Document Detail

Type: CLN

Document No.: CLN-00021[B]

Title: eSense Clinical Investigation Protocol

Owner: ADELE.CAMPBELL Adele Campbell

Status: CURRENT

Effective Date: 24-Aug-2021 **Expiration Date:**

Revision Notes

Document Build No.	Access Activity	Accessed By	Accessed Date
1	Check In	ADELE.CAMPBELL	20-Aug-2021
Note:	Draft was been approved by ANSM, only make changes if absolutely necessary.		
1	Check In	ADELE.CAMPBELL	23-Aug-2021
Note:			

Review

Build No.: 1 **Closed Date:** 8/24/2021 7:12:32PM

Review: Document Approval

Review Purpose: The purpose of this review is to approve the document for pre-release.

Review Note: SYSTEM AUTO CLOSE REVIEW

Level	Owner Role	Actor	Sign-off Date	Sign-off By
1	CP_Approver_Quality-UNV Change Plan Approver Quality Universal	LAURIE.BRADBURY Laurie Bradbury	24-Aug-2021 7:12 pm	LAURIE.BRADBURY
Note To Approver:				
Note From Approver:				
1	CP_Owner Change Plan Owner	ADELE.CAMPBELL Adele Campbell	23-Aug-2021 3:49 pm	ADELE.CAMPBELL
Note To Approver:				
Note From Approver:Ready for release				
1	CP_Approver_Regulatory-UNV Change Plan Approver Regulatory Universal	CHRISTA.BLAISDELL Christa Blaisdell	24-Aug-2021 12:55 pm	CHRISTA.BLAISDELL
Note To Approver:				
Note From Approver:				
1	CP_Approver_Quality-Corporate Change Plan Approver Quality - Corporate	NICOLE.BOSER Nicole Boser	23-Aug-2021 4:37 pm	NICOLE.BOSER
Note To Approver:				
Note From Approver:				
1	CP_Approver_Clinical-UNV Change Plan Approver Clinical Universal	GRASSO.EBAKO Grasso Ebako	23-Aug-2021 4:00 pm	GRASSO.EBAKO
Note To Approver:				
Note From Approver:				
1	CP_Approver_Clinical-UNV Change Plan Approver Clinical Universal	BRUNA.COURI Bruna Couri	23-Aug-2021 4:01 pm	GRASSO.EBAKO
Note To Approver:				
Note From Approver:				
1	CP_Approver_ExecutiveTeam-UNV Change Plan Approver Executive Team Universal	ROSS.MCQUIVEY Ross McQuivey	23-Aug-2021 3:52 pm	ROSS.MCQUIVEY
Note To Approver:				
Note From Approver:Approved as written				
1	CP_Approver_Marketing-UNV Change Plan Approver Marketing Universal	DEB.KURTZ Deb Kurtz	23-Aug-2021 7:58 pm	DEB.KURTZ
Note To Approver:				
Note From Approver:Approve				

CLINICAL INVESTIGATION PROTOCOL

DEVICE:

e·Sense® Electronic Vesical and Abdominal Urodynamic Catheters

STUDY NUMBER:

ESNS-PH01

STUDY NAME:

e·Sense® Clinical Investigation:

Assessing the Performance, Safety and Usability of e·Sense® Electronic Catheters for Performing Urodynamic Studies

Laborie Document Control ID:

CLN-00021

Version B

August 20, 2021

ESNS-PH01

e·Sense® Clinical Investigation:

Assessing the Performance, Safety and Usability of e·Sense® Electronic Catheters for Performing Urodynamic Studies

Document History

	Version	Date Effective	Changes	Rationale for Change
Creation	1.0	October 28, 2019	-	Initial Release
Amendment	1.01	December 30, 2019	New text under 10.1 to refer to CTA for country-specific safety definitions. New sentence after 1st paragraph in 10.3, referring to CTA for institution-specific safety reporting requirements and details.	Address comments from BfArM (German Regulatory Body) to clearly reference CTA for details of safety requirements.
Amendment	1.02	January 20, 2020	Revised Sections 7.4 (End of Study) and 7.5 (Follow-up) to clearly define end of the study for study subjects, further treatment and the follow-up plans. Revised text under 10.1 to refer to safety reporting guidelines for country-specific safety definitions. Added definition and Section *10.1.7 - Serious adverse device effect* Revised Section 10.3 with further information and	Additional feedback received from competent authority reviewer.

	Version	Date Effective	Changes	Rationale for Change
			reference to safety reporting guidelines for country-specific safety reporting requirements and details.	
Amendment	V1.03	March 10, 2020	Added e·Sense® terminology in Section 1 (List of Abbreviations & Definitions) Added part numbers of investigational devices under assessment in Section 3.3 (Medical Devices) Section 11.2.2 corrected Section references.	Additional feedback received from competent authority reviewer.
Amendment	V1.04	July 31, 2020	(1) Amend Section 7.2 of protocol to expand on methods that can be used for quality checks.	(1) Review of study methods against COVID-19 recommendations for good urodynamic practice.
			(2) New text added to Section 12 regarding pseudonymized data transfer.	(2) Clarify location of pseudonymized data transfer. Information is consistent with the patient consent and privacy consent.
			(3) General grammar / language updates (added EU and US abbreviations, corrected Section 11 tile to “STATISTICAL CONSIDERATIONS”).	(3) Newly used abbreviations added (EU and US), Section 11 title error required correction, previously stated “Adverse Event CONSIDERATIONS”.

	Version	Date Effective	Changes	Rationale for Change
			(4) Amend the anticipated dates as listed in Table 2.	(4) Due to delays experienced from the COVID-19 pandemic and project timelines, anticipated dates and durations are extended.
Amendment	B	Refer to SmartSolve (CHANGE-PLN-PNHL-01150)	(1) Additional sentence added on page 5 to clarify the applicable health code.	(1) European regulation (EU) 2017/45 entered in to force on May 26, 2021 prevails over public health code in EU Member States where applicable.
			(2) Amend the anticipated dates as listed in Table 2.	(2) Due to delays experienced from the COVID-19 pandemic and project timelines, anticipated dates and durations are extended.
			(3) Update to Section 10.1 Patient Safety Definitions.	(3) Include reference to the definitions and reporting procedures for serious adverse events and device deficiencies in accordance with the provisions of Article 80 of MDR (EU) 2017/745.
			(4) Update to Section 10.5 Contact Information regarding adverse event reporting to Laborie as study sponsor.	(4) IT system navigation made the existing telephone number for safety reporting telephone line obsolete, a new number is provided.

This is a premarket clinical research protocol for a pivotal human research study. This study is conducted in accordance with the clinical protocol, Good Clinical Practice, ISO 14155, local regulations, and with the ethical principles that have their origin in the Declaration of Helsinki. For clinical research conducted in the European Union (EU) Member States, the Medical Device Regulation EU 2017/745 entered in to force on May 26, 2021, which prevails over the national public health code in matters of conflicting information.

Table of Contents

1 List of Abbreviations & Definitions

ACC	Air-Charged Catheters
COGS	Cost of Goods Sold
CRF	Case Report Form
CTA	Clinical Trial Agreement
EC	Ethics Committee
EMA	European Medicines Agency
EN	European Standards
EOS	End of Study
e·Sense®	Tradename used to describe the urodynamics catheter technology being tested in this clinical investigation. The terminology used throughout this document refers to the previous version of the device as the "existing" or "currently marketed" e·Sense® catheter bearing CE-mark with part numbers as follows: • 37041005 – 7 FR Bladder (Single Sensor) Urodynamic Catheter • 37041105 – 7 FR Bladder (Single Sensor Coudé) Urodynamic Catheter • 37042005 – 7 FR Bladder & Urethral (Dual Sensor) Urodynamic Catheter • 37042105 – 7 FR Bladder & Urethral (Dual Sensor Coudé) Urodynamic Catheter • 37040005 – 7 FR Abdominal Urodynamic Catheter The new version (test product) is referred to as the "updated" e·Sense® catheter, and is the investigational device being evaluated as part of this study with part numbers as follows: • CATEB27 – e·Sense® 7 FR Single Sensor Bladder Catheter • CATEB37 – e·Sense® 7 FR Dual Sensor Urethral Catheter • CATEA17 – e·Sense® 7 FR Abdominal Catheter • CATEB27C – e·Sense® 7 FR Single Sensor Coudé Bladder Catheter (**NOT WITHIN SCOPE OF THIS STUDY**) • CATEB37C – e·Sense® 7FR Dual Sensor Coudé Urethral Catheter (**NOT WITHIN SCOPE OF THIS STUDY**)
EU	European Union
Exploratory	Synonymous with the term observational
FPFV	First Patient First Visit
GDPR	European General Data Protection Regulation (EU) 2016/679
Fr	French
ICF	Informed Consent Form

ICS	International Continence Society
IP	Investigational Product
ISO	International Organization for Standardization
LPLV	Last Patient Last Visit
LUT	Lower Urinary Tract
MCC	Maximum Cystometric Capacity
MMS	Medical Measurement Systems
NPRS	Numerical Pain Rating Scale
Pabd	Abdominal Pressure
Pdet	Detrusor Pressure
PI	Principal Investigator
Pura	Urethral Pressure
Pves	Intravesical Pressure
SCI	Spinal Cord Injury
Subject	Individual who participates in the clinical investigation. Synonymous with the term patient.
UDS	Urodynamics
UPP	Urethral Pressure Profile
US	United States
VUDS	Video Urodynamics
WFC	Water-Filled Catheters
WPU	Wireless Patient Unit

2 Clinical Study Summary

Number of Sites	Two to Four
Number of Subjects	Minimum 60 and Maximum 65 (minimum 15 recruited at each site)
Objective	The primary objective of this pivotal study is to gather clinical data as follows: • Confirm that the updated e·Sense® catheters are safe and effective for urodynamic use in subjects medically indicated for urodynamics (UDS) testing. The secondary objectives of this study are to gather clinical data as follows: • To report the severe complication-free rate for the updated e·Sense® catheters. The following exploratory objectives of this study are to gather data on the following: • Assess subjective subject feedback regarding the discomfort and pain levels. • Assess user impressions of the updated e·Sense® catheters compared with their experience using the existing catheters at their site, by evaluating the following subjective measures: ease of use, ease of insertion and removal, ease of securing the catheter, tracing stability (overall, during filling, voiding and UPP where applicable), tracing quality (overall, Pves, Pabd, Pura where applicable), channel subtraction quality, visibility on Video Urodynamics (VUDS, where applicable), catheter stiffness, sensor location, patient tolerance, and overall usability performance. • Assess pre-test resting pressures while sitting, standing and supine, where patient is able. • Assess resting pressures at the recorded patient position during various points of the UDS test (every 100mL of filling, at maximum cystometric capacity (MCC) and post-void).
Inclusion criteria	Male and Female subjects (Age: 21 years and over) who are medically indicated for UDS testing.
Exclusion criteria	• Subjects with significant cognitive deficiency that prevent the patient from giving informed consent • Subjects suffering from an active bladder infection (not including subjects with asymptomatic bacteriuria) • Pregnant women • Subjects with recent (less than 2 weeks) pelvic floor surgery • Subjects who require the use of a suprapubic catheter
Anticipated Study duration	The proposed recruitment phase following site initiation from First Patient First Visit (FPFV) to Last Patient Last Visit (LPLV) is approximately 18 weeks per site.

	Subjects will come to the clinic for one visit, the UDS procedure, where data pertaining to the safety, effectiveness, and usability aspects of the e·Sense® catheter will be collected. Test duration may be slightly longer than a standard test while assessment of the study materials is being made, and so discomfort and inconvenience associated with an extended test duration may occur.
Follow-up	Each subject will be contacted three to five days post-test in order to record the occurrence of any adverse events. Any subject with persistent symptoms shall be followed until it is resolved, and the site must notify Laborie of the outcome of the follow-up. Any follow-up medical intervention prescribed is at the discretion of the Investigator.
Study end point	Once each site has met the minimum recruitment goal of 15 subjects, the sponsor will be informed. Following this, the site may have the option to continue recruitment until the study-wide maximum is reached, based on the discretion of the sponsor. Additional enrolment following the minimum recruitment goal will be dictated by the final number of sites initiated.

3 INTRODUCTION

3.1 Background

UDS catheters are a urological device that are intended for transient (<60 min) and short-term use (>60 but <120 min) during conventional invasive UDS examinations. Ambulatory UDS monitoring (>120 minutes) conducted outside of a lab setting can also be prescribed when medically indicated, however ambulatory cases will not be performed as part of this study.

Initially, water-filled catheters (WFC) were the only UDS catheter technology available and only intravesical (Pves) pressure was assessed[1]. However, with the demand for different and better ways to assess lower urinary tract (LUT) dysfunction, multiple catheter technologies have been developed. Currently, there are several different UDS catheter-based technologies available: WFC, Air-Charged Catheters (ACC), and electronic catheters such as the e·Sense® solid-state catheters. The legal manufacturer for the 1st generation e·Sense® UDS catheters is PendraCare International B.V., however this technology is now owned by Laborie Medical Technologies.

The e·Sense® urodynamic catheters consist of three configurations, which were released on the market in February 2014:

1) 7Fr bladder and urethral (dual sensor) catheter

2) 7Fr bladder (single sensor) catheter

3) 7Fr abdominal (single sensor) catheter

The e·Sense® UDS catheters are intended to perform pressure measurement in the bladder, urethra, and rectum or vagina. The e·Sense® coudé tip catheters (part numbers CATEB27C, CATEB37C) are not within the scope of this study and will not be available for this clinical investigation.

3.2 Rationale

This study involves testing an updated e·Sense® catheter design, which is based on the currently CE marked e·Sense® catheter technology, on human subjects. The design has been changed to remove copper wires in the lumen and add the original flex print with the intent of making the product manufacturable in higher quantities. Since the updated e·Sense® catheter is based on an existing design, there are clinical and non-clinical data showing the safety, performance and usability of the existing catheter. However, due to the design changes, further clinical evidence is required to confirm the updated e·Sense® catheters are safe and effective prior to market release. The aim of this pre-market study is to collect clinical data on the updated e·Sense® catheters' usability, confirm they are safe and effective for UDS studies, and to assess subjective user impressions of the updated e·Sense® catheters compared with their experience using the existing catheters at each site.

3.3 Medical Device

The catheters used in the study will be design verified, sterilized and appropriately labelled before the clinical investigation can begin.

The catheter device models to be evaluated as part of this study include:

1. e·Sense® 7Fr Single Sensor Bladder Catheters (blue connector)
   - Part number: CATEB27
2. e·Sense® 7Fr Abdominal Catheters (red connector)
   - Part number: CATEA17
3. e·Sense® 7 Fr Dual Sensor Urethral Catheters, available for optional urethral pressure measurement studies (blue connector)
   - Part number: CATEB37

Traceability of investigational study materials will be captured and maintained via an Inventory Control Log. Any remaining investigational material stock after study close out, will be returned to the study sponsor at the sponsors' expense.

The e·Sense® urodynamic catheters are manufactured using a Technical Polyurethane (TPU) 55 Durameter, a silicone adhesive, a UV curing adhesive, and an epoxy adhesive. These materials are all verified as biocompatible in accordance with the standards EN ISO 10993-5 and -10 and -18 – Biological evaluation of medical devices.

None of the materials used in this study contain biologically active substances or pharmacological agents.

From a regulatory standpoint, the following medical device classification rules apply in Europe, the United States (US) and Canada, respectively:

- For the European Union (EU), Class IIa, Rule 5 per Annex IX of the Medical Device Directive and Annex VIII of the Medical Device Regulation (EU MDR 2017/745) entering in to force on May 26, 2021 in EU Member States.
- For the US, Class II per 21 CFR 876.1620

- For Canada, Class II, Rule 2 per Health Canada Medical Device Regulations (SOR/98-282)

3.4 Purpose & Use

Intended Use: The e·Sense® catheters are intended to be used to fill the bladder and/or measure pressure within bladder, urethra, and rectum or vagina during UDS study on a patient.

Indications for Use: The e·Sense® catheters are provided sterile and intended for single use on patients requiring UDS pressure monitoring through the measurement of bladder, urethral, and rectal (or vaginal) pressures.

Target Users: Use of product is restricted to health professionals with relevant and adequate training (e.g. urologist, gynaecologists, physician assistant urology/gynaecology, specialist urology/gynaecology nurses, urodynamicists), and who are familiar with the possible/conceivable complications in a urology examination room (e.g. hospital or medical clinic with appropriate facilities).

Medical Indications: Use of the product is limited to diagnostic examinations during UDS study of patients presenting with LUT symptoms suggestive of a medical disorder/dysfunction related to the urinary tract.

3.5 Prior Literature & Studies

Since the e·Sense® catheter is one of the newest urodynamics catheter technologies available on the market, there are limited published literature available making use of the technology.

Please refer to the Investigator's Brochure (ESNS-PH01-IB) for a detailed review of the literature and study data (clinical and non-clinical) available to date.

3.6 Risks and Benefits

Risks to the subject will be no greater than those of a conventional UDS test. Physicians are responsible for determining whether subjects are medically indicated and would benefit from UDS testing. There is no direct subject benefit for participating other than to gather evidence of e·Sense® urodynamic catheters' clinical use.

There is also no need for any repeat catheterization or UDS testing using an approved (non-investigational) UDS catheter. UDS test results using the investigational device will be provided back to the referring physician for test interpretation. The investigational device must first pass design verification and manufacturing process validation in accordance with ISO 13485 before it can be used in this clinical investigation. Given this, the sponsor has no reason to suspect device safety and performance will be any different as compared to the currently marketed e·Sense® UDS catheter. Therefore, the data collected using the investigational device will be used in the test interpretation for each subject enrolled, unless there is reason to believe the test should be repeated. This can happen under normal (non-investigational) circumstances if the test was inconclusive[2].

Subjects may experience temporary discomfort upon insertion of the catheters. Test duration may be slightly longer than a standard test while assessment of the study materials is being made, and so discomfort and inconvenience associated with an extended test duration may occur.

UDS testing exposes subjects to risks of urethral instrumentation which can result in infection, urethral trauma and pain[3]. Other risks can include transient discomfort during or following the procedure, transient dysuria or bleeding (haematuria) following the procedure, or urinary tract infection, which occurs in approximately 2-4% of subjects[4]. Autonomic dysreflexia can also occur in those patients with spinal cord injury (SCI), and those at the level of T6 or higher are particularly prone[5,6]. As well, accidental ureter catheterization, where the ureter orifice is accidentally catheterized, can occur. A summary of the available safety data concerning these risks is presented in the Investigator's Brochure.

The overall risks associated with the use of e·Sense® catheters within this study set-up are acceptable when weighed against the benefits and are no different than the risks encountered when using other UDS catheter technologies. Lastly, UDS is a widely performed test on subjects requiring specialized management for urinary incontinence/retention problems, as recommended by the International Continence Society (ICS)[7], and is useful in characterizing LUT function, identifying causes of symptoms and quantifying related pathophysiological processes[8]. Thus, the clinician must weigh the risks and benefits as to whether the UDS test offers additional diagnostic value beyond symptom assessment, physical examination and other diagnostic testing[3].

Refer to: ESNS-PH01-IB-01-VXX - eSense Investigator's Brochure (PRC-026597)

4 STUDY OBJECTIVES

4.1 Primary Objectives

The primary objective of this pivotal study is to gather clinical data as follows:

- Confirm that the updated e·Sense® catheters are safe and effective for urodynamic use in subjects medically indicated for urodynamics testing.

4.2 Secondary Objectives

The secondary objective of this pivotal study is to gather clinical data as follows:

- To report the severe complication-free rate for the updated e·Sense® catheters.

4.3 Exploratory Objectives

The following exploratory objectives of this study are to gather data on the following:

- Assess user impressions of the updated e·Sense® catheters compared with their experience using the existing catheters at each site, by evaluating the following subjective measures: ease of use, ease of insertion and removal, ease of securing the catheter, tracing stability (overall, during filling, voiding and UPP where applicable),

tracing quality (overall, Pves, Pabd and Pura where applicable), channel subtraction quality, visibility on VUDS (where applicable), catheter stiffness, sensor location, patient tolerance, and overall usability performance.

- Assess subjective subject feedback regarding their discomfort and pain levels.
- Assess pre-test resting pressures while sitting, standing and supine, where patient is able.
- Assess resting pressures at the recorded patient position during various points of the UDS test (every 100mL of filling, at MCC, and post-void).

5 STUDY DESIGN

5.1 Description

This premarket, single-arm, open-label study will be conducted where subjects will undergo a conventional UDS study that will be conducted according to Good Urodynamic Practices[9] using the investigational device. As explained in Section 3.6, there is no need for any repeat catheterization or repeat UDS test using an approved (non-investigational) UDS catheter. Urodynamic test results using the investigational device will be provided back to the referring physician for test interpretation. The urodynamic information collected using the investigational device will be used in the UDS test interpretation for each subject enrolled, unless there is reason to believe the test should be repeated (i.e. inconclusive results).

Subject data including age, relevant medical history, height, weight, adverse events during or after the test, etc., will be collected on each subject's Case Report Form (CRF).

The following table gives a high-level overview of the study design and subject flow-through, as well as identifying which items are considered standard of care vs. non-standard clinic/hospital procedures.

Table 1. High-level overview of subject flow-through within this study, indicating whether item is considered standard of care or non-standard clinic/hospital procedure.

Item #	Subject Study Flow-Through	Standard vs. Non-standard Procedures & Data Collection Points
1	Adult subjects are referred for UDS testing	Standard
2	Subjects are approached to enrol in the study during their UDS visit and provide voluntary informed consent	Non-standard
3	UDS testing is conducted according to Good Urodynamic Practices[9] and standard clinic/hospital procedures, as per the needs of the patient.	Standard
3a	Pre-test resting pressures are recorded while sitting, standing and supine, where patient is able.	Non-standard
4	CRFs are completed (UDS Visit, Relevant Medical History, Clinical User and Subject Questionnaires, Adverse Event, Device Deficiency and Follow-up)	Non-standard

Item #	Subject Study Flow-Through	Standard vs. Non-standard Procedures & Data Collection Points
4a	Adverse events are documented and followed until resolution. Telephone call 3-5 days to record any adverse events experienced post-test.	Standard/Non-standard*

*Depending on clinic/hospital policies, this item may be considered standard or non-standard.

5.2 Study Duration

The expected duration of each subject's participation is one clinic visit to receive their already requested UDS test. A follow-up call will be conducted three to five days later to collect adverse event information post-test.

Once ethics board approval is received, site training and initiation is expected to take 1-2 weeks. The duration of active recruitment for this study is estimated at 37 weeks. Database lockout and study report completion is estimated at approximately 7 weeks after the last subject is recruited. The entire study is anticipated to take a total of 43 weeks, refer to Table 2 for details.

Table 2. Proposed Study Timeline

PROPOSED STUDY TIMELINE	TOTAL DURATION (WEEKS)	ANTICIPATED DATES
PROPOSED SITE TRAINING & INITIATION PHASE	**2**	**June 2020**
PROPOSED RECRUITMENT:1st subject in to 30 (Primary Objective)	**20**	**June 2020 – December 2020**
PROPOSED RECRUITMENT: Thirty to last subject out (Secondary Objective)	**17**	**September 2021 – December 2021**
PROPOSED DATABASE LOCKOUT	**1**	**January 2022**
PROPOSED STUDY REPORT COMPLETION	**6**	**Q1 2022**
TOTAL (WEEKS)	**43**	
ESTIMATED COMPLETION (QUARTER)	**Q1 2022**	**March 2022**

NOTE: Anticipated dates and timeline may be updated based upon COVID-19 pandemic situation and recruitment rates.

5.3 Suspension or Premature Termination

The investigation may be suspended or prematurely terminated by the Investigator, Sponsor, EC or Regulatory Authority for significant and documented reasons. The terminating party shall justify its decision and promptly inform the other parties with whom they are in direct communication.

Should a new risk or serious health threat arise during the course of the investigation, a risk assessment may determine the risk to subjects is unacceptable when weighed against the benefits. The investigation may then be prematurely terminated by either the Sponsor, Principle Investigator, EC or Regulatory Authority.

All investigation subjects will be informed with appropriate follow-up should the study be suspended or prematurely terminated due to a safety concern or serious health threat.

Other reasons for suspension or premature termination include:

- Serious or repeated protocol deviations
- Slow recruitment exceeding project timelines
- Investigational device is not producing expected results

Following a suspension, the risk assessment may determine appropriate corrective actions necessary to allow the study to resume. The rationale and relevant data supporting this decision will be provided to the Investigator, EC and where appropriate, the regulatory authority. The Investigator or authorized designee shall inform enrolled subjects that the study has resumed, reasons for resumption, and reminded that they may withdraw from the study at any time, without penalty. The ICF shall be updated to include any new information pertaining to risks and potential adverse events.

Early stopping or continuation of recruitment will be at Laborie's discretion depending on project timelines and whether the minimums sample size has been recruited. Early stopping will not depend on interim results.

6 PATIENT SELECTION

6.1 Inclusion Criteria

- Male and Female subjects (Age: 21 years and over) who are medically indicated for UDS testing.

6.2 Exclusion Criteria

- Subjects with significant cognitive deficiency that prevent the subject from giving informed consent
- Subjects suffering from an active bladder infection (not including subjects with asymptomatic bacteriuria)
- Pregnant women
- Subjects with recent (less than 2 weeks) pelvic floor surgery
- Subjects who require the use of a suprapubic catheter

6.3 Vulnerable Populations

The targeted subject group is not considered a vulnerable population.

6.4 Recruitment Plans

To satisfy the primary objective, the target enrolment is a minimum of 30 subjects with an attempted UDS study (e·Sense® catheter has made contact with the patient's body). To satisfy the secondary objective, the target enrolment is a minimum 60 subjects with an attempted UDS study (e·Sense® catheter has made contact with the patient's body). In addition, the study sponsor will allow up to 65 subjects (5 additional) during the allowable recruitment and project time given the minimum recruitment goals are met. Please refer to Section 11 for details on sample size determination.

Subjects who are visiting the UDS clinic for their medically indicated UDS test will be approached regarding participation in this study. It is estimated that study-wide recruitment of 60 subjects should take approximately 18 weeks of active recruitment at each site. Recruitment will be monitored by Laborie through scheduled meetings with the site co-ordinator. If the subject signs the informed consent, this will be treated as the point of enrolment.

The minimum number of clinical sites shall be two. The maximum number of sites allowed for this study shall be four. A minimum of 15 subjects per site is required to ensure proper distribution across sites. Once each site has met the minimum recruitment of 15 subjects, the sponsor will be informed. Following this, the site may have the option to continue recruitment until the study-wide maximum is reached, based on the discretion of the sponsor. Additional enrolment following the minimum recruitment goal will be dictated by the final number of sites initiated.

6.5 Informed Consent Process

The ICF used by the Investigator for obtaining the subject's informed consent must be reviewed and approved by the Sponsor, if any changes pertaining to site are changed/modified prior to submission to the appropriate EC for approval/favourable opinion. Once the approval letter is received from EC, the letter must be submitted to the sponsor prior to recruitment of subjects.

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator and under the Investigator's responsibility, should fully inform the subject of all pertinent aspects of the clinical investigation, including the written information given approval by the Ethics Committee (EC). Any new information in regard to the study or investigational device will be provided to the subject by the site. All documentation given to subjects, including written consent, will be translated into the country's official language for each investigational site. As part of the written Informed Consent Form (ICF), the subject will be informed on the processing of his/her personal data in accordance with Art. 13, 14 GDPR including a relevant declaration of consent to be signed separately.

Prior to a subject's participation in the clinical investigation, the ICF should be signed, full name printed and personally dated by the subject or by the subject's legally acceptable

representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated ICF will be provided to the subject.

The study sponsor does not foresee any circumstances where emergency enrolment would occur due to the device indication (it is not used in emergency situations), and the fact that subjects being recruited are attending their UDS appointment as a pre-scheduled visit.

6.6 Subject Withdrawal

Subjects may withdraw voluntarily from the study at any time, without penalty, or the Investigator may terminate a subject's participation (see Section 5.3). The Investigator will notify the Sponsor when a subject has withdrawn from the study (and if possible, the reason for the withdrawal), and this will be recorded on the subject's CRF. Subjects who withdraw, or those not considered to be part of the primary analysis population, will be allowed to be replaced by another subject should project timelines allow. Subjects will **not** be replaced due to poor results. This also applies in cases in which the subject withdraws his or her consent under data protection law according to Art. 7 GDPR. Please refer to Section 11 Statistical Considerations for further details.

7 STUDY PROCEDURE

7.1 Study & Visit Schedule

The study consists of two parts (Clinic Visit & Follow-up). The subject consent and UDS Visit may or may not be condensed to one visit. Refer to Table 3 for details.

Table 3. Visit Schedule.

Evaluation	Clinic Visit	Post-Test
	UDS Visit	Follow-up
Informed Consent	X	
Inclusion Criteria	X	
Exclusion Criteria	X	
Relevant Medical History	X	
UDS Study	X	
Record any Adverse Events	X	
Complete CRFs 1, 2, 4, 5 for each subject and CRF 3 at the end of each clinic day. Complete CRF 6 (Device Deficiency Form) where applicable.	X	
Complete CRF 7, three to five days post-test.		X

7.2 Clinic Visit

- Determine if the subject is eligible for the study.
- Conduct informed consent discussion with the subject and complete signature section.
- Conduct urine sediment or dipstick test.
- Collect relevant medical history and record on the subject's CRF (ESNS-PH01-CRF-02*).
- Collect and record other subject details as required on ESNS-PH01-CRF-01* (weight, height, age, sex, subject condition (neurogenic or non-neurogenic), subject symptoms (storage or voiding), etc.).
- Study personnel will explain what will happen during the UDS test to the subject or subjects' representative.
- Study personnel will prepare UDS equipment, study materials, other sterile disposables and supplies as required for the UDS study and record catheter LOT number information on ESNS-PH01-CRF-01*.
- Follow the investigational device instructions for use to zero, place the catheters and record all necessary pre-test data on ESNS-PH01-CRF-01* (ie. insertion depth in cm, any problems during insertion).
- Record pre-test Pves and Pabd resting pressures in each position: sitting, supine and standing on ESNS-PH01-CRF-01, where patient is able.
- Conduct UDS study including quality checks according to ICS Good Urodynamic Practice[9] recommendations, ensuring good pressure transmission and catheter positioning wherever possible. A minimum of three quality checks (e.g. beginning, middle and end) must be performed during the study.
  - NOTE: As per ICS Good Urodynamic Practice, cough method is considered the gold standard as the primary quality check method[9]. However, in light of the COVID-19 pandemic valsalva manoeuvre or gentle external pressure on the abdomen can be also considered an acceptable quality check method[17]. The cough method still should be prioritized as the accepted gold standard, however should a situation arise where asking the patient to cough may not be appropriate (e.g. high-risk area, hospital policy) then valsalva or external pressure quality check methods can be performed.
- At the conclusion of the UDS test, study personnel will ask subjects to answer questions on urodynamic discomfort/pain experience and record all data on ESNS-PH01-CRF-04*.
- If the subject experiences any adverse events during their UDS test, the details are to be recorded on ESNS-PH01-CRF-05*.
- Review urodynamic tracings post-test, and record the observed Pves and Pabd resting pressures every 100 mL of filling or where pressures are first stable (+/- 50mL) on ESNS-PH01-CRF-01*. Add event markers at each point resting measurements are recorded and complete all other ESNS-PH01-CRF-01 sections*.
- Investigator to complete Investigator Assessment and signature page on ESNS-PH01-CRF-01*.

- After completing a day of Urodynamic procedures using the investigational device, the user will fill out the clinical user questionnaire and record all necessary data on ESNS-PH01-CRF-03*.

7.3 Telephone Follow-Up

- Three to five days post-test, site personnel will contact subjects by telephone to check whether any adverse events were experienced post-test. Call details to be documented on ESNS-PH01-CFR-07* and any adverse event information recorded on ESNS-PH01-CFR-05*.

Note: If an adverse event occurs during the study, any follow-up medical intervention prescribed is at the discretion of the Investigator. This information should also be recorded on the subject's CRF (ESNS-PH01-CRF-01*) and adverse event form (ESNS-PH01-CRF-05*).

Note: If a device deficiency occurs during the study, this information shall be recorded on the device deficiency case report form (ESNS-PH01-CRF-06)*.

*All CRF's, with de-identified subject tracings and video images (where applicable) must be sent to the sponsor (Laborie) for data collection/analysis.

7.4 End of Study (EOS)

At the conclusion of their UDS test and clinic visit, the subject is no longer required to undergo any further study-related procedures. Subject follow-up will be performed as described in Section 7.5 below.

Once a site has completed its target recruitment, the sponsor (Laborie) will schedule a time to close-out the site, either in person or by telephone as per the monitoring plan. All study related files will be collected and reviewed for completeness. The EOS is considered the point when all subjects have been followed up and data collection is completed.

7.5 Follow-Up

Study staff will telephone each subject three to five days post-test to inquire about possible adverse events that may have occurred after their UDS test. All follow-up call details will be recorded on the follow-up CRF (ESNS-PH01-CFR-07) and update the subjects' adverse event form (ESNS-PH01-CRF-05), where applicable.

The focus of the follow-up call is to gather information about study-related adverse events, which are adverse events that are possibly, probably or definitely related to the study procedure.

For subjects who did not experience any adverse events or were not experiencing symptoms at the time of their follow-up call, their direct involvement in the study ends at the time of the telephone follow-up call. All subjects who did experience adverse events will be followed until resolution, and this information shall be recorded on the subject's CRF (ESNS-PH01-CRF-01) and adverse event form (ESNS-PH01-CRF-05).

In the case of persistent adverse events, regular follow-up will be performed by study staff until resolution, at which point the subject's direct involvement in the study will end. Any follow-up medical intervention prescribed and frequency of future follow-ups to treat an adverse event, will be at the discretion of the Investigator.

Since subjects who experience adverse events are being followed until resolution, the length of time a subject is participating in the study can vary. A subjects participation will end if they report no adverse events at the three to five day follow-up call, or when the reported adverse event has resolved.

Follow-up on any treatment decisions made by the Investigator are not the focus of the present study and will not be followed up. Only adverse events related to the urodynamics procedure or use of the investigational device are the focus of the present study.

8 MANAGEMENT OF MEDICAL DEVICE

8.1 Description

The following devices and equipment will be required for each subject. Those indicated by asterisk (*) are to be sourced and provided by the sponsor and those indicated by "IP" are defined as investigational products:

- Medical Measurement Systems (MMS) Nexam Urodynamic System already in use by the site, or on loan from the Sponsor
- Uroflowmetry device configured with the UDS equipment and computer pressure-flow studies, already in use by site (optional)
- One e·Sense® 7Fr Abdominal Catheter per subject (*) (IP)
- One e·Sense® 7Fr Single Sensor Bladder Catheter or one e·Sense® 7Fr Dual Sensor Urethral Catheter per subject (*) (IP)
- EMG cable (optional component at the discretion of the site)
- EMG patches (optional component at the discretion of the site)
- Nexam wireless remote (optional component at the discretion of the site)
- Wireless Patient Unit (WPU)
- Pump tubing (*)
- 1000 mL beaker (optional)
- One saline bag per subject
- Tape
- Lubricant
- Gloves
- Any other supplies deemed necessary for conducting a UDS study

The clinical trial agreement (CTA) will further specify the equipment and disposables that will be provided to the site.

Note: The CTA will supersede materials provided by Laborie listed above.

Note: Monitoring of electromyography (EMG) activity is considered optional at the discretion of the site and is not included in analysis of study endpoints. The measurement of UDS pressures is not influenced by EMG activity also being measured simultaneously.

8.2 Regimen

N/A – there is no treatment regimen required as part of this study.

8.3 Assignment to Groups

No stratification of subjects will be utilized based on study design.

8.4 Preparation and Handling

The UDS system and e·Sense® catheters will be prepared and maintained by the physician or delegated site personnel.

8.5 Packaging and Labelling

Investigational device labelling will appear on all investigational materials under Laborie's and national regulations. A copy of the investigational label is shown in the Investigator's Brochure.

8.6 Device Accountability

All e·Sense® devices used directly for UDS procedures on enrolled subjects must be recorded using the device LOT number on the subjects CRF form and inventory control log. Any unused investigational devices shall be returned to the sponsor. The sponsor will provide the appropriate instructions for their safe return.

8.6.1 Laborie to Study Site:

All investigational devices or equipment transferred between Laborie and the study site must be recorded through the Inventory Control Log. This includes postal deliveries and any deliveries made in person by Laborie. Any equipment or devices that are not used and are not returned to Laborie must also be recorded on the Inventory Control Log. It is Laborie's responsibility to ensure that all inventory both at Laborie and the study site correlate. All investigational device accountability will be recorded through the Inventory Control Form.

8.6.2 Study Site Usage:

All investigational devices used directly for testing subject samples must be recorded on the Inventory Control Form. All investigational devices used by the study site that are not directly used for the testing of subject samples must also be recorded on the Inventory Control Form. This includes any devices used for training or demonstration or any devices which are noted to be defective when opened. All non-investigational devices or material usage will not be recorded or traced.

8.6.3 Study Site to Laborie:

Any equipment or devices that are not used and are returned to Laborie must be recorded on the Inventory Control Form.

When the devices have been received by Laborie, it is Laborie's responsibility to ensure that all inventory control forms, both at Laborie and at the study site, correlate.

Note: All investigational devices must be returned to Laborie, however, non-investigational materials/accessories can be left at the site for continued use or returned as agreed upon with the sponsor. Please reference the CTA for further details.

8.7 Concomitant Treatment

Not applicable for this study.

8.8 Subject Compliance Monitoring

Not applicable for this study.

9 ASSESSMENT OF INVESTIGATIONAL DEVICE

9.1 Endpoints

The ESNS-PH01 study consists of one primary objective, one secondary objective and four exploratory objectives.

Primary Objective:

The primary endpoint will be measured by recording the clinician safety and effectiveness rating for each subject on their CRF. The clinicians will indicate whether each of the e·Sense® bladder and abdominal catheters are safe & effective for urodynamic use in at least 30 enrolled subjects. Given the intended use of the device, and the fact that there is no single or combined objective measures generated from the UDS test that can establish the safety and effectiveness, it is justified to obtain clinicians' feedback via a binary response whether the device is safe and effective for urodynamic use.

Secondary Objective:

The secondary endpoint will be measured by recording the number of severe complications and serious adverse events for each subject on their CRF. Due to the low risk profile of UDS, the sponsor would like to report the severe complication-free rate for any severe complications associated with UDS, and therefore this secondary safety endpoint was planned. Additionally, the sponsor would like to collect and assess this information due to a lack of available published data using the e·Sense® catheter technology.

First Exploratory Objective:

The first exploratory endpoint will be measured by collecting usability data in a questionnaire format. At the end of each clinic day a trained clinical user shall complete the questionnaire on CRF 3. When evaluating the usability of a device, the sponsor feels it's appropriate to use a subjective ordinal scale response while assessing human and device usability factors.

Second Exploratory Objective:

The second exploratory endpoint will be measured by collecting subject feedback regarding the level of discomfort and pain experienced during their Urodynamic test using the Numerical Pain Rating Scale (NPRS) on CRF 4. Subjects will grade their discomfort/pain on the NPRS from 0 ("No Pain") to 10 ("Worst Pain"). Given the subject population, use of the NPRS is a validated tool in evaluating pain ratings in adults[10-12].

Third Exploratory Objective:

The third exploratory endpoint will be measured by recording initial resting pressures using the updated e‧Sense® catheters while each subject is positioned in a sitting, standing and supine position, if patient mobility allows. Resting pressures will be recorded on each subjects' CRF 1 during their UDS visit. Resting pressure is considered an important quality control parameter in urodynamics[9,13,14,16]. As described in the Good Urodynamic Practices[9] (albeit in the context of WFC), the initial intravesical and abdominal resting pressures are real, are different between patients, and depend significantly on patient's position. The sponsor would like to collect and assess initial resting pressures for the e‧Sense® catheters, due to a lack of available published data using the e‧Sense® catheter technology.

Fourth Exploratory Objective:

The fourth exploratory endpoint will be measured by recording resting pressures using the updated e‧Sense® catheters during various points of the UDS test as applicable (every 100 mL of filling, MCC, and post-void) at the recorded patient position (sitting, standing, or supine). Patients are to remain in the same position throughout, however supplemental positions can be used (e.g. performing provocative manoeuvres). Resting pressures and patient position will be recorded on each subjects' CRF 1 during their urodynamics visit. Again, resting pressure is considered an important quality control parameters in urodynamics[9,13,14,16]. The sponsor would like to collect and assess resting pressures during the UDS test for the e‧Sense® catheters, due to a lack of available published data using the e‧Sense® catheter technology.

Table 4 shows the relationship between all study endpoints and case report forms.

Table 4. CRF data and relationship to study objectives

Case Report Form	Relationship of data recorded to study objectives
CRF 1 (UDS Visit)	Primary endpoint for safety and effectiveness Third and fourth exploratory endpoints for UDS
CRF 2 (Relevant Medical History)	N/A – Collected for patient demographic and eligibility reasons
CRF 3 (Clinical User Questionnaire)	First exploratory endpoint for usability evaluation
CRF 4 (Subject Questionnaire)	Second exploratory endpoint for discomfort/pain levels
CRF 5 (Adverse Events)	Secondary safety endpoint for adverse events and severe complications. Supports primary endpoint and collected for safety data collection purposes

Case Report Form	Relationship of data recorded to study objectives
CRF 6 (Device Deficiency)	Supports primary endpoint and collected for safety data collection purposes
CRF 7 (Follow-Up)	Supports secondary safety endpoint for adverse events and severe complications. Supports primary endpoint and collected for safety data collection purposes.

9.2 Methods of Assessment

The e·Sense® catheters will be used to assess and record bladder pressure (vesical and/or urethral - for applicable subjects) and abdominal pressure, which are in turn interpreted by the clinician to identify UDS events. These measurements will be recorded using an MMS Nexam UDS system. The resulting interpretations and conclusions regarding safety, effectiveness, and usability of the investigational device, will be made by the Investigator overseeing the subject's case on the relevant case report form.

All study outcome data captured will be compiled and analysed by the Laborie study team to determine if the endpoints were successfully achieved based on whether the null hypotheses were rejected.

10 PATIENT SAFETY

10.1 Definitions

Investigators shall refer to the Safety Reporting Guidelines (ESNS-PH01-SRG-01) for country-specific safety definitions and requirements, which includes the provisions of Article 80 of MDR (EU) 2017/45 prevailing over the public health code in EU Member States, where applicable.

10.1.1 Adverse Events (MDR EU 2017/45):

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs, including abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

10.1.2 Adverse Device Effect (ISO14155:2020):

Any adverse event related to the use of an investigational medical device.

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

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

NOTE 3 This includes 'comparator' if the comparator is a medical device.

10.1.3 Device Deficiency (MDR EU 2017/45):

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

10.1.4 Serious Adverse Event (MDR EU 2017/45):

Any adverse event that led to any of the following:

a) death;
b) serious deterioration in health of the subject, that resulted in any of the following:
   i. life-threatening illness or injury,
   ii. permanent impairment of a body structure or a body function,
   iii. hospitalisation or prolonged hospitalization,
   iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function,
   v. chronic disease,
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

NOTE per ISO 14155: Planned hospitalization for a pre-existing condition, or a procedure required by this protocol, without serious deterioration in health, is not considered a serious adverse event.

10.1.5 Unanticipated Serious Adverse Device Effect (ISO14155:2020):

Serious adverse device effect which by nature, incidence, severity or outcome has not been identified in the current risk assessment.

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

10.1.6 Severe Complications (sponsor definition):

A severe complication is defined an adverse event (whether expected or non-expected) that has been evaluated on CRF 5 as:

- Severity graded as either Severe (3) or Life-Threatening (4) and;

- Study Procedure Relationship graded as Probably Related (3) or Definitely Related (4) and;
- Action taken with respect to study device required Invasive Medical Intervention (4) and/or resulted in Hospitalization (5) and;
- The outcome for the subject resulted in recovered with Major Sequelae (3), Ongoing/Continuing Treatment (4), Condition Worsened (5) or Death (6).

Or otherwise any adverse event categorized as a Serious Adverse Event (See Section 10.1.4 for definition).

NOTE: An invasive medical intervention refers to any medical intervention or oral medication treatment lasting one week (seven days) or longer. Conversely, a non-invasive treatment refers to any medical intervention or oral medication lasting less than one week (seven days).

10.1.7 Serious adverse device effect (ISO14155:2020)

An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

10.2 Data Collection

All adverse events, device deficiencies or any other event or information for potential unanticipated safety concerns shall be recorded and reported to the sponsor on the appropriate CRF:

- ESNS-PH01-CRF-01: For initial of recording of any adverse event, device deficiency or other event/information regarding a potential unanticipated safety concern.
- ESNS-PH01-CRF-05: For reporting adverse event full details
- ESNS-PH01-CRF-06: For reporting device deficiencies full details
- ESNS-PH01-CRF-07: For recording patient follow-up details

These data shall be recorded and reported for both the primary and secondary analysis populations (see Section 11.5). Where required, EC and/or regulatory authorities shall be notified within a specified time period.

10.3 Reporting

All adverse events, device deficiencies and other events or information for potential unanticipated safety concerns will be reported as soon as possible to the sponsor for evaluation. The Sponsor is responsible for the classification of adverse events and will review the Investigator's assessment to determine seriousness and relationship to the investigational device. Laborie will carefully evaluate all serious adverse events, regardless of whether or not they are related to the investigational medical device or anticipated. Likewise, not only safety endpoint events but all serious adverse events have to be assessed with regard to patient safety and are to be compared to acceptable occurrence rates.

In the case of disagreement between the Sponsor and Investigator, the Sponsor shall communicate both opinions to the concerned parties (EC/regulatory authority, where

required). Reports to EC and regulatory authorities will be made within the required time period. All Investigators shall be informed, in writing, of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that they are reported to their EC.

Investigators shall make reference to the Safety Reporting Guidelines (ESNS-PH01-SRG-01) for details on country-specific safety reporting requirements and other pertinent details.

Should a suspension or premature termination occur due to a serious health threat, the EC and regulatory authority shall be notified as well (see Section 5.3). Deviations from this protocol under emergency circumstances where the rights, safety or well-being of the subject were of concern, must be reported as soon as possible to the sponsor, EC and/or regulatory authority where required (see Section 14).

The number and type of adverse events will be summarized in the clinical study report.

10.4 Foreseeable Events

For a complete Risk Management Report please refer to the Risk Management File. The residual risks have been deemed acceptable and the benefits overweighs the risks. Please also refer to Section 3.6 above and the Investigator's Brochure for a detailed analysis of expected risks.

10.5 Contact Information

In the event of a serious adverse event or serious adverse device effect, please inform Laborie personnel within 24 hours. A safety reporting telephone line is available at the number below:

Telephone: +1 (603) 766-3308 (North American, Eastern Time)

10.6 Follow-Up

Site personnel will telephone the subject three to five days post-test and inquire as to whether any adverse events have occurred after their UDS test.

If an adverse event occurred, any follow-up medical intervention prescribed is at the discretion of the Investigator and shall be recorded on the subjects' Adverse Event Case Report Form (ESNS-PH01-CRF-05). Please refer to Section 7.5 above for further detail.

11 STATISTICAL CONSIDERATIONS

11.1 Primary Analyses

11.1.1 Primary Endpoint

The primary safety and effectiveness endpoint is a composite endpoint based on clinician response after each UDS study using the investigational device (e·Sense® catheter) to determine whether the urodynamic use of the catheter was clinically adequate (success) or inadequate (failure). A procedure is considered a success when the clinician determines the investigational device to be both safe and effective as per the Investigator Assessment on CRF 1. If these criteria are not met, the procedure is classified as a failure. The primary effectiveness

hypothesis is a comparison of the lower bound for the estimate of the success rate to a minimally acceptable target value of 75%:

H_0: Composite Safety and Effectiveness Success Rate is ≤ 75%

versus

H_A: Composite Safety and Effectiveness Success Rate is > 75%

This 1-sided hypothesis will be evaluated by comparing the lower limit of the 97.5% 1-sided Clopper-Pearson confidence interval to the target value. If the lower limit of the 97.5% 1-sided Clopper-Pearson confidence interval is greater than the target value, the null hypothesis will be rejected, and it will be concluded that an effectiveness rate ≤ 75% is inconsistent with the investigation findings. The lower limit of the 97.5% 1-sided Clopper-Pearson confidence interval is identical to the lower limit of a 2-sided 95% Clopper-Pearson confidence interval, so the 2-sided Clopper-Pearson 95% confidence interval may be calculated for computational ease. In addition, a 1-sided, 1-sample binomial test will be performed to calculate a p-value. $P < 0.025$ will be considered statistically significant.

11.1.2 Sample Size Determination & Power:

The null hypotheses for the primary composite effectiveness endpoint is designed to rule out success rates ≤ 75%. Based on clinical judgement and previous testing, the true success rate for both safety and effectiveness are assumed to exceed 95%. Thus, the power calculation assumes a true success rate of 96% for the composite safety and effectiveness endpoint.

Power was determined by 10,000 binomial simulations (assuming success rate 96%) for each sample size, and power was calculated as the proportion of simulations for which the null hypothesis would be rejected based on the lower limit of the 2-sided 95% Clopper-Pearson confidence interval. Analysis of 30 subjects would provide 88% power to rule out a success rate ≤ 75% when the true success rate is assumed to be 96%, based on a 1-sided test with type I error rate of 2.5%. This primary analysis and endpoint requires a minimum of 30 subjects to ensure adequate power[15].

11.2 Secondary Analyses

11.2.1 Secondary Endpoint:

The secondary safety endpoint is to report the severe complication-free rate for the updated e·Sense® catheters. The secondary safety hypothesis is a comparison of the lower bound for the estimate of the success rate to a minimally acceptable target value of 95%:

H_0: Severe complication-free rate of ≤ 95%

versus

H_A: Severe complication-free rate of > 95%

This 1-sided hypothesis will be evaluated by comparing the lower limit of the 95% 1-sided Clopper-Pearson confidence interval to the target value. If the lower limit of the 95% 1-sided

Clopper-Pearson confidence interval is greater than the target value, the null hypothesis will be rejected, and it will be concluded that a severe complication-free rate ≤ 95% is inconsistent with the investigation findings. The lower limit of the 95% 1-sided Clopper-Pearson confidence interval is identical to the lower limit of a 2-sided 90% Clopper-Pearson confidence interval, so the 2-sided Clopper-Pearson 90% confidence interval may be calculated for computational ease. In addition, a 1-sided, 1-sample binomial test will be performed to calculate a p-value. $P < 0.05$ will be considered statistically significant.

11.2.2 Sample Size Determination & Power:

The null hypothesis for the secondary safety endpoint is designed to rule out success rates ≤ 95%. Based on clinical judgement and previous testing, a true success rate of 100% is assumed.

Power was determined by 10,000 binomial simulations (assuming success rate 100%) for each sample size, and calculation of the proportion of simulations or which the null hypothesis would be rejected based on the lower limit of the 2-sided 90% Clopper-Pearson confidence interval. Analysis of 60 subjects would provide 99% power to rule out a success rate ≤ 95% when the true success rate is assumed to be 100%, based on a 1-sided test with type I error rate of 5%. This study requires a minimum of 60 subjects for adequate power to reject the null hypothesis when the true assumed rate is 100%, however the final sample size will be based on site enrolment capabilities within the project timeline. In addition, the study sponsor will allow up to 65 subjects (5 additional) during the allowable recruitment and project time given the minimum recruitment goals are met. The additional subjects will ensure the desired confidence and reliability levels are met should any data or subjects be excluded from the primary analysis population (See Section 11.5) or if the subject withdraws (See Section 6.6). If the enrolment target is not reached, the exact confidence interval will be calculated for the data available, but no hypothesis test will be conducted.

11.3 Exploratory Analyses

Descriptive statistics will be used to summarize and analyse the results of each of the exploratory endpoints at the completion of the study.

11.3.1 First Exploratory Endpoint:

The first exploratory endpoint is to assess user impressions of the updated e·Sense® catheters compared with their experience using the existing catheters at their site, by evaluating the following subjective measures: ease of use, ease of insertion and removal, ease of securing the catheter, tracing stability (during filling, voiding and UPP where applicable), tracing quality (overall, Pves, Pabd and Pura where applicable), channel subtraction quality, visibility on VUDS (where applicable), instruction for use evaluation, catheter stiffness, sensor location, patient tolerance, and overall usability performance.

The reported value in the usability performance survey will be analysed using proportions of levels and combined proportions of groupings. This includes levels (1 to 5), “Yes and No”, “Better, Same or worse” and any other questions related to usability. The results will also be

analysed grouped by the site's existing catheter technology (e.g. grouping by water, air, or electronic technology results). Additionally, the results will be plotted over time to observe the trend as the study continues (preferably a line plot with daily responses over time).

11.3.2 Second Exploratory Endpoint

The second exploratory endpoint is to assess subjective subject feedback regarding their discomfort and pain levels.

The reported value in the patient survey will be analysed using proportions of levels and combined proportions of groupings. This includes levels (0 to 10) and "Yes and No".

11.3.3 Third Exploratory Endpoint

The third exploratory endpoint is to assess pre-test resting pressure of the e·Sense® catheters at sitting, standing, and supine patient positions.

11.3.4 Fourth Exploratory Endpoint

The fourth exploratory endpoint is to assess resting pressure of the e·Sense® catheters at the recorded patient position during various points of the UDS test (every 100mL of filling, MCC, and post-void).

11.4 Randomization / Blinding

Randomization and/or blinding is not utilized in this study based on the study design.

11.5 Analysis Population

The primary analysis population to be considered in this study will include enrolled subjects who have been successfully catheterized using the investigational device. Should catheterization fail due to a device deficiency, and/or adverse event, these subjects will still be included in the primary analysis and this information shall be recorded on the subjects' CRF#1 (ESNS-PH01-CRF-01), as well as on the adverse event form (ESNS-PH01-CRF-05), or device deficiency form (ESNS-PH01-CRF-06) as applicable. However, should catheterization fail due to patient factors (i.e. the characteristics of the catheter didn't meet patient anatomical needs, coudé tip required, inappropriate French size), these subjects will be considered as part of the sensitivity analysis population.

All subjects in the primary analysis population will be included in the primary analysis of the hypotheses tests. The sensitivity analysis population will also be analysed as the "intent to treat" population, however results of this population will not dictate success or failure of the study and are meant for comparison purposes only. Data will be analysed as outlined in Section 12.1.

Any subjects who are enrolled but for any reason subsequently withdraw from the study prior to being catheterized with the investigational device, will be excluded from analysis. The justification being they were never touched, and no measurements were made with the investigational device.

If any CRFs are found to be incomplete, the study monitor will follow-up as to the reasoning. If for some reason a clinical user is unable to fully complete their questionnaire, the questions they have completed will be included in the analysis. Data will be monitored as the study progresses, refer to Section 6.7 for details pertaining to suspension or premature termination.

11.6 Deviations

In any event there are deviations from the original statistical plan, they will be described and justified in the final report.

11.7 Interim Analysis

Once 30 primary analysis population subjects complete the study the primary composite safety and effectiveness analysis will be conducted for regulatory purposes. Once all (60-65) subjects are complete, the secondary endpoint analysis will be performed. In addition, the exploratory endpoints will be assessed and an exploratory analysis of the composite (primary) safety and effectiveness endpoint including all subjects will be performed.

There are currently no criteria for stopping the study early on statistical grounds. Refer to Section 5.3 for details about suspension or premature termination.

12 DATA HANDLING & RECORD KEEPING

12.1 Direct Access

The investigator/institution will permit investigation-related monitoring, audits, EC review, and regulatory inspections by providing direct access to the source data/documents as needed. Regarding the subjects' personal data including health data, such data is provided in a de-identified (pseudonymized) form wherever possible and not otherwise necessary.

12.2 Confidentiality & Security

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Investigation, including, but not limited to, the Clinical Investigation Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Investigation, is confidential. The Investigator or any person under his/her authority agrees to undertake to keep the information confidential. In particular, the Investigator undertakes (1) not to make the information accessible to third parties - directly or indirectly, in writing, orally or in any other way - without the prior written approval of the Sponsor, (2) to use it exclusively within the scope defined by this Clinical Investigation Protocol and (3) to take all necessary measures to prevent third parties from becoming aware of and exploiting the information (obligation to secrecy, non-use and security). This does not apply in cases where the Investigator is obliged by law or other relevant regulations (e.g. ISO 14155) to grant third parties (e.g. such as regulatory authorities, ECs) access to the data. The Investigator will inform the sponsor immediately if a third-party requests access to the data.

However, the submission of this Clinical Investigation Protocol and other necessary documentation to the EC is expressly permitted, the EC members having the same obligation of confidentiality.

If Sub-Investigators are utilized, the Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Investigation.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Investigation, to the exclusion of any use for their own or for a third party's account.

All data sent to Laborie will be confidential and all subject identifiers will be blacked out/redacted before being sent to Laborie. Documents will be kept in a secure location and all digital information will be kept following General Data Protection Regulation (GDPR) and local government regulations.

If the Investigator and/or Sub-Investigators transmit personal data to Laborie, or Laborie itself collects personal data within the European Union, the personal data will also be transmitted to Canada and to the United States, where members of Laborie's team involved in the study are situated. With regards to the transmission of data to Canada, there is a European Commission Adequacy Decision (Commission Decision of 20.12.2001 - 2002/2/EC). With regards to the transmission of data to Laborie in the United States, the relevant Laborie entities have entered into standard contractual clauses according to Art. 46 para. 2 (c) GDPR, regarding appropriate safeguards for the protection of personal data.

Regarding the transmission of personal data, including health data, to supervisory authorities and/or government regulators in the United States insofar as mandatory for Laborie in order to comply with the relevant US legal obligations to which they may be subject, this may only take place on the condition of consent, per Art. 49 para. 1 (a) GDPR, together with the information that there is no equivalent level of data protection in the United States to that of the European Union, and that personal data may be further processed and transmitted by the receiving supervisory authorities and government regulators in a way which would not be possible under European data protection regulations.

12.3 Data Handling

A list of individuals will be maintained who are authorized to make any changes to the data. Data will be reviewed by the Sponsor (outside of monitoring personnel), and requests for clarification and/or corrections will be made through the monitor. Once the review is conducted, the database will be considered clean and ready for analysis. Missing values will remain missing, i.e. no attempt will be made to input missing values and only observed values will be used in data analysis and presentations. The data management plan will further describe data handling.

12.4 Case Report Form (CRF) & Source Documents

All study staff will be trained on the protocol requirements, CRF and questionnaire completion, and their training documented. It is the responsibility of the Investigator to maintain adequate

and accurate CRFs designed by Laborie to record all observations and other data pertinent to the clinical investigation. All CRFs and questionnaires should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Should a correction be made, the information to be modified must not be overwritten, but rather crossed out, corrected and initialled by the study staff member authorized to make entries and/or corrections to the CRFs. Source documents worksheets for recording data will be created as agreed upon by the sponsor or the site, as required. Data from the source documents should be entered into the CRF after each subject's visit.

To confirm the quality of the study, pseudonymized UDS data files will be requested by the sponsor for each subject. A unique subject code will be assigned to each subject based on the site number and sequential subject number (e.g. 101-001). The Investigator is responsible for maintaining subject identifying information strictly confidential, secure and inaccessible to unauthorized persons. CRFs will be treated as source data in the event that the original information is entered on the CRFs first (and no source document worksheet is utilized for that data point).

12.5 Record Retention

An Investigator or Sponsor shall maintain the records required by European Medicines Agency (EMA) during the investigation and for a period of 25 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes supporting a premarket approval application or a notice of completion of a product development protocol. The Investigator must maintain confidential all study documentation and take measures to prevent accidental or premature destruction of these documents. All essential documents from the Investigator will be kept in the Investigator binder. All sponsor essential documents will be kept in the study master file. If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

12.6 Performance Monitoring

Study Monitors will periodically check questionnaire data to ensure all fields are entered as complete as possible and inquire as to whether any usability issues are being encountered as the study progresses.

13 MONITORING, AUDITING, AND INSPECTING

13.1 Study Monitoring Plan

Laborie is responsible for developing a monitoring plan prior to study initiation, the monitoring plan will consist of a risk-based approach depending on monitoring needs for the clinical investigation.

The Investigator agrees to provide reliable data and all information requested by the Clinical Investigation Protocol (with the help of the CRFs, questionnaires or other appropriate

instrument) in an attributable, legible, complete, original, and accurate according to the instructions provided and to ensure direct access to source documents to Sponsor representatives. Any changes to the sourced data shall be traceable and not obscure the original entry.

The Sponsor of this Clinical Investigation is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Investigation Protocol as regards ethics, Clinical Investigation Protocol compliance, integrity and validity of the data recorded on the CRFs and questionnaires. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Investigation.

At regular intervals during the Clinical Investigation, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and subject compliance with Clinical Investigation Protocol requirements, and any emergent problems. The monitoring plan will describe the frequency, extent, and nature of monitoring.

During these monitoring visits, the following but not exhaustive list of points will be inspected with the Investigator: subject informed consent, subject recruitment and follow-up, Serious Adverse Event documentation and reporting, outcome events documentation and reporting, Investigational Product allocation, Investigational Product accountability, use and quality of data.

13.2 Auditing and Inspecting

For the purpose of ensuring compliance with the Clinical Investigation Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit inspection by applicable regulatory authorities.

The Investigator agrees to allow the official inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy and as such, will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the inspections, granting access to all necessary facilities, data, and documents to the designated inspectors.

As soon as the Investigator is notified of a future inspection by the authorities, the Investigator will inform and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified, and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor. The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14 DEVIATIONS

All departures from the approval protocol shall be documented by the Investigator. All deviations will be recorded on the subject CRF, and a deviation report will be sent to Laborie and the ethics board, as required. Timelines for notification will be subject to ethics board standard operation procedures. Deviation will be reviewed and signed off by the sponsor. If deviations are observed/reported that significantly affect or have the potential to significantly affect human subject protection or reliability of the investigation results, then Laborie will conduct a root cause analysis and implement appropriate corrective and preventative actions.

Serious deviations from the approved protocol are considered to be those which impact subject rights and safety, or data integrity and security. Serious or repeated protocol deviations on the part of the Investigator may be grounds for termination of the clinical investigation (see Section 6.7 above). The sponsor may also consider other corrective actions including protocol re-training, site visit, conference call or a formal warning letter.

Investigators may request prior written approval for a study deviation or change in study protocol. A protocol amendment may be required, and EC/regulatory authorities notified where applicable.

Deviations from the protocol to protect the rights, safety and well-being of subjects under emergency circumstances may proceed without prior approval from the sponsor, EC or regulatory authority. Such deviations shall be documented and reported to the sponsor and EC as soon as possible.

15 AMENDMENTS

If there are any changes to the protocol during the clinical study application process or during the length of the clinical study in progress, the protocol with amendments will be sent to the applicable EC and regulatory authorities for notification and review. If an amendment is made to the protocol during an ongoing study, the amended protocol will be sent to the applicable institution within the timelines required. The Investigator should not implement any deviation from or changes to the clinical protocol without prior written agreement by the Sponsor, and prior review and documented approval/favourable opinion from the EC and regulatory authorities (as applicable) of an amendment, except when necessary to eliminate an immediate hazard(s) to a clinical study subject. In some instances, an amendment may require a change to the ICF. The Investigator must receive an EC approval/favourable opinion concerning the revised ICF prior to implementation of the change.

16 STUDY ADMINSTRATION

16.1 Funding Source and Conflicts of Interest

Laborie will be the sponsor and the financial details are covered in the CTA.

16.2 Subject Stipends or Payments

If allowable under national and institutional policies, subjects can be offered a 40€ stipend for their participation in the study to offset the cost of parking and/or meals required during their clinic visit. This amount is subject to change pending ethics review, and if allowable, the final stipend amount will be indicated in the subject ICF.

The sponsor has covered this study by means of an insurance covering bodily injury or property damage arising out of the clinical investigation. The certificate of insurance evidencing the coverage, insurance company, policy number, and the sum insured are provided in the study file.

16.3 Committees

A Data Monitor Committee will not be utilized in this study based on the evaluation of the level of potential risks.

17 ETHICS AND REGULATORY APPROVAL

The clinical study will not begin until the appropriate approvals from the EC and regulatory authority have been obtained. Any additional requirements imposed by the EC and regulatory authority will be followed. This clinical study will be conducted in compliance with all international laws and regulations, and national laws and regulations of the countries in which the clinical investigation is performed, as well as any applicable guidelines. The investigation will be registered on eudract.ema.europa.eu and on www.clinicaltrials.gov publicly accessible databases.

18 PUBLICATION POLICY

The results of this clinical investigation may be submitted for peer-reviewed publication, regardless of positive or negative results. Publication rights and details are covered in the CTA.

19 RELATED STUDY DOCUMENTS

19.1 Informed Consent Documents

- ESNS-PH01-ICF-01 eSense Informed Consent Form

19.2 Case Report Forms

- ESNS-PH01-CRF-01 eSense UDS Visit Case Report Form
- ESNS-PH01-CRF-02 eSense Medical History Case Report Form
- ESNS-PH01-CRF-03 eSense Clinical User Questionnaire Case Report Form
- ESNS-PH01-CRF-04 eSense Subject Questionnaire Case Report Form
- ESNS-PH01-CRF-05 eSense Adverse Event Case Report Form
- ESNS-PH01-CRF-06 eSense Device Deficiency Case Report Form
- ESNS-PH01-CRF-07 eSense Follow-Up Case Report Form

19.3 Investigator Brochure

- ESNS-PH01-IB-01 eSense Investigator's Brochure

20 REFERENCES

1. Perez, L. M., & Webster, G. D. (1992). The history of urodynamics. *Neurourology and Urodynamics*, 11(1), 1–21. https://doi.org/10.1002/nau.1930110102

2. Abrams P. Urodynamics. Springer Science & Business Media; 2006. p.287

3. Winters, J. C., Dmochowski, R. R., Goldman, H. B., Herndon, C. D. A., Kobashi, K. C., Kraus, S. R., …Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. (2012). Urodynamic studies in adults: AUA/SUFU guideline. The Journal of Urology, 188(6 Suppl), 2464–2472. https://doi.org/10.1016/j.juro.2012.09.081

4. Chapple, C. R., MacDiarmid, S. A., & Patel, A. (2009). Urodynamics Made Easy. Elsevier Health Sciences

5. Curt A, Nitsche B, Rodic B, Schurch B & Dietz V. Assessment of autonomic dysreflexia in patients with spinal cord injury. Journal of Neurology, Neurosurgery, & Psychiatry 1997, 62:473-77.

6. Giannantoni A, Di Stasi SM, Scivoletto G, Mollo A, Silecchia A, Fuoco U & Vespasiani G. Autonomic dysreflexia during Urodynamics. Spinal Cord 1998; 36:756-60.

7. Abrams, P., Andersson K.E., Artibani W., Birder L., Bliss D., Brubaker L., Cardozo, L., Chapple, C., Cottenden, A., de Ridder D., Dmochowski R., Dumoulin C., Drake M., Fry C., Hanno P., Herschorn S., Kelleher C., Koelbl H., Khoury S., Madoff R., Maher C., Milsom I., Moore K.H., Moore K.N., Newman D., Nijman R., Rosier P., Staskin D., Thuroff J., Tubaro A., Vodusek D., Wein A. (2013) Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse and faecal incontinence Abrams P., Cardozo L., Khoury S., Wein A. (Eds.) Incontinence: 5th International Consultation on Incontinence, Paris, February 2012. (pp. 1904-1907). ICUD-EAU

8. Rosier P.F. The evidence for urodynamic investigation of patients with symptoms of urinary incontinence. F1000prime Rep. 2013;5:8. https://doi.org/10.12703/P5-8

9. Rosier PFWM, Schaefer W, Lose G, Goldman HB, Guralnick M, Eustice S, et al. International Continence Society Good Urodynamic Practices and Terms 2016: Urodynamics, uroflowmetry, cystometry, and pressure-flow study. *Neurourology and Urodynamics*. 2017 Jun;36(5):1243-1260.

10. Childs, John D., Sara R. Piva, and Julie M. Fritz. “Responsiveness of the Numeric Pain Rating Scale in Patients with Low Back Pain.” Spine 30, no. 11 (June 1, 2005): 1331–34. https://doi.org/10.1097/01.brs.0000164099.92112.29.

11. Jensen, M. P., and C. A. McFarland. “Increasing the Reliability and Validity of Pain Intensity Measurement in Chronic Pain Patients.” Pain 55, no. 2 (November 1993): 195–203.

12. Rodriguez, C. S. “Pain Measurement in the Elderly: A Review.” Pain Management Nursing: Official Journal of the American Society of Pain Management Nurses 2, no. 2 (June 2001): 38–46. https://doi.org/10.1053/jpmn.2001.23746.

13. Sullivan JG, Swithinbank L, Abrams P. Defining achievable standards in urodynamics—a prospective study of initial resting pressures. Neurourol Urodyn. 2012 Apr 1;31(4):535–40.

14. Gammie, A., Abrams, P., Bevan, W., Ellis-Jones, J., Gray, J., Hassine, A., … Hashim, H. (2015). Simultaneous in vivo comparison of water-filled and air-filled pressure measurement catheters: Implications for good urodynamic practice. *Neurourology and Urodynamics*, n/a-n/a. https://doi.org/10.1002/nau.22827

15. Fleiss, J.L., Levin, B., & Cho Paik, M. *(2003). Statistical Methods for Rates and Proportions* (3rd ed.). New York, NY: Wiley

16. Liao L., Kirschner-Hermanns R., and Schaefer W. (1999) Urodynamic quality control: quantitative plausibility control with typical value ranges. *Neurourology and Urodynamics 18(abstract 99a):365-366.*

17. Hashim H, Thomas L, Gammie A, Farullo G, Finazzi-Agrò E. Good urodynamic practice adaptations during the COVID-19 pandemic. *Neurourology and Urodynamics*. 2020;39:1897–1901.https://doi.org/10.1002/nau.24441