TITLE OF STUDY:
Sexual and vaginal health in breast cancer women receiving aromatase inhibitors before and after CO2 laser therapy: a randomized, double-blind, sham-controlled trial.

NCT number: Not yet assigned

Document date: 24th August 2020

GLOSSARY:

BCS: Breast cancer survivors
AI: Aromatase inhibitors
GSM: Genitourinary syndrome of menopause
PLISSIT Model: Permission, Limited information, Specific suggestions, intensive therapy
FSFI: Female sexual function index
VAS: Visual analogue scale
S-BIS: Spanish- Body image scale
SF-12: Short form-12 healthy survey
AEs: Adverse events
SAEs: Serious adverse events

SUMMARY (max 300 words):

Please summarise the background, aims, methods and expected impact in simple terms

Background: Vulvovaginal health, directly linked to sexual health, is a key factor for female pleasure. BCS receiving AI are likely to present severe GSM and sexual complaints. Innovative options, as vaginal laser therapy, are emerging to treat GSM and sexual dysfunctions. Nowadays, data in BCS is scarce, moreover, few studies included patients receiving AI [16]. Different meta-analysis [17-23] found GSM [24, 25] and sexual function [9, 10] may improve significantly at short-term, however, the body of evidence is of low quality. Therefore, before recommendation of laser therapy for sexual complaints in BCS with GSM, there are unmet needs to be solved: efficacy and safety at long-term, biases related to patients' expectations and a detailed assessment of the complex underpinnings of sexuality.
Aims: To evaluate sexual and vaginal health in BCS receiving AI with GSM, before and after CO2 laser therapy compared to a sham-controlled group.
Methods: Prospective, randomized, double-blind controlled study with two parallel study arms: 1) Fractional CO2 laser therapy (5monthly sessions). 2) Sham laser therapy (5monthly sessions). After end-treatment, patients are followed up at 1 month and 6 months. BCS treated or undergoing AI with GSM and sexual function impairment, will be suitable. All patients will maintain first-line non-hormonal treatment and sexual assessment (PLISSIT Model) according with usual care. The primary outcome is improvement in sexual function (FSFI total score). As secondary outcomes: resumption sexual activity, sexual activity frequency, dyspareunia (VAS), female sexual dysfunction, sexual dimensions (FSFI), body image (S-BIS), quality of life (SF-12), vaginal pH acidification, maturation index and Vaginal Health Index of Gloria Backmann, adverse events, satisfaction (Likert scale) and adherence to treatment.
Expected impact: Emergent, non-invasive, laser therapy has significant benefit for BCS with AI, improving subjective and objective sexual and vaginal health outcomes and adding value to the usual care multidisciplinary approach.

BACKGROUND (max 500 words)**:**

Sexuality is a central aspect of being human throughout life encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction [1]. Most of these aspects may be affected in breast cancer survivors (BCS). In a recent meta-analysis [2, 3] focused on sexual function through Female Sexual Function Index (FSFI) among BCS, female sexual dysfunction prevalence was 73,4% (95 % CI 64–82.8 %, I2 = 96.8 %) and mean FSFI 19.28 (95 % CI 17.39–21.16, I2 = 97.6 %). Several modifiable risk factors for sexual dysfunction in BCS may be optimum targets for intervention: amelioration of vaginal discomfort and urinary incontinence, the benefits of breast conserving surgery on body image or the evaluation of relationship quality [4, 5] Due to the multifaceted nature of the factors affecting sexuality in BCS, most authors [3-10] encouraged the need for comprehensive assessment and for a multidisciplinary approach.

BC diagnosis and/or its treatments (surgery, chemoradiotherapy, hormonal therapy) may altered sexual health. Vulvovaginal health, directly linked to sexual health, is a key factor for female pleasure. Genitourinary syndrome of menopause (GSM) is caused by decline in estrogen at menopause, which may also appear or worsen after systemic cancer treatments as aromatase inhibitors (AI). GSM is associated with sexual symptoms (lack of lubrication, discomfort or pain, impaired function), genital symptoms (dryness, burning, irritation) and urinary symptoms (urgency, dysuria, recurrent urinary tract infections). BCS receiving AI are one of the groups most likely to present severe GSM and sexual complaints [11]. A cross-sectional study [12] on 129 BCS during the first 2 years of adjuvant AI therapy, found 3 out of 4 women were distressed about their sexual problems. Only 52% of women had been sexually active when endocrine therapy began, but 79% of that group developed new sexual problems.

The first line of treatment for GSM is non-hormonal therapy (regular sexual activity, moisturizers-lubricants, pelvic-floor relaxation techniques, dilators) although in many women these options will not adequately control symptoms. Hormonal therapies must be used with caution in women with estrogen-dependent cancers [13-15]. So, alternative options are emerging for this subset of patients, such as vaginal laser therapy. Different studies [16-18] provided short-term data on non-cancer patients that showed laser therapy was feasible, safe and improved objective and subjective GSM. Data regarding sexuality derived from secondary endpoints and suggested that laser therapy may improve sexual function, mainly decreasing sexual pain [16, 18]. To date, data on laser therapy in BCS is scarce, moreover, few studies included patients receiving ongoing AI [19]. The CO2 laser was the most frequently used device. Different reviews and meta-analysis [20-26] found GSM [27, 28] and sexual function [9, 10] may improve significantly at short-term, however, the body of evidence is of low quality. Therefore, before recommendation for the use of laser therapy for sexual complaints in BCS with GSM, there are unmet needs to be solved as efficacy and safety at long-term, biases related to patients' expectations of therapy and a detailed assessment of the complex underpinnings of sexuality.

AIMS (max 200 words)**:**

To answer the unmet needs previously mentioned, the aim of the current study is to verify the outcomes of sexual and vaginal health in breast cancer women receiving AI, who were experiencing symptoms of GSM, before and after CO2 laser therapy compared to a sham-controlled group.

Specifically, we will compare the following subjective and objective measurements of sexual and vaginal health:

MAIN GOAL: Report an improvement in sexuality:
- Primary outcome: sexual function (FSFI total score)

- Secondary sexual outcomes: resumption sexual activity (sexually active vs non-sexually active), sexual activity frequency (nº sexual activity/week), dyspareunia (VAS), female sexual dysfunction (VAS sexual life distress), sexual dimensions: desire, arousal, lubrication, orgasm, satisfaction and pain (FSFI) and body image (S-BIS)

OTHER OBJECTIVES: Report an improvement on GSM symptoms (efficacy) and quality of life, feasibility and safety of laser therapy in BCS:
- Secondary non-sexual outcomes: quality of life (SF-12). Verify an acidification of the vaginal pH, an improvement in the maturation index and an improvement in the Gloria Backmann Index: Vaginal Health Index. To evaluate toxicity associated with vaginal laser therapy in this population (AEs and SAEs). To determine how many women with the defined patient eligibility will complete all treatments.

METHODS (max 500 words):

DESIGN: Prospective, randomized, double-blind controlled study with two parallel study arms: ARM I: Patients undergo fractional CO2 laser therapy at 5 times points 30 days apart. ARM II: Patients undergo sham laser therapy at 5 time points 30 days apart. After completion of the treatment, patients are followed up at 1 month and 6 months.

RANDOMIZATION PROCESS: A randomization list will be generated in multiple blocks of 2 and 1: 1 ratio with STATA version 15.1 or higher.

STUDY SUBJECTS: Patients treated or undergoing AI for BC in the Breast Cancer Unit of the Hospital Clínic and who present symptoms related to GSM that condition their sexual function and quality of life, despite receiving first-line non-hormonal treatment: regular sexual activity (such as mutual and self-touch masturbation, manual or vibrator stimulation, oral sex, sexual intercourse, massage and other forms of physical intimacy), moisturizers, lubricants, pelvic-floor relaxation techniques and/or dilators. Inclusion and exclusion criteria are summarized in Table 1.

STUDY GROUPS: All patients will receive instructions to maintain first-line non-hormonal treatment, as well as sexual assessment using the PLISSIT Model according with usual care in our hospital.
The study group will be treated with a vaginal fractionated CO2 laser protocol (The SMARTXIDE TOUCH (Deka) equipment with an autoclavable vaginal probe following the manufacturer's protocol (Annex 9).
The control group will receive treatment with a sham-CO2 laser using a double-blinded protocol.

STUDY STRUCTURE (See Annex 1).

SAMPLE CALCULATION
Considering FSFI score as the main variable of the study, we performed a calculation of the hypothesis contrast study sample with the comparison of two independent means. Accepting an alpha risk of 0.05 and a beta risk of less than 0.1 in a bilateral contrast, 44 subjects in the first group and 44 in the second. The common standard deviation is assumed to be 1. A follow-up loss rate of 15% has been estimated.

STATISTIC ANALYSIS
Descriptive statistics will be used according to standard calculation methods.

The comparison between the two treatments at the end of the study will be evaluated through the change with the baseline using a mixed repeated measures model (MMRM) adjusted for the baseline value and including the treatment and the time in the model.
The variables of repetitive evaluation over time are analyzed according to the following strategy: (a) continuous variables with a repeated measures mixed longitudinal model (MMRM); (b) binary or non-normal variables with marginal models (Generalized Estimating Equation: GEE). Other variables will be studied as follows: Fisher's exact test for categorical variables, Student's t test for continuous variables between 2 groups. Non-parametric methods for independent data (Mann-Whitney U for 2 groups or Kruskall-Wallis test for more than 2 groups) will be used if necessary. The level of statistical significance will be 5% bilateral. The main analysis will be by Intention to Treat (ITT).

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IMPACT (max 300 words):

What would be the impact of the project on sexual medicine field when it is successfully completed? Please explain how your project fits to the specific call

The BCS receiving AI are at higher risk of developing GSM symptoms. Sexual issues are common, either secondary to painful sex or as a direct effect of estrogen deprivation in the brain. However,

addressing sexual health issues in BCS still meets several barriers from both, patient and health care professionals. GSM symptoms do not put survival at risk, however, have a significant impact in the quality of life [26].

The first-line treatment for GSM symptoms should be non-hormonal therapies according clinical guidelines, although frequently it will be insufficient to alleviate symptoms. Hormonal therapies are not currently recommended and must be used with caution in BCS [13-15]. So, energy-based treatments have emerged as a promising option in this subgroup of patients. However, the body of evidence is lacking to make decisive recommendations [18], specially to treat sexual complaints. There is an urgent need to carry out RCT with larger sample size, long-term follow-up and blinded control group for answer various unmet needs in this field: short/mid and long-term safety issues and efficacy, treatment modalities (type of laser) and protocols (laser parameters, sessions numbers, repetitions).

This project aims to demonstrate that emergent, non-invasive, non-anesthetic laser therapy has significant benefit for BCS with AI, measured in a prospective, randomized, double-blind controlled trial using validated tools for subjective and objective sexual and vaginal health outcomes and quality of life.

Moreover, sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality which requires the possibility of having pleasurable and safe sexual experiences [1]. So, both arms of study groups will benefit from multidisciplinary approach including non-hormonal therapies (regular sexual activity, moisturizers, lubricants, pelvic floor relaxation techniques and/or dilators) and sexual assessment using the PLISSIT Model according with usual care in our hospital and with international recommendations [7, 8, 18].

ETHICAL AND REGULATORY PERMISSIONS:

Please explain the ethical and regulatory permissions already obtained or to be obtained for (if applicable):

1) *Animal research*
2) *Human tissue*
3) *Research with human participants*

If the permissions have not been obtained already, please give timelines of when they are expected to be obtained and how obtaining such permissions will affect the overall project timelines.

This study will be conducted according to the Helsinki Declaration and to Good Practice Guidelines. Approval from Ethics Committee of Hospital Clínic de Barcelona has been recently applied (August 2020) and the study will be registered on ClinicalTrials.gov. As we are on holiday time in Spain (August) and also due to the current COVID-19 situation in Barcelona, a delay in the usual approval rhythm of our ethical committee is expected. However, we hope to obtained such a permission on October 2020, which will not affect the overall project timelines.

All eligible women will be informed about the study by briefing the participants on the study objectives and taking into account their willingness to participate (telematic visit). After an interval of at least 48h the patient will have a second visit (presential) and if she wants to participate the signed informed consent form will be checked. Both in- and exclusion criteria will be reviewed and if found suitable, the patient will be randomized. Both the patient information letter and informed consent form are attached as a separate document. Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from

the study for urgent medical reasons. Patients who withdrew their informed consent will not be replaced. We will replace patients that are randomized by mistake, for example because of technical errors with online randomization. Patients withdrawn from the intervention but not from informed consent will be followed up.

None of the subjects will receive any (financial) compensation for participating in this trial. However, to minimize dropouts and build patient loyalty, we will offer them at the end of the study an additional laser treatment session, and those in the placebo group will be offered the 5 treatment sessions.

BUDGET:

Please give a detailed and itemized budget, see T&C for eligible and ineligible costs

Execution Expenses
A) Personnel costs

A postgraduate research student (Dr. Mension) will be hired 15h/week during 18months in order to perform task described in the Workplan. In addition, will be in charge of:
- Transcription of data to database.
- Management and coordination of patient appointments, as well as evaluation and resolution of problems derived from the study.
- Evaluation of results.
- Writing of manuscript.

B) Acquisition of materials and contracting of services

PH meter paper roll 5m x 2 IU x 10 = € 20
Maturation index (provided by Hospital Clinic de Barcelona): 12€ x 264 (88 patients throughout the study in 3 timepoints) = 3168€
Kit Silicone vaginal dilator (ref 69-4805-05-3) 44 units x 34,95 € (50% patients of the study) = 1537,8€
Vaginal vibrator (ref. 729232) x 88 units x € 8.95 =787,6€
Vaginal lubricant tube 100 mL x 616 IU x € 3,5 (for 88 patients throughout the study) = 2156€
Moisturizer hyaluronic acid-based ovules (Cerviron®) provided free of charge by Interpharm (for 88 patients throughout the study) = 0€
CO2 laser equipment: The SMARTXIDE TOUCH provided free of charge by DEKA = 0€
Tablet:
Smartphone and phone line (18 months - study phone contact):

C) Travel Expenses
Dissemination of the results of the study of national / international conferences 1500€

COST CATEGORY	COST
1. Personnel	**20.830,6 €**
2. Consumables and services	**7669,4 €**
3. Travel expenses	**1.500 €**
TOTAL	**30.000**

SCHEDULE:

	0-1	2-3	4	5	6	7	8	9	10	11-14	15	16	17	18
Database design														
Recruitment														
Baseline visit														
Treatment														
Follow-up visits														
Cytology														
Questionnaires														
Analysis results														
Manuscript edition														

ATTACHMENTS:
Please attach:
CV of the PI including list of all peer reviewed publications
Copies of ethics and regulatory permissions
Any figures or tables

Table 1: inclusion and exclusion criteria

Inclusion Criteria	
	BC treated with aromatase inhibitors ± GnRH analogues (aGnRH)
	Menopause (natural or induced) and signs / symptoms of GSM; Vaginal pH ≥5
	Negative Human Papillomavirus (HPV) cytology and / or determination
	Intention or willingness to have sex
	Signed informed consent
Exclusion criteria	
	Vaginal hormonal treatment in the last 6 months
	Vaginal moisturizers and / or lubricants during the 30 days prior to study treatment
	Laser treatment, radiofrequency, hyaluronic acid, lipofilling in the vagina during the last 2 years
	Ospemifene treatment
	Being affected for: active infection of the genital tract; intraepithelial neoplasm of cervix, vagina, or vulva; have or have been treated for genital cancer; Genital prolapse stage ≥II.

ANNEXED:

Annex 1: STUDY STRUCTURE (Table 2):
A) Screening/Recruitment telematic visit (T-2): to select elegible patients and to deliver information sheet and explanation of the project.
B) Screening/Recruitment presential visit (T-1): to perform physical examination and sexual assessment, to confirm elegibility and to sign informed consent.
C) Baseline presential Visit (T0): to fill in baseline questionnaires and to assess sexuality using PLISSIT Model according usual care in our hospital.
D) Treatment visits: T1 (session 1), T2 (session 2), T3 (session 3), T4 (session 4), T5 (session 5): to perform the intervention according previous description.
E) Follow-up visits: T6 (1 month after session 5), T12 (7 months after session 5): to perform physical examination and fill in questionnaires at short and mid-term. Out of timeline project, a visit T24 (13 months after session 5) is planned as usual care practice in our hospital to assess outcomes at long-term follow-up (also approved by our Ethical Committee).

Table 2. Study structure

Endpoint	Instrument	T-2	T-1	T0	T1-T5	T6	T12
Inclusion/exclusion criteria	Checklist database	X					
Trial information	Delivery Written and verbal information	X					
	Signature Informed consent		X				
Baseline characteristics	General Anamnesis	X					
	BC Anamnesis	X					
	Sexual Anamnesis			X			
	Socio-demographic data	X					
Physical examination	Gynaecological examination		X			X	X
	VHI of Gloria Bachmann *[1]		X			X	X
	Vaginal pH *[2]		X			X	X
	Maturation index *[3]		X			X	X
	(vaginal cytology)						
	Liquid cytology		X			X	X
	(reflex HPV determination)						
	Pelvic floor muscle function			X		X	X
GSM symptoms	VAS dispareunia *[4]			X		X	X
	VAS dryness *[4]			X		X	X
	VAS burning *[4]			X		X	X
	ICIQ-IU-SF + CACV			X		X	X
Sexual symptoms	FSFI total score *[5]			X		X	X
	VAS sexual life distress *[4]			X		X	X
Body image	S-BIS *[6]			X		X	X
Generic quality of life	SF-12 *[7]			X		X	X
Intervention	Laser vs sham				X		
Adherence to treatment	Adherence diary				X		
Adverse events	Database/ AEs form				X	X	X
Treatment satisfaction	Likert scale					X	X

*[1]Evaluation of the Vaginal Health Index of Gloria Bachmann: An exploration of the lower genital tract will be carried out and the degree of AVV will be assessed through

(https://www.maturitas.org/article/0378-5122(95)00956-6 / pdf). This index subjectively assesses the vagina's staticity, the amount of discharge, the integrity of the epithelium and humidity, along with pH as the only objective criterion. A score of ≤ 15 indicates AVV. It is the Index most used in publications reporting improvement of AVV with the use of lasers.

*[2]Vaginal vaginal pH: Using a pH test strip, colorimetric analysis of the pH of the vaginal discharge is performed.

*[3]Maturative Index: Using vaginal cytology, the percentage of parabasal, intermediate and superficial cells is calculated, allowing us to calculate the epithelial thickness indirectly.

*[4] Visual Analog Scale (VAS): Evaluates 3 symptoms of AVV: dyspareunia, dryness and burning. Score from 0 to 10 (unbearable symptom). Symptoms are considered moderate from ≥ 4.

*[5] Female Sexual Function Index (FSFI): Generic sexual questionnaire validated for cancer survivors. We used the 19-item self-reported Spanish validated questionnaire to assess 6 sexual dimensions (desire, arousal, lubrication, orgasm, satisfaction and pain) and the global sexual function. Score ranges from 1,6 to 36, with the higher score indicating a better sexual
Function. Function. A cut-off value of ≤ 26.55 indicates risk of sexual dysfunction, however, it could inflate female sexual dysfunction rates in those women whose sexual activity frequency is lower than once a month or in non-sexually active women. (https://scielo.conicyt.cl/pdf/rchog/v69n2/art06.pdf)

*[6] Body Image Scale-Spanish version (S-BIS): Assesses 10 domains of body image in 10 questions and is applicable in patients with any type of cancer and different therapeutic regimens. The total score ranges from 0 to 30. The higher the score, the greater the concern regarding body image. (https://www.ncbi.nlm.nih.gov/pubmed/25135839).

*[7] Quality of life Short Form 12 (SF-12): It consists of 12 items from the 8 dimensions of the SF-36 Physical Function (2), Social Function (1), Physical Role (2), Emotional Role (2), Mental health (2), Vitality (1), Body pain (1), General Health (1). (http://www.ser.es/wp-content/uploads/2015/03/SF12_CUESTIONARIO.pdf)

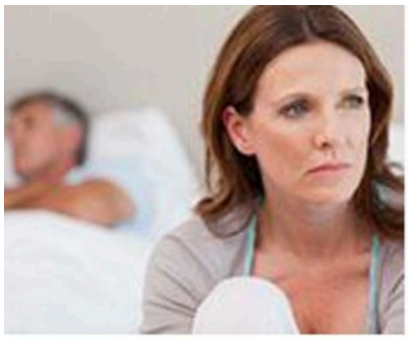
Annex 2: Vaginal Health Index of Gloria Bachmann

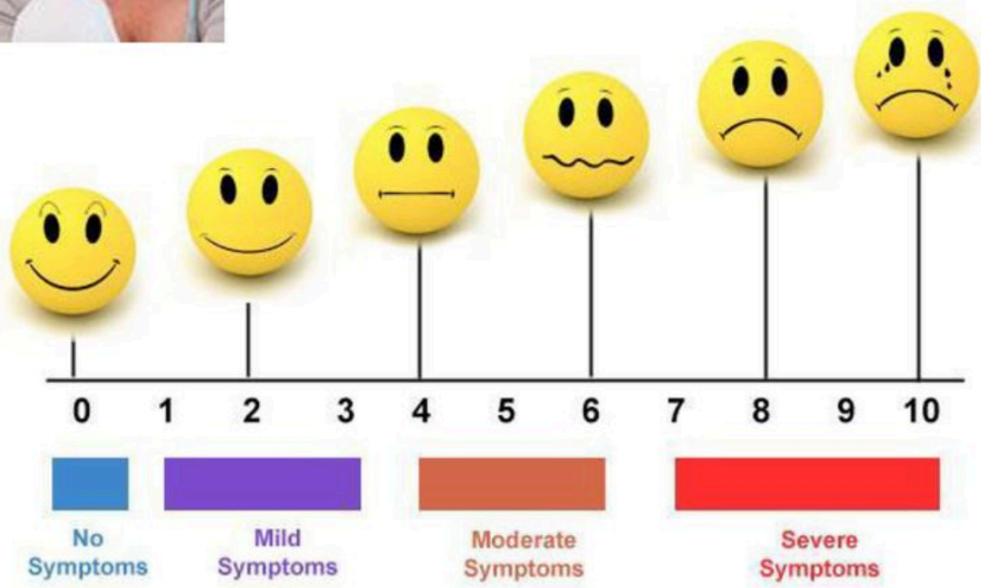
VVA: Severity classification / assessment
Vaginal Health Index (Gloria Bachmann)

Score	1	2	3	4	5
Elasticity	none	poor	fair	good	excellent
Fluid Volume (Pooling of Secretion)	none	Scant amount, vault not entirely covered	superficial amount, vault entirely covered	moderate amount of dryness (small areas of dryness on cotton tip applicator)	normal amount (fully saturates on cotton tip applicator)
pH	≥ 6.1	5.6 - 6.0	5.1 - 5.5	4.7 - 5.0	≤ 4.6
Epithelial Integrity	petechiae noted before contact	bleeds with light contact	bleeds with scraping	not friable – thin epithelium	normal
Moisture (Coating)	none, surface inflamed	none, surface not inflamed	minimal	moderate	normal

Table 1: Gloria Bachman Vaginal Health Index (VHI).

Annex 3: VAS




0
1
2
3
4
5
6
7
8
9
10
No Symptoms
Mild Symptoms
Moderate Symptoms
Severe Symptoms

Annex 4: FSFI

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   - ☐ Very high
   - ☐ High
   - ☐ Moderate
   - ☐ Low
   - ☐ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Very high
   - ☐ High
   - ☐ Moderate
   - ☐ Low
   - ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Very high confidence
   - ☐ High confidence
   - ☐ Moderate confidence
   - ☐ Low confidence
   - ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

Annex 5: S-BIS

BIS/BAS

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

1. A person's family is the most important thing in life.
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness.
3. I go out of my way to get things I want.
4. When I'm doing well at something I love to keep at it.
5. I'm always willing to try something new if I think it will be fun.
6. How I dress is important to me.
7. When I get something I want, I feel excited and energized.
8. Criticism or scolding hurts me quite a bit.
9. When I want something I usually go all-out to get it.
10. I will often do things for no other reason than that they might be fun.

11. It's hard for me to find the time to do things such as get a haircut.
12. If I see a chance to get something I want I move on it right away.
13. I feel pretty worried or upset when I think or know somebody is angry at me.
14. When I see an opportunity for something I like I get excited right away.
15. I often act on the spur of the moment.
16. If I think something unpleasant is going to happen I usually get pretty "worked up."
17. I often wonder why people act the way they do.
18. When good things happen to me, it affects me strongly.
19. I feel worried when I think I have done poorly at something important.
20. I crave excitement and new sensations.

21. When I go after something I use a "no holds barred" approach.
22. I have very few fears compared to my friends.
23. It would excite me to win a contest.
24. I worry about making mistakes.

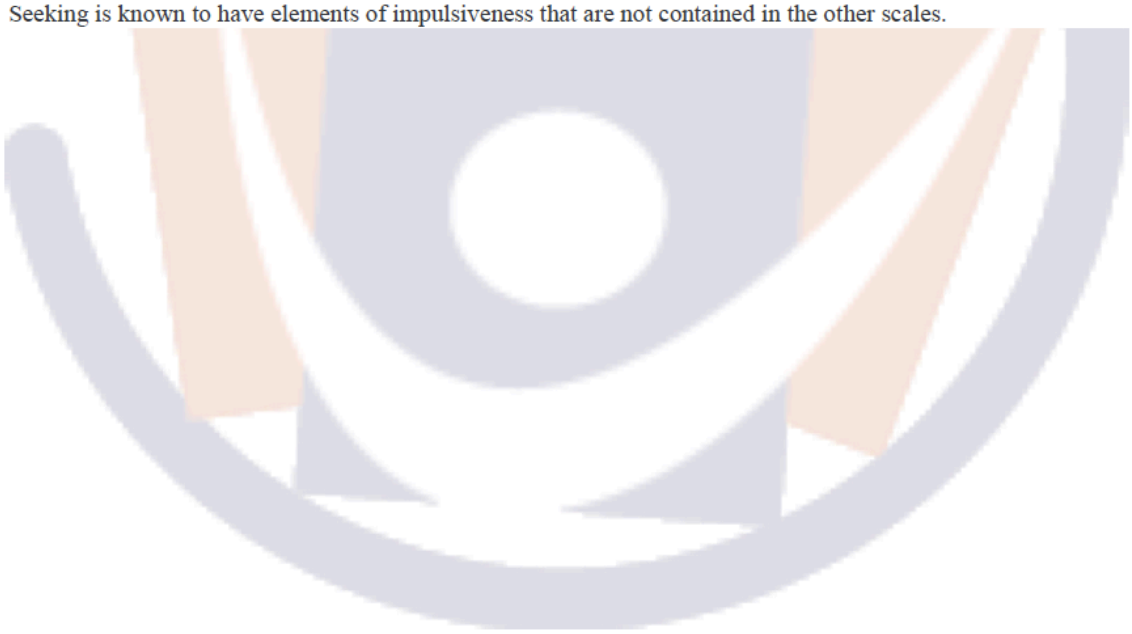
Items other than 2 and 22 are reverse-scored.

BAS Drive: 3, 9, 12, 21
BAS Fun Seeking: 5, 10, 15, 20
BAS Reward Responsiveness: 4, 7, 14, 18, 23

BIS: 2, 8, 13, 16, 19, 22, 24

Items 1, 6, 11, 17, are fillers.

The fact that there are three BAS-related scales and only one BIS-related scales was not planned or theoretically motivated. The factors emerged empirically, from an item set that was intended to capture diverse manifestations of the BAS, according to various theoretical statements. It is likely that a broader sampling of items on the BIS side would also have resulted in more than one scale. I do not encourage combining the BAS scales, however, because they do turn out to focus on different aspects of incentive sensitivity. In particular, Fun Seeking is known to have elements of impulsiveness that are not contained in the other scales.



Annex 6: SF-12

SF-12 Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. **Answer each question by choosing just one answer**. If you are unsure how to answer a question, please give the best answer you can.

1. **In general, would you say your health is**:

☐1 Excellent ☐2 Very good ☐3 Good ☐4 Fair ☐5 Poor

The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	YES, limited a lot	**YES, limited a little**	**NO, not limited at all**
2. **Moderate activities** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	☐1	☐2	☐3
3. Climbing **several** flights of stairs.	☐1	☐2	☐3

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	YES	**NO**
4. **Accomplished less** than you would like.	☐1	☐2
5. Were limited in the **kind** of work or other activities.	☐1	☐2

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	YES	**NO**
6. **Accomplished less** than you would like.	☐1	☐2
7. Did work or activities **less carefully than usual**.	☐1	☐2

8. **During the <u>past 4 weeks</u>, how much <u>did pain interfere</u> with your normal work (including work outside the home and housework)?**

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

These questions are about how you have been feeling during the <u>past 4 weeks</u>.
For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm & peaceful?	☐1	☐2	☐3	☐4	☐5	☐6
10. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5	☐6
11. Have you felt down-hearted and blue?	☐1	☐2	☐3	☐4	☐5	☐6

12. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?**

☐1 All of the time ☐2 Most of the time ☐3 Some of the time ☐4 A little of the time ☐5 None of the time

Patient name: Date: PCS: MCS:

Visit type (circle one)
Preop 6 week 3 month 6 month 12 month 24 month Other:_____

Annex 7: Adherence diary

	MONDAY				TUESDAY				WEDNESDAY				THURSDAY				FRIDAY				SATURDAY				SUNDAY			
WEEK	M		L		M		L		M		L		M		L		M		L		M		L		M		L	
1																												
2																												
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20																												

- Mark with an "X" in the corresponding box if you have completed the treatment as indicated by your health care professional: M (moisturizer) and/or L (lubricant).
- If you used some other therapies as D (dilator) or V (vibrator), please fill in.

Annex 8: Laser protocol

The laser parameters will be as follows:
(1) Power: 30 W.
(2) Dwell time: 1000 ls.
(3) Spacing: 1000 lm.
(4) Depth: SmartStak parameter from 1 to 3 depending on the treatment status.
(5) D-pulse mode.
(6) At the introitus the power will be reduced to 24 W.

Annex 9: AEs form

Adverse Event	
Has the patient experienced any Adverse Event between this visit and the previous visit?	O Yes O No *If "Yes", please fill in the Adverse Event Page for each Adverse Event.*

(Serious) Adverse Events

Patient Identification Number[1]: |__|__|__|__|__| **Date of birth (dd mm yyyy: |__|__|__|__|__|_|__|__|**

ADVERSE EVENTS*

Description *(diagnosis (if known) or sign/symptoms)*	**Start date** **End date (if applicable)**	**Severity**	**Relation to study device**	**Action study treatment**	**Other action taken**
…… ……. …… ……. …… …….	**Start** |__|__| - |__|__|__| - |__|__|__|__| |__|__|:|__|__| *d d - m m m - y y y y h h : m m* **End** |__|__| - |__|__|__| - |__|__|__|__| |__|__|:|__|__| *d d - m m m - y y y y h h : m m* *OR* O if ongoing	O mild O moderate O severe	O Definitely not Device-related O Remotely Device-related O Possibly Device-related O Probably Device-related O Definitely Device-related O unassessable	O none O temporary stop O permanent stop O modification, specify : …… …… O unknown O not applicable[6]	O none O comedication: *please fill out comedication page* O (prolongation of) hospitalisation O other, specify: …… …… O unknown O not applicable

Outcome	**Serious Adverse Event?** *(check one or more of the boxes below)*	
O recovered/resolved O not recovered/resolved If stabilized, specify date: |__|__|-|__|__|__|-|__|__|__|__| *d d - m m m - y y y y* O recovering/resolving O recovered/resolved with sequelae O fatal, date of death: |__|__|-|__|__|__|-|__|__|__|__| *d d - m m m - y y y y* O unknown	O Yes, specify: …… …… …… …… O No	☐ results in death ☐ life threatening ☐ (prolonged) hospitalisation ☐ persistent or significant disability/ incapacity ☐ congenital anomaly/ birth defect ☐ other medically important serious event: ……..

**: The study period during which adverse events must be reported is normally defined as the period from the time of signed informed consent to the end of the study treatment follow-up.*

#: Any event meeting the definition of "serious" requires notification.

Annex 10: Likert scale

Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
1	2	3	4	5

Annex 11: ICIQ-IU-SF

Appendix. International Consultation on Incontinence Questionnaire for Urinary Incontinence Short Form

Initial number

ICIQ-UI Short Form

CONFIDENTIAL

DAY MONTH YEAR

Today's date

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1 Please write in your date of birth: DAY MONTH YEAR

2 Are you *(tick one)*: Female ☐ Male ☐

3 How often do you leak urine? *(Tick one box)*

never ☐	0
about once a week or less often ☐	1
two or three times a week ☐	2
about once a day ☐	3
several times a day ☐	4
all the time ☐	5

4 We would like to know how much urine <u>you think</u> leaks.
How much urine do you <u>usually</u> leak (whether you wear protection or not)?
(Tick one box)

none ☐	0
a small amount ☐	2
a moderate amount ☐	4
a large amount ☐	6

5 Overall, how much does leaking urine interfere with your everyday life?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

ICIQ score: sum scores 3+4+5 ☐☐

6 When does urine leak? *(Please tick all that apply to you)*

never – urine does not leak ☐
leaks before you can get to the toilet ☐
leaks when you cough or sneeze ☐
leaks when you are asleep ☐
leaks when you are physically active/exercising ☐
leaks when you have finished urinating and are dressed ☐
leaks for no obvious reason ☐
leaks all the time ☐

Thank you very much for answering these questions.

Annex 12: CACV

BLADDER CONTROL SELF-ASSESSMENT QUESTIONNAIRE

ARE YOU: MALE ☐ FEMALE ☐

Please put the NUMBER that applies to you in the boxes shown by the arrows based on the following:

NOT AT ALL = 0 A LITTLE = 1 MODERATELY = 2 A GREAT DEAL = 3

SYMPTOMS	BOTHER
☐ ← Is it difficult to hold urine when you get the urge to go?	
+	How much does it bother you? → ☐
☐ ← Do you have a problem with going to the toilet too often during the day?	+
+	How much does it bother you? → ☐
☐ ← Do you have to wake from sleep at night to pass urine?	+
+	How much does it bother you? → ☐
☐ ← Do you leak urine?	+
=	How much does it bother you? → ☐
	=
☐ NOW ADD THE TWO COLUMNS DOWNWARDS AND PUT THE SCORES IN THESE BOXES	☐
My symptom score ↘	My 'bother' score ↙

SYMPTOM SCORE	THIS SYMPTOM SCORE MEANS:	THIS 'BOTHER' SCORE MEANS:	'BOTHER' SCORE
0	You are fortunate and don't have a urinary problem	You aren't bothered by a urinary problem	0
1-3	Your symptoms are mild	You are bothered slightly by your symptoms	1-3
4-6	You have moderate symptoms	You are moderately bothered by your symptoms	4-6
7-9	You have significant symptoms	Your symptoms are of significant bother for you	7-9
10-12	You have very significant problems	Your symptoms are a major problem for you	10-12

If your symptom score (above) is 4 or over you should seek help.

If your bother score (above) is 1 or over you may benefit by seeking help

IMPORTANT – if you have blood in your urine, have difficulty passing urine, or pain on passing urine, you MUST talk to your doctor about it.