study:	Phase 1
Protocol Number:	ION 03 – OAB
Protocol Version:	Amendment 5
Protocol Date:	October 1, 2015
Sponsor:	Ion Channel Innovations, LLC 969 Park Ave., 1G New York, NY 10028
CRO Preparing SAP:	CE3 INC, 246 Goose Ln Guilford CT 06437

SIGNATURE PAGE

This docwnent has been prepared, reviewed and approved by:

STUDY BIOSTATISTICIAN APPROVAL:

Printed Name/Title Signature Date

SPONSOR APPROVAL:

SHARON JA CAB, M.D. 1/12/17

Printed Name/Title Signature Date

REVISIONS HISTORY LOG

Version	Revision Date"h	Author of Revision*	Section(s) Modified	Description and/or Reason(s) for Revision

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** Update the last revision dates on the cover page and the header.

SYNOPSIS

Sponsor: Ion Channel Innovations, LLC	
Product: *h*Maxi-*K*	**Phase of Development:** Phase 1
Protocol title: ION 03-OAB, Amendment 4	
SAP Date: 12 JAN 2017	**SAP Version:** 1.0
Total duration of the study: 6 months (24 weeks) per participant with an additional 18 month safety follow-up	

Objectives:

Primary: The primary objective of this study is to evaluate occurrence of Adverse Events and their relationship to *h*Maxi-K following multiple intramuscular (IM) injections into the bladder wall. Two dose levels (16,000 μg and 24,000 μg by IM injection into the bladder wall) in females with moderate OAB/DO of ≥ six months duration are initially planned.

- Treatment Emergent Adverse Events (TEAEs) – frequency and percentage of TEAEs, TEAEs by maximum severity and by relationship to study drug by treatment; summary of any AEs resulting in discontinuation of administration of study drug, serious adverse events (SAEs), and deaths during the study
- Secondary: The secondary objectives of this study are to evaluate the following safety parameters:
  - Clinical laboratory tests - changes and shift (whether the tests are within clinical normal range, whether they are clinically significant) from baseline by treatment
  - Electrocardiogram – change and shift from baseline (per ECG over-reader) by treatment
  - Vital Signs (systolic and diastolic blood pressure, and pulse rate) - change and shift from baseline

The last assessment made prior to dosing of double-blind study drug will be used as the baseline for all analyses of these safety parameters.

In addition, efficacy parameters will be evaluated as change from baseline compared to placebo. Comparisons will be made between combined placebo (N = 6) vs. 16,000 μg (N = 6) and 24,000 μg (N = 6) active *h*Maxi-K group separately, and also between combined placebo and combined active group (N = 12), as well as between treatment comparisons for a dose response analysis. Efficacy evaluations will include the number of micturitions per day, volume per micturition, urgency episodes (1 or greater on urgency scale), and incontinence episodes from voiding diary, and pad weight. Efficacy evaluations will also include the following cystometric evaluations performed by the overreader at week 4 and 24: 1) Detrusor overactivity ≥ 5 cm H_2O (yes/no- INCLUSION CRITERIA); 2) Volume at first desire to void; 3) Detrusor pressure at beginning of voiding (prior to onset of first contraction, either volitional or involuntary); 4) Volume at first involuntary contraction; if detrusor overactivity (DO) present-Not applicable if no DO present; 5) Maximum detrusor pressure at FIRST contraction.

Post void residual (PVR) on bladder scan, and general and bladder specific quality of life assessments measured by participant evaluation using Kings Health Care Questionnaire (KHQ) and participant evaluation of response to treatment will also be evaluated.

Methodology:

This study is a double blind, placebo-controlled, multicenter, sequential active dose, Phase 1 study in females with moderate OAB/DO of ≥ six months duration. The proposed study period is approximately 6 months following a single administration of study drug by multiple IM injections into the bladder wall per participant. The protocol sample size of this Phase I study is not intended to support the statistical significance of the primary endpoint as outlined in the study objectives. Rather, the sample size takes into account clinical safety considerations. Nine participants per dose level are planned: [6 assigned active treatment and 3 assigned placebo (PBS-20% sucrose only control group)]. Therefore a total of up to 9 participants will be enrolled in each dose group. Each arm of participants will be enrolled sequentially and enrollment into the next higher dose level will be dependent on assessment of safety. The participants chosen will be assigned in a randomized fashion to either placebo or an active treatment group within each group.

Number of subjects planned: Maximum of 18 participants.

Main criteria for inclusion:

The study population is women ≥ 18 years old of non-child bearing potential with overactive bladder (OAB) and detrusor overactivity who are otherwise in good health.

The target population is women with idiopathic (non-neurogenic) OAB and detrusor overactivity (DO) who have been unable to tolerate, do not wish to continue, or have had unsuccessful results with, prior therapy for OAB/DO. OAB is characterized by a decreased bladder capacity, frequent voiding, frequent sensations of a strong urge to void, and in some participants, episodes of incontinence. DO is one or more uncontrolled phasic contraction(s) of the detrusor of at least 5 cm/H_20 pressure that are observed during urodynamic testing with or without urinary leakage.

Inclusion criteria will include clinical symptoms of overactive bladder of ≥ 6 months duration including at least one of the following:

a. Frequent micturition (≥ 8/24hrs)
b. Symptoms of urinary urgency (the complaint of sudden compelling desire to pass urine, which is difficult to defer) or nocturia (the complaint of *waking* at night two or more times to void)
c. Urge urinary incontinence (average of 5 per week – Urge urinary incontinence is defined as: the complaint of involuntary leakage accompanied by or immediately preceded by urgency)

Participants must also have a bladder scan at screening demonstrating a residual volume of ≤ 200 mL and detrusor overactivity documented during baseline urodynamic testing of ≥ 1 uncontrolled contraction(s) of the detrusor of at least 5 cm/ H_2O.

Investigational product:

Treatment: *h*Maxi-K

Mode of Administration: Multiple intramuscular (IM) injections into the bladder wall during a single administration.

Duration of Treatment: The study will consist of up to a 14 day screening period prior to the single administration *h*Maxi-K on Day 0 (V2). A 6 month period for follow-up will complete the study for each participant. The total participation duration will be approximately 184 days; however each

participant on active treatment will be required to be followed for an additional 18 months (every 6 months) for safety evaluations only.

Comparator product:

Treatment: PBS-20% sucrose

Mode of Administration: Multiple intramuscular (IM) injections into the bladder wall.

Duration of Treatment: The study will consist of up to a 14 day screening period prior to the single administration PBS-20% sucrose placebo on Day 0 (V2). A 6 month period for follow-up will complete the study for each participant.

Criteria for evaluation:

Safety:

Safety will be assessed by analysis of adverse experiences (treatment emergent adverse events), clinical laboratory tests, electrocardiogram, and vital signs.

Efficacy:

Efficacy evaluations will include the number of micturitions per day, volume per micturition, urgency episodes and incontinence (or accident) episodes from voiding diary, and pad weight. Efficacy evaluations will also include the following cystometric evaluations performed by the site and/or the overreader at week 4 and 24: 1) Detrusor overactivity $\geq$ 5 cm H_2O (yes/no- INCLUSION CRITERIA); 2) Volume at first desire to void; 3) Detrusor pressure at beginning of voiding (prior to onset of first contraction, either volitional or involuntary); 4) Volume at first involuntary contraction; if detrusor overactivity (DO) present-Not applicable if no DO present; 5) Maximum detrusor pressure at FIRST contraction.

PVR on bladder scan, and general and bladder specific quality of life assessments measured by participant evaluation using Kings Health Care Questionnaire (KHQ) and participant evaluation of response to treatment will also be evaluated.

Statistical methods:

Both the safety data and data to assess efficacy will be summarized using summary descriptive statistics by treatment group (combined placebo vs. 2 active treatment groups and combined placebo vs. combined treatment groups) and the total study population.

Linear mixed effect models will be used to estimate difference of changes from baseline between placebo and active treatment and to test whether there is dose-response for different outcomes. Generalized estimating equation (GEE) model will be used to estimate effects for the binary endpoints.

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1. LIST OF ABBREVIATIONS

AE	adverse event
BMI	body mass index
BP	blood pressure
CRO	Clinical Research Organization
CS	clinically significant
CSR	clinical study report
DBP	diastolic blood pressure
DO or DH	detrusor overactivity
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EF	erectile function
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	good clinical practices
GMP	good manufacturing practice
KHQ	King's Health Questionnaire
IIEF	International Index of Erectile Function
LLN	lower limit of normal
LOCF	last observation carried forward
GEE	generalized estimating equation
HR	heart rate
ICIQ-SF	International Consultation on Incontinence Questionnaire- Short Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NCS	not clinically significant
OAB	overactive bladder syndrome
OBA	Office of Biotechnical Activities, NIH
OHSR	Office of Human Subject Research, NIH
PT	preferred term
PTT	partial thromboplastin time

PVR	post void residual
QoL	quality of life
QTcB	QTc Bazett
QTcF	QTc Fridericia
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-12	Health Status Questionnaire
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UUI	urge urinary incontinence

2. INTRODUCTION

This statistical analysis plan (SAP) is intended to describe the planned analyses and presentation of study data to be included in the clinical study report (CSR) for Protocol ION 03-OAB. This SAP has been developed according to CE3 SOP 700: *Developing and Maintaining a Statistical Analysis Plan*, and accordingly, this plan and any deviations from this plan must be finalized, approved, and placed on file before the blind is broken.

Overactive Bladder Syndrome (OAB) resulting in urinary incontinence is a common and significant problem that affects millions of men and women in the United States. It is estimated that over 17 million men and women in the United States have OAB. It is also estimated that 15 to 30 percent of people over the age of 60 who live at home have incontinence. OAB affects men and women at approximately the same rate.

OAB is characterized by a decreased bladder capacity, frequent voiding, frequent sensations of a strong urge to void, and in some patients, episodes of urge incontinence or UUI which is often used interchangeably with OAB. According to the International Continence Society these symptoms are defined as follows:

- Urgency: the sudden, compelling desire to urinate. This symptom can occur with and without urge incontinence (leakage). Sufferers experience strong, sudden urges to urinate, even if their bladder is not full.
- Frequency: urinating 8 or more times per 24 hour period
- Urge Incontinence: an involuntary, accidental loss of urine, also called "leakage" or "incontinence"

The parasympathetic nervous system provides the major control of bladder contractility mainly through muscarinic receptors (M_2 and M_3) and is a key target for presently administered pharmacological therapy for patients with OAB/UUI and detrusor overactivity.

The current treatment of choice for OAB/UUI remains the non-selective muscarinic receptor antagonists that are associated with an increased incidence of dry mouth and other side effects.

Overall, the mechanistic basis for increased detrusor overactivity is not fully understood, but the general importance of ion channel activity to bladder smooth muscle function is well established. The loss of smooth muscle control is likely to be a basic cause of urge incontinence.

pVAX/hSlo (*h*Maxi-K is the name we have established for the GMP product) consists of the gene for the α-pore subunit of the maxi-K channel, *hSlo*, inserted into a plasmid vector. Administration of this gene into the corpora increases expression of the maxi-K channel in the smooth muscle cells and an increased efflux of K^+ across the cell membrane resulting in decreased entry of Ca^{++} ions.

Pre-clinical studies in rat and rabbit models demonstrate potential efficacy and safety of pVAX/hSlo.

In humans, the safety and tolerability of *h*Maxi-K administered intracorporally has been assessed in an open-label single-escalating dose study that evaluated the safety and efficacy of doses

ranging from 500 μg up to 7,500 μg (Stage 1 of study) and 8,000 μg to 16,000 μg (Stage 2 of study) in men with recalcitrant ED. No serious safety concerns were raised and potential efficacy in a small sample was observed when assessing the efficacy using change from baseline in the International Index of Erectile Function (IIEF score – Erectile Function [EF] Domain).

A dose-escalating study for female participants with moderate OAB and detrusor overactivity (DO) was evaluated for safety following administration of a single intravesicular instillation of *h*Maxi-K at three dose levels compared to placebo in a double blind increasing dose tolerance study. In the two doses evaluated, 5,000 μg/90 mL and 10,000 μg/90 mL, there was no serious safety concerns and there were some positive efficacy findings. The highest dose was never evaluated due to slow enrollment.

3. STUDY OBJECTIVES

3.1. Primary Objectives

The primary objective of this study is to evaluate the occurrence of treatment emergent adverse events (TEAEs) and their relationship to a single treatment of approximately 20 to 30 bladder wall intramuscular injections of *h*Maxi-K compared to placebo (PBS-20% sucrose). Two dose levels (16,000 μg and 24,000 μg) in females with moderate OAB/DO of ≥ six months duration are planned. In each dose level, 6 participants will receive *h*Maxi-K and 3 will receive placebo.

3.2. Secondary Objectives

The secondary objectives of this study are to evaluate the following safety parameters:

- Clinical laboratory tests - changes from baseline
- Electrocardiogram - changes from baseline
- Vital signs - changes from baseline

In addition, efficacy parameters will be evaluated as change from baseline compared to placebo. Comparisons will be made between combined placebo (N = 6) vs. 16,000 μg (N = 6) and 24,000 μg (N = 6) active *h*Maxi-K group separately, and also between combined placebo and combined active group (N = 12), as well as between treatment comparisons for a dose response analysis. Efficacy evaluations will include the number of micturitions per day, volume per micturition, urgency episodes (1 or greater) and incontinence episodes (accidents) from voiding diary, and pad weight. Efficacy evaluations will also include the following cystometric evaluations performed by the overreader at week 4 and 24: 1) Detrusor overactivity ≥ 5 cm H^2O (yes/no- INCLUSION CRITERIA); 2) Volume at first desire to void; 3) Detrusor pressure at beginning of voiding (prior to onset of first contraction, either volitional or involuntary); 4) Volume at first involuntary contraction; if detrusor overactivity (DO) present-Not applicable if no DO present; 5) Maximum detrusor pressure at FIRST contraction.

PVR on bladder scan, and general and bladder specific quality of life assessments measured by participant evaluation using Kings Health Care Questionnaire (KHQ) and participant evaluation of response to treatment will also be evaluated.

4. STUDY DESIGN

4.1. General Study Design and Plan

This study is a double blind, placebo-controlled, multicenter, sequential active dose, Phase 1 study in females with moderate OAB/DO of ≥ six months duration.

Up to 9 female participants (6 participants on active treatment and 3 on placebo) will be enrolled per dose level "arm". The 2 active doses to be evaluated sequentially are 16,000 µg and 24,000 µg compared to intramuscular injections into the bladder wall of PBS-20% sucrose (control group). Additional participants may be enrolled for evaluating the tolerability to a given dose. Each arm of 9 participants per dose level will be enrolled sequentially, beginning with the lowest dose. Enrollment of the first 5 participants in each cohort will be managed directly by the sponsor (or their designee) with a 2 day waiting period following each participants dosing. The next participant will be enrolled only after the site has contacted the previously dosed participant on Day 3 following gene transfer to determine if a clinically significant adverse event occurred. The site will provide the clinical monitor with the result of that contact. In the event that no event occurred the next participant will be enrolled. The Data Safety Monitoring Board (DSMB) will review eligibility and all available safety data after the 5th participant has been administered study drug in the first dosing cohort. This first review will occur as soon as possible after the 5th participant's 3 day post-visit 2 telephone contact. Following their review of the safety data, the DSMB will recommend whether enrollment into the first dosing cohort may proceed. This process will be repeated through the 5th participant in each cohort before the balance of the cohort (4 additional participants) is enrolled. If a clinically serious sign or symptom is reported the medical monitor will contact all sites and no further enrollment will be done until the Medical Monitor or Sponsor gives permission. In addition, enrollment into the next cohort or arm in the series (at the next highest dose) will be dependent on safety dose-limiting toxicity assessments as per Protocol Section 5.2.

Protocol Table 1 shows the detailed event schedules of the study.

4.2. Study Population

4.2.1. Selection of Study Population

About 18 women ≥ 18 years old of non-child bearing potential with overactive bladder (OAB) and detrusor overactivity who are otherwise in good health and meet the inclusion and exclusion criteria as outlined in Protocol Section 4 will be enrolled in the study.

4.2.2. Subject Withdraw and Replacement

The participants may withdraw from the study if they decide to do so, at any time and irrespective of the reason, or at the Investigator's decision. Participants who have been withdrawn from the study cannot be re-included in the study. Their inclusion and treatment number must not be re-used.

Up to 3 replacements per dose will be allowed for participants who received study drug and discontinue without follow-up data of at least one-month post study drug administration.

4.3. Randomization and Blinding

This is a double blinded randomized study.

Sites will be provided blinded treatment code identities. For each participant there is supplied a tear off label which should be kept in the participant's source records, affixed to a study treatment label page. This removable panel contains a scratch off laminate which would serve to unblind the treatment if necessary. The DSMB will receive the blinded codes from the unblinded statistician.

The treatment code must not be broken by the site unless there is an emergency situation where the appropriate management of the participant necessitates knowledge of the treatment allocation. Every attempt must be made to contact appropriate sponsor personnel prior to breaking any participant's treatment code.

Two doses of *h*Maxi-K will be evaluated: 16,000 µg and 24,000 µg. Up to 9 female participants (6 participants on active treatment and 3 on placebo) will be enrolled per dose level "arm". Each dose arm will be randomized using an imbalanced-block design (eg, 6 active and 3 placebo participants per treatment group).

4.4. Study Assessments

Pharmacokinetics, efficacy and safety assessment are detailed in Protocol Sections 6 and 7 and depicted Protocol Table 1, which is replicated below:

Table 1: Procedures by Visit

Phase	**Screening Phase**			**Post-Treatment Follow up Visits**						
Visit/Period	**Visit 1**	**Visit 1A[n]**	**Visit 2**	**Telephone Follow-up[j]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Day	**-14**	**-14 to -8**	**0 (Baseline)**	**Day 1 & 3**	**8**	**15**	**29**	**57**	**85**	**169 (Final)**
Week	**-2**		**0**	**0**	**1**	**2**	**4**	**8**	**12**	**24**
Visit Window (days)		**+2**	**+2**	**Day 3±1**	**+2**	**+2**	**±2**	**±3**	**±5**	**±5**
Signed Informed Consent	▲									
Evaluation of Inclusion / Exclusion Criteria	▲	▲	▲[f]							
Demographics and Medical / Surgical History	▲									
Physical Examination	▲		▲[f]		▲	▲	▲	▲	▲	▲
ECG	▲		▲[a]		▲		▲			▲
Previous / Concomitant Medication Assessment	▲	▲	▲[f]		▲	▲	▲	▲	▲	▲
Vital Signs[h]	▲		▲[f, l]		▲	▲	▲	▲	▲	▲
Objective OAB /DO Evaluation (Cystometry)[b]		▲[d]					▲			▲
Bladder scan[c]	▲					▲		▲		▲
Dispense Daily Voiding Diary/Urgency questionnaire[i]	▲	▲	▲[f]		▲	▲	▲	▲	▲	
Pad Test[m]		▲	▲		▲	▲	▲	▲	▲	▲

Table 1: Procedures by Visit (Continued)

Phase	**Screening Phase**			**Post-Treatment Follow up Visits**						
Visit/Period	**Visit 1**	**Visit 1A[n]**	**Visit 2**	**Telephone Follow-up[j]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Day	**-14**	**-14 to -8**	**0 (Baseline)**	**Day 1 & 3**	**8**	**15**	**29**	**57**	**85**	**169 (Final)**
Week	**-2**		**0**	**0**	**1**	**2**	**4**	**8**	**12**	**24**
Visit Window (days)		**+2**	**+2**	**Day 3±1**	**+2**	**+2**	**±2**	**±3**	**±5**	**±5**
QoL (King's Health Questionnaire) and SF-12			▲[f]				▲	▲	▲	▲
Subjective Evaluation of Disease State[k]			▲[f]		▲	▲	▲	▲	▲	▲
Subjective Evaluation of Response to Treatment[k]					▲	▲	▲	▲	▲	▲
ICIQ-SF			▲[f]				▲	▲	▲	▲
Urinalysis and Urine Cultures[d]	▲	▲	▲[f]		▲	▲	▲		▲	▲
Hematology Laboratory Tests[e]	▲		▲		▲	▲	▲		▲	▲
Chemistry Laboratory Tests[e]	▲				▲	▲	▲		▲	▲
Pharmacokinetic Assessment (urine and blood *hSlo* cDNA)			▲[f, g]		▲	▲	▲	▲	▲	▲[g]
Adverse Event Assessment		▲	▲[f]	▲[j]	▲	▲	▲	▲	▲	▲
Study Drug administered			▲							

a. ECG will be done prior to administration of study drug and at 2 hours post dosing.
b. Cystometry includes: volume at first desire to void, detrusor pressure, abdominal pressure, detrusor pressure at beginning of voiding, detrusor pressure at maximum flow, maximum detrusor pressure, volume at strong urge to void, peak flow rate during voiding, voided volume, volume at DO, post-void residual volume, total bladder volume (voided volume + residual volume), number of detrusor contractions during procedure and duration of DO
c. Inclusion criteria specify residual volume ≤ 200 mL. Bladder scans at V1 and V8 to be done before catheterization.
d. Urinalysis with microscopic RBC and WBC, protein, glucose, nitrites, pH, and specific gravity at V 1, 3-5 and V7 and V8. At V1A and V2, urinalysis by Dipstick will be done. Urine cultures at V1 (by catheterization with the urodynamic catheter), V3 (clean void); at V1A, V2, V5 and V8 prior to cystometry or cystoscopy (by catheterization with the urodynamic catheter) and before discharge by clean void (at V2 use first voided urine after drug administration). Visit 2 urinalysis by Dipstick will be done prior to dosing and urine culture will be performed both prior to study drug administration and prior to discharge
e. Lab tests to be done at V1, V2 - 5, V7 and V8 include: Hematology- CBC with differential, platelet count, sedimentation rate, PTT, PT (no PT and PTT at V2 and V4), CRP, Antinuclear antibody; Fasting chemistry- BUN, creatinine, Na^+, K^+, Mg^{++}, Ca^{++} , CO2, Cl^-, albumin, alkaline phosphatase, ALT, AST, GGT, total bilirubin, total protein, CPK, LDH, glucose; Serum Pregnancy Test for beta-HCG required for women of child bearing age who have not had hysterectomy at Screening V1 and on as need basis. In addition, FSH > 40 IU/L if last menstrual cycle not > 12 months prior to study enrollment. HbA1c will be done at screening Visit 1 only. No chemistries will be done at 2 (Week 0). At V4, chemistries will include only BUN, creatinine, electrolytes (Na^+, K^+), CRP, glucose, and ANA. No lab tests will be done at Visit 1A or V6. Lab tests should be taken at the same time of day at all study visits.
f. Test or procedure will be done prior to administration of study drug at Visit 2. At V2 there is also a urine culture after dosing.
g. At V2, blood and urine pre-dosing and at 2 hour post-dosing. If specimen is still positive at Week 24, participant must return monthly until two successive specimens are negative for *hSlo* DNA.
h. Vital signs will include height at V1 only; weight at V1 and V8; oral body temperature at all visits (except V1A). Same arm should be used for all BP measurements and specified.
i. Diaries are to be completed prior to V1A (to test for compliance and inclusion criteria), for 7 days prior to Visit 2 and 7 days prior to each visit, thereafter.
j. Participants will be contacted by telephone on Study Day 1 and 3 (1 day and 3 days ±1**,** following drug administration at Visit 2) for assessment of adverse events.
k. Subjective assessments are based on the following questions in Appendix C: "How bothersome do you consider your bladder problem?" and "Has the treatment been of benefit to you?"
l. BP will be taken every 15 minutes for 2 hour post administration of study drug.
m. Participants will bring in pads/diapers worn for 3 days prior to Visit 1A & 2 (if V1A after screening V1) and 3 days prior to all subsequent visits (Visit 3 to Visit 8); also bring in clean pad/diapers to use as baseline.

n. Visit 1A may occur on same day as V1. In this case all V1A procedures not already to be done at V1 should be completed. Cystoscopy should be performed after all other V1 procedures and post cystoscopy urine culture obtained using clean void. If V1A coincides with V1, then since pad collection and diaries will not be completed prior to V1, these must be checked for compliance at V2.

4.4.1. Safety Assessment

Safety and tolerability of the study drug will be evaluated by analysis of adverse experiences, clinical laboratory tests (including measurements for the presence of *h*Slo), electrocardiogram, and physical examinations including vital signs.

4.4.2. Outcome Assessments

OAB / DO Objective Assessment: Cystometry

Clinical assessment of the efficacy hypothesis that *h*Maxi-K will reduce detrusor overactivity. Detrusor overactivity will be assessed with two standardized, sitting position, saline cystometries followed by pressure flow studies (see Protocol Appendix D). Every attempt should be made to perform the studies at the same time of day and in the same way for each participant. Studies are to be completed at V1A (screening), V5 (4 weeks post dosing with study drug) and V8 (or Final Visit). An over-reader will interpret the results as well as the investigator, however, the over reader's interpretation will take priority for the analysis.

Clinical Evaluation of OAB / DO

Voiding Diary

Clinical signs and symptoms of OAB / DO will be determined by a daily voiding diary. The participants must complete the diaries for the 7 days prior to the Baseline Visit (Visit 2), and for 7 days prior to Visits 3 to 8. The participants will also complete the diaries prior to Visit 1A to test for compliance and evaluate for some inclusion criteria. The site will contact the participant 7 to 8 days prior to the scheduled visit (Visits 2 to 8) to remind the participant to complete the diary. The daily voiding diary will collect standard bladder function and frequency parameters including frequency of micturitions, volume voided and urgency (1 or greater on scale) and incontinence (accidents) episodes. The urgency questionnaire is a 4 point scale with 1 to 4 indicating the presence of urgency. See Protocol Appendix F.

Pad Test

Each participant will record their use of any pads/panty liners (eg, Poise® pads or Depends®, etc.) in their diary. The participant will bring in pads/diapers worn prior to Visit 1A and for the three days prior to Visit 2 (as well as a new pad/diaper to use as a baseline) and for the 3 days prior to all subsequent visits (Visits 3 to V8). Used pads/diapers will be stored in a plastic bag provided by the site and weighed upon receipt and compared to the clean pad. All pads/diapers used by the participants for the 7 days prior to each visit, will be counted by the participants and entered in the voiding diary by them.

King Health Questionnaire and Assessment of Disease State/Treatment

Participants will also complete a disease-specific quality of life tool, the King's Health Questionnaire (KHQ) at Baseline (Visit 2 prior to dosing), V5, V6, V7, and end of study (V8). See Protocol Appendix B. Participants will also be queried on subjective assessment of their disease state at Baseline (V2), and subsequent visits. Participants will also be asked to evaluate

their response to treatment at Visits 3 to 8. Participants will rate their perceived bladder condition severity at Baseline (V2) and Visits 3 to 8 using a 6-validated point rating scale (1, no problems; 2, very minor problems; 3, minor problems; 4, moderate problems; 5, severe problems; and 6, many severe problems). Participants' assessment of their response to treatment will be measured by asking "Has the treatment been of benefit to you?" with possible responses of no benefit; yes, a little benefit; and yes, very much benefit. See Protocol Appendix C.

International Consultation on Incontinence Questionnaire-Short Form

The International Consultation on Incontinence Questionnaire- Short Form will be completed in this study by all participants at V2, 5, 6, 7, and 8. Please refer to Protocol Appendix E.

SF-12

The SF-12 which includes 12 questions evaluating general quality of life will be completed in this study by all participants at V2, 5, 6, 7, and 8. Please refer to Protocol Appendix G.

Bladder Scan

Residual volume will be measured using a scan of the bladder. This examination will be carried out at the Screening visit (V1) and V4, V6, and V8. At Visit 1 and Visit 8 urine cultures by catheterization should be done after bladder scans are performed. Copies of the bladder scan figures supplied by the device or a report of the examination must be appended to the participants' source documents.

5. SAMPLE SIZE DETERMINATION

The proposed study period is approximately 6 months following a single administration of study drug per participant. The protocol sample size of this Phase 1 trial is not intended to find statistically significant differences between placebo and treatment for the primary endpoint as outlined in 2. Rather, the sample size takes into account clinical safety considerations.

However, the study is designed to observe a 30% reduction in the number of voids following gene transfer using the following calculations with NCSS/PASS program (NCSS, Kaysville, Utah, 84037).

Power	N1	N2	Ratio	Alpha	Beta	Mean1	Mean2	S1	S2
0.80251	9	10	1.111	0.05000	0.19749	10.0	6.6	2.5	2.5

Nine participants per dose level are planned: [6 assigned active treatments and 3 assigned placebo (PBS-20% sucrose only control group)]. Therefore a total of up to 9 participants will be enrolled in each dose group. Each arm of participants will be enrolled sequentially and enrollment into the next higher dose level will be dependent on assessment of safety. The participants chosen will be assigned in a randomized fashion to either placebo or an active treatment group within each group.

6. ANALYSIS POPULATIONS

Safety Analysis Population: For safety analyses, the Safety Population will be used. This population consists of subjects who have been dosed including partial/incomplete doses.

Efficacy Population will be used to for efficacy analyses. This population include subjects who are dosed and have at least one post-dose efficacy assessment.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1. Interim Analyses and Data Monitoring

Multiple safety data reviews by the Data Safety Monitoring Board will occur for enrollment and dose escalation decision as specified in Protocol Section 5. No statistical analyses will be performed for these data reviews.

7.2. Multi-Center Studies

This is a multi-center study. Up to 6 clinical sites could be enlisted for the study. However, given the small sample size of the study, no statistical adjustment will be made.

7.3. Multiple Comparisons / Multiplicity

Given the small sample size and exploratory nature of the efficacy study, no adjustment will be made for multiple comparison. Therefore, all the p-values presented will be nominal *P* value.

7.4. Examination of Subgroups

No subgroup analyses are planned for this study given the small sample size.

7.5. Handling of Dropouts or Missing Data

Handling of missing concentration data will be detailed in PK analysis plan and/or report. Missing data for adverse events, laboratory test will not be imputed. Last observation carried forward (LOCF) will be used to impute efficacy endpoints.

7.6. Outlier Handling

Potential data entry errors manifested as outliers will be handled following data management process through edit check.

7.7. Adjustments for Covariates

We may use time as a covariate when test certain efficacy endpoints.

8. SUMMARY OF STUDY POPULATION DATA

8.1. Subject Disposition

Subject disposition will be provided for all the subjects in the Safety Population. The total numbers of subjects who received study drug will be displayed in Table 14.1.1. Frequency and percentage of participants who completed study drug per protocol, prematurely discontinued and reasons for discontinuation (adverse event, protocol violation, withdrawal of consent, lost to follow-up, study terminated by sponsor, other reasons) will be tabulated in Table 14.1.1 by treatment group.

Per subject disposition information, eligibility and assignment to analysis population will be displayed in Listings 16.2.1.1, 16.2.1.2, and 16.2.3.

8.2. Protocol Violations

Protocol violations, if any, will be listed in Listing 16.2.1.1. The frequency and percentage of subjects discontinued due to protocol violation will be summarized in Table 14.1.1.

8.3. Demographics and Baseline Characteristics

Descriptive statistics of demographic measurements such as age, sex, ethnicity, race at Screening and measurements of height, weight, and Body Mass Index (BMI) at Visit 1 (Screening Visit) will be summarized for the Safety Population in Table 14.1.2.

Individual subject demographics will be listed in Listing 16.2.4.1. Individual subject baseline medical, surgical history/physical findings displayed in Listings 16.2.4.2. Laboratory test records at screening will be listed with on-treatment laboratory records. Participant OAB history and previous treatment and response to treatment will be detailed in Listings 16.2.4.3 and 16.2.4.4.

8.4. Dosing and Extent of Exposure

Dosing information will be summarized in Table 14.4.1. The frequency and proportion of participants who received the entire dose and reasons for not receiving the entire dose will be presented. The descriptive statistics for total volume of injection, mean injection volume number of injections will be presented. Also the frequency and proportion of participants received prophylactic antibiotics and whether the syringe is primed with PBS 20% will also be presented.

Per subject dosing information will be displayed in Listing 16.2.5.1.

8.5. Concomitant Medications

The WHO Drug Dictionary Enhanced version Dec 2013 will be used to classify prior and concomitant medications and listed by therapeutic class for the Safety Population in Listing 16.2.5.2. Non-drug treatments or Procedures will be displayed in Listing 16.2.5.3.

9. EFFICACY ANALYSES

9.1. Primary Efficacy Analyses

The per participant listing for voiding diary (Dispense Daily Voiding Diary/Urgency Questionnaire) will be presented in Listing 16.2.6.1. The cystometry overread parameters will be presented in Listings 16.2.6.2.1 and 16.2.6.2.2, and in Listings 16.2.6.2.3 through 16.2.6.2.5 for site investigator read. The bladder scan per subject will be detailed in Listing 16.2.6.3 and the pad test in Listing 16.2.6.4. The QoL survey will be presented in two listings with King's Health Questionnaire (KHQ) in Listing 16.2.6.5.1 and SF-12 in Listing 16.2.6.5.2. Per participant assessment of disease and response to treatment will be detailed in Listing 16.2.6.6. Also, participant response to International Consultation on Incontinence Questionnaire (ICIQ) Short Form will be presented in Listing 16.2.6.7. The primary efficacy result, the reduction of the number of voids per day compared to placebo using voiding diary data, will be presented in Table 14.2.1.1. Assuming the number of voids follows a normal distribution, we will test whether there is significantly more reduction in the treatment group at each time point, where there are difference between treatment groups for the pooled *h*Max-K group vs. the placebo group using linear mixed effect model adjusting for the clustering effect by each individual with treatment, time and interaction of time and treatment. We will also present the summary statistics of voiding at each visit and change from baseline at each postdose time point. Difference in change and corresponding 95% confidence interval from baseline for each treatment group vs. placebo and 24,000 μg vs. 16,000 μg will also be presented in Table 14.2.1.1.

9.2. Secondary Efficacy Analyses

Change in the mean number of urge incontinence episodes per 24 hours, change in mean number of urgency episodes, and change in the mean volume voided per micturition will be analyzed similarly as the primary efficacy endpoint and presented in Tables 14.2.1.2 through 14.2.1.4. Change in weight of 72 hour pad test and change in residual volume from bladder scan will also be analyzed and presented similarly in Tables 14.2.2 and 14.2.3 respectively.

Definitions of cystometric parameters are displayed in Table 2. The site readings and many of the overreader readings will be presented by subject in listings. Five of the overreader parameters will be analyzed, variables 1, 2, 3, 4 and 12, are displayed in Table 2. The corresponding output table numbers and titles for these 5 variables are displayed in Table 3. We may do additional exploratory analyses for additional cytometry parameters, if necessary.

Table 2: Cystometric Parameters and Definitions

Parameter	Description	Definition
DO; Yes/No	Detrusor overactivity ≥ 5 cm H_2O	Any involuntary contraction that has a pressure > / = 5 cm H_2O **(INCLUSION CRITERIA)**[a]
$V_{First\ des}$ (mL)	Volume at first desire to void	The volume attained during filling cystometry that would lead the patient to pass urine at the next convenient moment but voiding can be delayed if necessary *(ICS definition)*.[a]
$P_{det.\ open}$ (cm H_2O)	Detrusor pressure at beginning of voiding (prior to onset of first contraction (either volitional or involuntary)	Detrusor pressure at onset of the first detrusor contraction (either volitional or involuntary).[a]
V_{1st} (mL)	Volume at first involuntary contraction; if detrusor overactivity (DO) present. Not applicable if no DO present.	Volume infused at the point of maximum detrusor pressure during the 1st contraction.[a,b]
Det_{frq}	Total number of detrusor contractions during procedure (voluntary **AND** involuntary)	Total number of detrusor contractions including voluntary **AND** involuntary[c]
Leak (Yes/no)	Was there a leak with overactivity	Involuntary detrusor contractions resulting in leak (NOT counting voluntary voids)[c]
DO $_{Leak\ freq}$	Number of involuntary detrusor contractions resulting in leak (if DO present)	Number of involuntary detrusor contractions resulting in leak (if DO present)[b,c]
V_{leak} (mL)	If yes, Volume of each leak	Volume of each leak for each episode of leak[c,d]
$V_{leak\ cum}$ (mL)	If yes, cumulative volume of ALL leaks during procedure	Cumulative volume of leaks (calculated by computer from individual volumes)[c,d]
DO $_{No\ Leak\ freq}$	Number of involuntary detrusor contractions NOT resulting in leak	Total number of involuntary detrusor contractions that do not have an associated leak[b,c]
$P_{det\ Max}$ (cm H_2O)	Maximum detrusor pressure at involuntary contraction	Maximum amplitude of detrusor contraction during an involuntary contraction (if present)[c,e]
$P_{det\ 1st}$ (cm H_2O)	Maximum detrusor pressure at FIRST contraction	Max detrusor pressure at **FIRST** contraction (voluntary or involuntary)[a,b]
$P_{Det\ Any}$ (cm H_2O)	Maximum detrusor pressure at ANY contraction	MAXIMUM detrusor pressure attained during the entire study (voluntary or involuntary)[c,f]
Cys Cap (mL)	Cystometric Capacity: Volume at strong urge to void	The volume at which the patient feels that he/she can no longer delay micturition (has a strong desire to void).[c] *(ICS definition)*

Table 2: Cystometric Parameters and Definitions (Continued)

Parameter	Description	Definition
Q_{max} (mL / sec)	Peak flow rate during voiding (for both leaks and voluntary voids)	The Maximum rate of flow during any void (for both involuntary and voluntary voids)[c]
V_{voided} (mL)	Total voided volume (leaks and voluntary)	Total volume voided for leak and volitional voids during the procedure[c]
PVR (mL)	Post Void Residual Volume (PVR) (from catheterization)	Volume left in bladder after voiding at the conclusion of the study. This is measured by urodynamic catheterization[c]
($V_{total\ bladder}$) (mL)	Total Bladder Volume (Total voided volume +catheterized PVR)	Post void residual volume + total voided volume (will be *calculated*)[c]
DO_{dur} (seconds)	Duration of detrusor overactivity	Duration of MAXIMUM detrusor activity[c, d]
$P_{Det, Q\ Max}$ (cm H_2O)	Detrusor pressure at maximum flow during an involuntary contraction	Maximum detrusor pressure during terminal void (voluntary or involuntary)[c, d]
$V_{bladder\ DO}$ (mL)	Bladder volume at each involuntary detrusor contraction	Infused bladder volume at the peak pressure of each involuntary contraction minus the amount leaked at each point for each involuntary contraction; Total will be calculated by the computer[c, d]
P_{abd} (cm H_2O)	Maximum abdominal pressure during any contraction	MAXIMUM abdominal pressure during **ANY** contraction. This will assess the abdominal straining component to voiding[c, d]

a To be analyzed
b This is done by overreader, but not the sites
c Listing only; not analyzed
d Done by site only
e Detrusor pressure at first involuntary contraction is called "**Detrusor Pressure**" for sites on eCRF.
f Maximum detrusor pressure at ANY contraction is called "**Maximum Detrusor Pressure**" for sites on eCRF.

The Cystometry overread parameters will be used for objective evaluation analyses. Binary outcomes will be estimated using generalized estimating equation (GEE) model with binary distribution and a logistic link clustered by participant. The parameters that can be treated as continuous variables will be analyzed similarly to the primary efficacy endpoint using linear mixed effect model adjusting for clustering effect by participants.

The mapping of the cystometry parameters that will be analyzed and the corresponding tables that will be used to present the results are shown in Table 3.

Table 3: Cystometry Parameter Analysis Endpoints and Tables that will present the Analysis Results

1) Detrusor overactivity ≥ 5 cm H_2O (yes/no- INCLUSION CRITERIA)	Table 14.2.4.1: Cystometry Overread: Change in the Presence and Absence of Detrusor Overactivity (DO)
2) Volume at first desire to void	Table 14.2.4.2: Cystometry Overread: Change of Volume at First Desire to Void (mL)
3) Detrusor pressure at beginning of voiding (prior to onset of first contraction (either volitional or involuntary)	Table 14.2.4.3: Cystometry Overread: Change from Baseline for Detrusor Pressure Prior To Onset of First Contraction (Either Volitional Or Involuntary) (cm H2O)
4) Volume at first involuntary contraction; if detrusor overactivity (DO) present-Not applicable if no DO present	Table 14.2.4.4: Cystometry Overread: Change from Baseline for Volume of First Involuntary Detrusor Contraction (mL) in Presence of Detrusor Overactivity
5) Maximum detrusor pressure at FIRST contraction	Table 14.2.4.5: Cystometry Overread: Change of Maximum Detrusor Pressure at FIRST Contraction (Voluntary or Involuntary) (cm H2O)

KHQ scores for the nine domains will be calculated according to the Protocol Appendix. Change from baseline at each time point for the QoL endpoints will be analyzed and presented similarly to primary efficacy endpoint using linear mixed effect models in Tables 14.2.5.

We will tabulate the frequency and proportion of participant perception of response to treatment by time point and treatment group in Table 14.2.6. The Cochran–Armitage test will be used whether the treatment group has better response.

Exploratory Figures may also be generated for change from baseline by treatment for frequency of urination (Figure 14.2.1), volume of urination per day, number of incontinences episodes, and urgency (Figures 14.2.1.1 through 14.2.1.3) from voiding diary data, number of detrusor contractions (Figures 14.2.2). The contents and layout of the figure will be similar to that displayed in Figure 14.2, a figure for illustrative purpose only. Possibly other variables may be presented as figures if the data justifies the presentation.

Participant cystometry detailed measures from both overreader and site Investigators will be displayed in Listings 16.2.6.2.1 through 16.2.6.2.5.

9.3. Exploratory Efficacy Analyses

In addition, for exploratory analysis, ANOVA (or ANCOVA with baseline measure as covariate) will be applied to test for treatment difference at each separate week. Other univariate and multivariate models could be explored, if warranted.

10. SAFETY ANALYSES

The safety analysis will be performed based on the Safety Population. Safety variables include AEs, clinical laboratory parameters, vital signs, physical examinations, and ECG.

10.1. Adverse Events

Safety summaries will include the incidence of treatment-emergent adverse events (TEAEs), which are defined as any event that began on or after the date of the first treatment dose or worsened in severity or frequency after treatment dose was initiated. Events worsening in severity will be considered new AEs. AEs recorded on the CRF that began prior to treatment and did not worsen in severity will be recorded as medical history will not be included in the AE summary tables and data listings. Any AEs happens in long-term safety follow-up will be reported in a separate listings and not included in the main planned analyses.

All TEAEs will be coded using version 17.1 of Medical Dictionary for Regulatory Activities (MedDRA) and summaries will present data by System Organ Class (SOC) and preferred term (PT).

The following conventions will be followed in summarizing multiple occurrences of an adverse event for a certain assessment period when summarizing data from individual participant:

- Each subject will be counted only once within a body system (SOC) or a preferred term;
- The highest known severity within a body system or a preferred term will be assigned to the event;
- The strongest relationship within a body system or a preferred term will be assigned to the event.

The denominator used for calculation of the percentages will be the number of subjects in the Safety population per treatment.

Specifically, TEAEs will be summarized in the Safety Population. An overall summary of TEAEs, including number of subjects in population, number of subjects with one or more TEAEs, number of participants with one or more Serious TEAEs, number of deaths (if any), and number of subjects experiencing AEs resulting in discontinuation, will be presented in Table 14.3.1.1 by treatment group. The frequency and percentage of AEs by SOC and PT for each treatment group will be presented in Table 14.3.1.2.

The frequency and percentage of AEs related to study drug (Possibly Related, Probably Related, and Definitely Related) by treatment group will be displayed by treatment in Table 14.3.2.

A listing of all AE data sorted by subject, including the verbatim term, MedDRA SOC and preferred term, and all other information from the AE CRF will be displayed in Listing 16.2.7.1. This listing will include a field for Study Day calculated as [(AE start date, minus date of first dose of study medication) +1]. Similarly, individual AE records of SAEs will be listed in

Listing 16.2.7.2. Any deaths occurring on study will be displayed in Listing 16.2.7.3. AEs that lead to discontinuation will be listed in Listing 16.2.7.4.

10.2. Clinical Laboratory Evaluations

Clinically significant abnormal laboratory values will be reported as AEs and the grade will be assessed according to Protocol Appendix A and will be reported in the AE analyses.

Summary statistics of numerical laboratory test results (mean, standard deviation, median, min and max) of test results and changes of test results from screening (V1) and V2 predose for laboratory tests (the last evaluation prior to treatment) will be reported for hematology and clinical chemistry at each scheduled time point. Specifically, information of pooled *h*Maxi-K and placebo will be displayed in Table 14.3.4.1 for hematology and Table 14.3.4.2 for clinical chemistry.

Individual test result records, including repeat assessments, and comments for hematology, clinical chemistry, urinalysis and other miscellaneous tests will be displayed in Listings 16.2.8.4.1, 16.2.8.4.2, 16.2.8.5.1, 16.2.8.5.2, 16.2.8.6.1, 16.2.8.6.2. The urine culture per participant results will be displayed in Listing 16.2.8.7.

10.3. Vital Signs

Summary statistics (mean, standard deviation, median, min and max) of vital sign measurements and changes of measurements from predose for vital sign at each time point will be reported for pooled *h*Maxi-K and placebo in Table 14.3.4.3.

Individual vital sign records will be displayed in Listings 16.2.8.1 and 16.2.8.2.

10.4. ECGs

Using the ECG overreader results, frequency and percentage of subjects in different degrees of QTcF categories (QTcF > 450, > 480 and > 500 msec) will be tabulated by treatment at each scheduled timepoint in Table 14.3.4.4. Summary statistics of ECG test parameters, ventricular heart rate (bpm), PR interval (ms), QRS duration (ms), QT/QTc (ms), P-R-T axes, average RR (ms), QTcB (ms), QTcF (ms), and change of these parameters from pre-dose to each post-dose timepoint will be calculated Table 14.3.4.5.1 for pooled *h*Maxi-K and placebo and Table 14.3.4.5.2 for 16,000 ug and 24,000 ug *h*Maxi-K group.

ECG overread overall assessment records will be displayed in Listing 16.2.8.3.1 and individual ECG site reading parameters will be listed in 16.2.8.3.2.

10.5. Other Safety Measures

None.

11. CLINICAL PHARMACOLOGY ANALYSES

Urine and serum sample collection details for *hSlo* concentration studies will be displayed in Listings 16.2.8.9 and 16.2.8.10.

12. OTHER ANALYSES

None.

13. REPORTING CONVENTIONS

The table and listing reporting layout will be detailed in the companion document *ION-OAB Safety Table, Listing and Graphic Shells*. The general reporting conventions are summarized in the two following sections.

13.1. General Reporting Conventions

All tables, figures and data listings will be presented in landscape orientation for easy visual comparison of different dose escalation cohorts. If figures presented, legends will be used for all figures with more than one variable or item displayed. Figure lines should be wide enough to see the line after being copied.

All titles will be centered on a page. The ICH numbering convention will be used for all TLFs. All tables, figures, and data listings will have the name of the relevant SAS (or Stata) program and a date-time stamp on the bottom of each output.

Number precision will be specified in the companion *ION-OAB Safety Table, Listing and Graphic Shells*.

13.2. Statistical Conventions

For tables, sample sizes for each treatment group will be presented as totals in the column header (N = xxx), where appropriate. Sample sizes shown with summary statistics are the number (n) of participants with non-missing values.

Summaries for categorical variables will include only categories that subjects had a response in. Percentages corresponding to null categories (cells) will be suppressed. All summaries for continuous variables will include: N, mean, and SD. Other summaries (eg, median, quartiles, 5%, 95% intervals, CV or %CV) will be used as appropriate. All percentages should be rounded and reported to a single decimal place (xx.x%). If percentages are reported as integers, percentages greater than 0% but < 1% will be reported as < 1%, whereas percentages greater than 99% but < 100% will be reported as > 99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank. Summaries that include *P* values will report the *P* value to three decimal places with a leading zero (0.001). *P* values < 0.001 will be reported as < 0.001.

14. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

None

15. REFERENCES

Ware JE, Kosinski M, Keller, SD. SF-12: How to score the SF-12 Physical and Mental Health Summary Scales. Lincoln, RI: Quality Metric Incorporated, third Edition, 1998

Avery K, Donovan J, Abrams P. Validation of a new questionnaire for incontinence: The International Consultation on Incontinence Questionnaire (ICIQ). Abstract nº 86 of the International Continence Society 31st annual meeting. Seoul, Korea. *Neurourol Urodynamics* 2001;20:510-1.

16. TABLES, FIGURES, LISTINGS

Tables, listings and, if applicable, figures will be generated according to the companion document, *ION-OAB Safety Table, Listing and Graphic Shells,* which detailed the layout of the output. Minor style variation in the final production is permissible