Imperial College Healthcare NHS Trust

STUDY PROTOCOL

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Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

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This protocol describes the **"**Physiological study to determine the role of the melanocortin-4 receptor in brain activity in women with hypoactive sexual desire disorder. It provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Principal Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

1. INTRODUCTION

This study will be conducted according to International Council for Harmonisation Good Clinical Practice (GCP) guidelines, Declaration of Helskinki and local institutional research policies and procedures.

1.1. Background

1.1.1 Hypoactive Sexual Desire Disorder

Abnormalities of female sexual function are common. In the US, approximately 43% of adult women experience some form of sexual difficulty, with approximately 12% of these women reporting being distressed by their sexual dysfunction (Laumann 1999, Shifren 2008). Women may experience difficulties with sexual desire, arousal, or achieving orgasm, as well as dyspareunia (pain during intercourse). These disorders are commonly and broadly characterised as female sexual dysfunction (FSD).

Abnormalities of female sexual desire or arousal, occurring as an acquired condition reflecting loss of prior function not associated with depression, relationship dysfunction, or other identifiable causes, and accompanied by distress, have been characterised as hypoactive sexual desire disorder (HSDD) or female sexual arousal disorder (FSAD), respectively. This classification is used in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM IV TR) of the American Psychiatric Association (APA 2000). HSDD is the most common type of FSD.

1.1.2 Consequences of Hypoactive Sexual Desire Disorder

HSDD can be devastating to premenopausal women and significantly impacts the quality of the relationships with their partners. HSDD is not only a women's health concern, but also a couple's problem. The loss of a fulfilling sex life causes women to suffer with stress, anxiety, sadness, and fears of abandonment, i.e., that their partners might become unfaithful or might want a divorce. Some feel angry, worthless, inadequate, like a "bad wife", and experience a loss of self-esteem and self-confidence. Many women describe how losing physical closeness and intimacy causes loss of emotional closeness and distances partners from each other, causing tension and mistrust in the relationship. These themes are consistent with those expressed at public meetings (e.g. Voice of the patient 2014).

1.1.3 Treatment of Hypoactive Sexual Desire Disorder

The female sexual response cycle is dependent on physiological, psychological, and social factors. Sexual therapy and education presently form the basis of treatment for HSDD and/or FSAD, with limited pharmacologic treatment options. While a few pharmacologic agents (e.g. testosterone and bupropion) have been or are being evaluated for the management of HSDD, there is only one approved treatment to date, Addyi® (flibanserin), but it is not licensed in the UK.

Although transdermal testosterone (Intrinsa®) is able to restore testosterone levels to a normal range and improve sexual function in surgically postmenopausal women receiving estrogen replacement therapy, concerns around the safety associated with chronic use in this population prevented its approval (FDA Intrinsa Advisory Committee 2004; Spark 2005, Moynihan 2004). While flibanserin, a daily administered 5-HT agonist/5-HT2A antagonist, has been shown to improve the decreased desire and increased distress associated with HSDD, its use remains

limited. This is due to a modest treatment effect, accompanied by a significant side effect profile including sedation, fatigue, and a dangerous interaction with alcohol, causing hypotension and syncope (Baid and Agarwal, 2018). As such, there remains significant limitations to the availability of safe and effective treatment options for women with HSDD.

Therefore, studying the pathways involved provides a unique opportunity to address this unmet need with the ultimate aim of developing new therapies for women with HSDD.

1.2. Melanocortin 4 receptor (MC4R) and sexual behaviour

Previous work in animals suggests that MC4R stimulation may be involved in sexual behaviour and cause potential modulation of related brain pathways (Wilkberg et al., 2000, Pfaus et al., 2004). However, the precise location of action remains unclear. Bremelanotide (BMT or PT-141) is a synthetic cyclic heptapeptide and is a high-affinity ligand and agonist for melanocortin receptors (MCRs), particularly the type-4 receptor (MC4R) and so can be used to investigate this pathway further.

1.3. Clinical Data with the MC4R agonist BMT

BMT has been administered to approximately 3500 human subjects in 43 completed clinical studies using various formulations and modes of administration (intranasal [IN], intravenous [IV], or subcutaneous [SC]). During the development of BMT for the treatment of women with HSDD, more than 1500 subjects received at least 1 dose of SC BMT, 430 received IN BMT, and 10 received IV BMT.

The dose range for SC that has been studied extends from 0.1 mg up to 10 mg, the maximum tolerated dose. A fixed dose of 1.75 mg SC was evaluated in premenopausal women with HSDD when administered once daily for up to 24 weeks in Phase 3 studies that also included an open-label extension (OLE) phase with up to 52 weeks of additional treatment.

1.3.1 Pharmacokinetics of BMT

In two studies (PT-141-56 and PT-141-54), BMT absorption was rapid and complete after SC injection with the typical T_{max} occurring at approximately 60 minutes in the plasma; the half-life ($t_{½}$) is approximately 2 to 3 hours. After an SC dose of 1.75 mg BMT, the typical maximum concentration (C_{max}) in the plasma was 77.1 ng/mL. Human material studies showed that BMT had low binding to human plasma protein. The proposed biotransformation in humans is the breakdown of BMT into its constitutive amino acids through hydrolysis of the amide bonds. BMT and its breakdown products are predominantly renally cleared and excreted in the urine (64.8%); there is also some hepatic clearance but no BMT is detected in faeces.

1.3.2 Summary of the Efficacy of BMT in patients with HSDD

Two identically-designed Phase 3, randomised, double-blind, placebo-controlled studies (BMT-301 and BMT-302 were conducted to evaluate the safety and efficacy of BMT 1.75 mg SC, self-administered on demand in approximately 1200 premenopausal women with HSDD (with or without decreased arousal). Bremelanotide 1.75 mg showed statistically significant and clinically meaningful treatment benefit compared with placebo on the co-primary endpoints of change from baseline in the Female Sexual Function Index (FSFI) Desire Domain

and the Female Sexual Distress Scale – Desire/Arousal/Orgasm (FSDS-DAO) Question 13 measure of distress associated with low sexual desire. The analysis of the co-primary endpoints in the pooled Phase 3 studies, which assessed the two key cardinal symptoms of HSDD (low sexual desire and related distress), demonstrated statistically significant increases in sexual desire from Baseline to End of Study (EOS) ($p<0.0001$) and reductions in related distress from low sexual desire from Baseline to EOS ($p<0.0001$) for BMT 1.75 mg compared to placebo. These effects were maintained in those who continued in the 52-week OLE phase of these 2 studies.

1.3.3 Summary of Safety of BMT administration in humans

Across the two Phase 3 studies (BMT 301 and BMT 302), nausea was the most common adverse event (AE); 16.2% of all BMT injections were associated with a nausea event. Most events (>95%) of nausea were mild to moderate in severity and most events resolved spontaneously without the need for concomitant treatment (87.3%).

Less common treatment-emergent adverse events (TEAEs) associated with the use of BMT but reported in <2% of subjects and at an incidence greater than in the placebo group were restless leg syndrome, arthralgia, upper abdominal pain, and skin hyperpigmentation. Approximately 20% of subjects discontinued long-term BMT due to an AE, the most common reasons being nausea (8.1%), headache (1.8%), vomiting (1.1%), and flushing (1.0%).

Transient, mild increases in systolic blood pressure (BP) and diastolic BP were noted and peaked approximately 2 hours after BMT dosing, and were accompanied by similarly mild decreases in pulse rates, such that there were no increases in the overall heart rate (HR)-BP product. Effects disappeared within 4 hours of dosing.

No clinically significant results were observed for clinical laboratory test results, electrocardiogram (ECG), heart rate, weight changes, depression or suicidal ideation, or changes in alcohol consumption.

Overall, the totality of data supports the view that BMT is safe and generally well tolerated.

1.4. Rationale for the current physiological study to determine the effects of MC4R activation (by BMT) on brain activity patterns in women with HSDD

Two recent functional magnetic resonance imaging (fMRI) studies have examined the specific patterns of brain activation and sexual interest or response in women. Bianchi-Demicheli et al. conducted a study in 28 healthy, heterosexual, sexually active women, of which 13 had HSDD and 15 had no history of sexual dysfunction (NHSD), to compare the regional cerebral blood flow responses by fMRI between these 2 groups while they were looking at erotic vs. non-erotic stimuli (Bianchi-Demicheli et al., 2011). The study demonstrated a differential recruitment of higher-order cognitive brain areas (inferior parietal lobule, inferior frontal gyrus) in subjects with HSDD compared with subjects with NHSD when viewing erotic stimuli, which was not seen for non-erotic stimuli. To investigate brain activation and sexual response, Arnow et al. conducted a study in 20 women with NHSD and 16 women with HSDD using an fMRI and potentiometer to permit continuous assessment of subjective arousal (Arnow et al., 2009). The authors concluded that exposure to erotic stimuli was associated with significant differences in both subjective arousal and brain activation in women with HSDD compared with women with NHSD across 3 time points. These findings support the use of fMRI as a tool to investigate brain activation and sexual function in women with HSDD.

The primary purpose of this study is to examine brain activation patterns (by fMRI) during visual erotic stimuli in premenopausal women with HSDD in response to MC4R activation (by BMT). Data gathered from this study will help us understand which areas of the brain BMT activates to mediates its effects and therefore better understand the physiological roles of the MC4 receptor.

Primary hypothesis: MC4R activation causes differential brain activity patterns compared to placebo in response to visual erotic stimuli.

1.4.1 Study Population Rationale

The population for this study is consistent with the premenopausal population of women with HSDD studied in the existing literature and in the BMT Phase 3 clinical trials. In this study, subjects who are right-hand dominant will be recruited since subjects will be required to operate a response box with their right hand while in the scanner, and also because handedness has established implications for the organisation of functional regions in the brain (e.g. Cuzzocreo et al., 2009), which can be a potential confounding factor.

Dose Justification for the MC4R agonist BMT

Based on clinical studies, the 1.75 mg SC dose of BMT was shown to be safe and effective in premenopausal women with HSDD.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the effect of MC4R activation on brain activity patterns using functional neuroimaging (fMRI) during visual erotic stimuli in premenopausal women with HSDD.

2.2. Secondary Objectives

Secondary objectives of the study include the following:

- To evaluate the effect of MC4R activation on behavioral psychometric measures relating to sexual arousal during visual erotic stimuli in premenopausal women with HSDD
- To evaluate hormonal profiles following MC4R activation in premenopausal women with HSDD

3. STUDY DESIGN

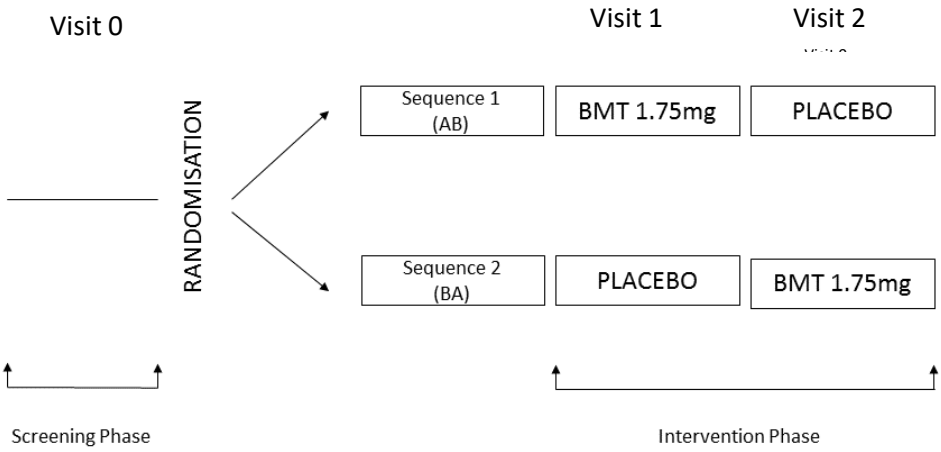
3.1. General Design

This is a randomised, double-blind, placebo-controlled, two-way crossover physiological study. It is designed to evaluate the effects of MC4R activation on brain activity patterns and behavioral psychometric measures of sexual arousal during visual erotic stimuli in approximately 40 right-handed, heterosexual, premenopausal women ≥18 years of age with HSDD (≥6-month duration) (see power calculation for determination of sample size).

The study will consist of two Phases: Screening & Intervention (MC4R agonist (BMT) or placebo). **(Figure 1).**

- Screening Phase (Visit 0).
- During the Intervention Phase, eligible subjects will be randomised (1:1) to one of two intervention sequences (AB or BA). Subjects will receive a single dose of BMT or matching placebo, administered SC, during each of the two Intervention Phases (Visit 1 and Visit 2) based on the randomisation intervention sequence they are assigned. The crossover design, which allows subjects to serve as their own control, will minimise inter-participant variability. Participants will return for Visit 2 in the same phase of the menstrual cycle of a subsequent month.
- Subjects who are randomised to intervention sequence AB will receive BMT 1.75 mg SC (Intervention A) during Intervention Phase 1 (Visit 1) and will receive placebo (Intervention B) during Intervention Phase 2 (Visit 2). Subjects who are randomised to intervention sequence BA will receive placebo (Intervention B) during Intervention Phase 1 (Visit 1) and will receive BMT 1.75 mg SC (Intervention A) during Intervention Phase 2 (Visit 2). Subjects will remain at the study centre for approximately seven hours during each of the Intervention Phases. Subjects may be required to remain at the study centre longer at the discretion of the Investigator.

Figure 1: Study Schematic



4. SUBJECT SELECTION

We will recruit approximately 40 women to allow for subject and technical drop-out (e.g. head movement during fMRI), aiming for a minimum of 30 women in the final study who complete the full protocol successfully.

We will collaborate with the Sexual Medicine clinic to identify potential participants, as well as advertise via print (including local and regional newspapers, transport network), radio and online advertisements. Additionally, we will liaise with the North West London Clinical Research Network (CRN) to contact potentially eligible patients via their GP practice (via letter or SMS). We will also inform GP's regarding the study who can opportunistically provide contact details to patients they see in their practice who may be eligible and display posters in GP practices. Potential participants who contact us via advertisements will initially be electronically sent a participant information sheet and self-report questionnaire, to be returned via email. If, following this, they are keen to take part and no obvious exclusion criteria are detected, they will be screened via telephone by a sexual health nurse using a questionnaire. If they appear eligible and are keen to participate, they will then be invited to attend a screening interview, where further questions regarding the study will be answered.

4.1. Inclusion Criteria

A subject will be eligible for enrollment in the study if all the following criteria apply:

1. Heterosexual premenopausal females ≥ 18 years of age with normal menstrual cycles ≤ 35 days.
2. Right hand dominant.
3. Body mass index (BMI) 18-35kg/m^2.
4. Currently in a relationship with a male partner and the relationship has been stable for at least 6 months before screening.
5. Male sexual partner classified as "not impotent" on the Massachusetts Male Aging Study (MMAS) (O'Donnell et al., 2004) single-question assessment of erectile dysfunction.
6. In the subject's opinion, previously experienced "normal sexual function," defined as a normal level of desire at some point in the past, for a period of at least 2 years.
7. For all subjects of childbearing potential who are sexually active, agree to routinely use adequate non-hormonal contraception from randomisation throughout the duration of the study and for 30 days after.
8. For at least 6 months before Screening, met the diagnostic criteria for HSDD according to the Diagnostic Screening Guide for HSDD **(Appendix B),** including categorisation of the sexual dysfunction as both acquired (versus lifelong) and generalised (versus situational).
9. All of the following at Screening:
    a. Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) total score is <10.
    b. PHQ-9 score for Question 9 is 0.

a. Either Female Sexual Function Index (FSFI) **(Appendix C)** total score ≤26 if diagnosed with HSDD (with or without symptoms of decreased arousal) or subjects diagnosed with HSDD only (without symptoms of decreased arousal), FSFI desire domain score of ≤5 (regardless of total FSFI score).
b. Female Sexual Distress Scale - Desire/Arousal/Orgasm (FSDS-DAO) **(Appendix D**) total score is >18.

10. Capable of understanding and complying with the protocol requirements and available for the duration of the study.
11. Subjects must have prior experience in viewing sexually explicit material.

4.2. Exclusion Criteria

A subject will not be eligible for enrollment in the study if any of the following criteria apply:

1. Cardiovascular disease
2. Current diagnosis of uncontrolled hypertension defined as:
   a. Two sequential assessments (seated, approximately 4 minutes apart and no more than 15 minutes apart) with readings above 140 mmHg systolic BP or 90 mmHg diastolic BP, and upon repeat at least 24 hours later.
   b. Treatment for hypertension that has been changed at least once in the 4 weeks prior to Screening.
3. Any other medical condition that is unstable or uncontrolled despite current therapy.
4. Previously received BMT.
5. A history of unresolved sexual trauma or abuse.
6. Female subjects who are pregnant, intend to become pregnant, are breastfeeding, have a positive serum/urine pregnancy test, or are not willing to use effective contraceptive precautions during the study.
7. Participated in any research study within the preceding 30 days of screening.
8. Any FSD other than acquired HSDD with or without decreased arousal (e.g. lifelong anorgasmia, sexual pain disorder, sexual aversion disorder, primary female sexual arousal disorder).
9. FSD caused by untreated endocrine disease (e.g. hypopituitarism, hypothyroidism, diabetes mellitus).
10. Acute or chronic hepatitis.
11. In the Investigator's opinion, any urologic or gynecologic condition, such as condyloma, uterine fibroids, vulvar or vaginal lesions, vulvodynia, vaginismus, or pelvic pain that may contribute to impaired sexual activity and function or be a cause of the FSD or that may interfere with the subject's ability to comply with study procedures.
12. Receiving any treatment for HSDD (e.g. psychotherapy, physical therapy) at the time of Screening.
13. Has used any of the following types of medications, which are prohibited during the study:

a. Implanted or injected testosterone product within 6 months of Screening.
b. Within 3 months of Screening:
   - Neuroleptics (e.g. risperidone)
   - Lithium (e.g. lithium carbonate)
   - Antidepressants (e.g. amitriptyline, fluoxetine, bupropion)
   - Mood stabilisers (e.g. valproate)
   - Benzodiazepines (e.g. lorazepam, diazepam)
   - Cognitive enhancers or stimulants (e.g. donepezil or Adderall®)
   - Centrally-acting antihypertensives (e.g. clonidine)
   - Any other prescription, non-prescription, hormonal, herbal, or nutritional medication or supplement that the investigators believe would confound the results of the study (e.g. St. John's wort, black cohosh, dehydroepiandrosterone, dehydroepiandrosterone sulfate)
   - γ-Aminobutyric acid agonists (e.g. Ambien® [zolpidem], Lunesta® [eszopiclone])
c. Topical or systemic androgen therapy within 30 days of Screening.
d. Subject is unwilling or unable to refrain from using the aforementioned products for the duration of the study.

14. Mental health history that includes any of the following:
    a. Psychosis, bipolar disorder, depression, and/or alcohol/substance abuse; depression or alcohol/substance abuse that resolved >1 year prior to Screening/Visit 0 will not be exclusionary.
    b. Prior suicide attempt or increased suicidality as indicated by a score greater than zero on Questions 1-5 inclusive (interpreted increased risk) and/or Question 20 (interpreted history of suicide) of the Beck Scale for Suicidal Ideation (BSS) (Kleim et al., 2017).
15. Any abnormality in vision that would impair viewing images.
16. Any contraindication to MRI or otherwise unable to undergo an MRI (e.g. pacemaker, recent wound clips, severe claustrophobia, unable to lay flat).
17. Any other condition or subject responsibility that in the Investigator's opinion may interfere with a subject's ability to give informed consent or adhere to the protocol or has the potential to interfere with the studied endpoints or serves as a contraindication to the subject's participation in the study.

4.3. Criteria for Randomisation

Subjects who sign consent and meet eligibility criteria may be randomised to the study by an independent investigator. All subjects will be randomised in a 1:1 ratio in a two-way crossover design to one of two intervention sequences: AB or BA, where BMT is Intervention A, and placebo is Intervention B. Blinding will be performed by a member of the research team not directly involved in running the study, following the dispensing of the medication from pharmacy.

5. STUDY OUTCOMES

5.1. Primary Endpoint

The primary endpoint is change in brain activity patterns with MC4R activation compared to placebo in scanning session 1 (SS1) as measured by fMRI during visual erotic stimuli.

5.2. Secondary Endpoints

- Change in brain activity patterns with MC4R activation compared to placebo in scanning session 2 (SS2) as measured by fMRI during visual erotic stimuli.
- Change in psychometric measures related to sexual arousal with MC4R activation compared to placebo in SS1 as measured with a behavioral potentiometer during visual erotic stimuli.
- Change in psychometric measures related to sexual arousal with MC4R activation compared to placebo in SS2 as measured with a behavioral potentiometer during visual erotic stimuli.

5.3. Exploratory Endpoints

Exploratory endpoints include the following:

- Changes in blood and hormonal parameters including follicle stimulating hormone (SH), luteinizing hormone (LH), kisspeptin, oestradiol, progesterone, sex-hormone binding globulin (SHBG) and testosterone levels.

5.4. Safety Assessment

Safety will be assessed based on:

- incidence of adverse events (AE's), clinical laboratory assessments (haematology, chemistry, and urinalysis), vital signs (systolic and diastolic BP, pulse rate, and oral temperature), 12-lead ECG, and physical examination findings.

6. STUDY INTERVENTION

6.1. Description of Study Intervention

The two study interventions are:

- MC4R agonist (BMT 1.75 mg SC - prefilled autoinjector containing 1.75 mg BMT in a 0.3 mL solution volume)
- Placebo (1.75 mg equivalent SC - prefilled autoinjector containing BMT formulation without the active ingredient in a 0.3 mL solution volume)

6.2 Supply

- BMT autoinjectors will be shipped in a validated shipping container with cold packs.
- The study intervention will be supplied from AMAG's packager in the United Kingdom.

6.3 Storage

- All study interventions will be stored in a secure, limited access area (Imperial College Healthcare Trust Pharmacy) and refrigerated at 2ºC to 8ºC. It should be removed from the refrigerator approximately 45 minutes prior to dosing to allow the intervention to reach room temperature (20°C to 25°C) prior to dosing,

7. STUDY PROCEDURES

7.1. Subject Informed Consent, Screening, and Randomisation

7.1.1 Subject Informed Consent

Study personnel will adhere to GCP guidelines when obtaining consent from any potential study candidate, including explaining the rationale for and the details of the study, the risks of study intervention, and the extent of involvement. An information leaflet will be provided, with at least 24 hours for consideration of participation. Once the essential information has been provided to the subject and fully explained by the Investigator (or a qualified designee), and it is felt that the subject understands the implications and risks of participating in the study, the approved informed consent form (ICF) will be signed and dated. The right of the participant to refuse to participate without giving reasons will be respected.

The subject will be given a copy of the ICF, and the original will be maintained with the subject's record. A note summarising the consent process will also be included in the subject's record.

7.1.2 Procedures for Assigning Subjects to Intervention Groups

Eligible subjects who meet all inclusion criteria and do not meet any exclusion criteria will be randomised. Randomisation will be carried out using standard procedures. Randomisation numbers will not be reused for any reason.

7.2. Procedures by Study Phase

The assessments and procedures to be completed during each of the study phases are described in the sections that follow and in the Schedule of Events and Procedures provided in **Appendix A.** Detailed descriptions of the study assessments and measurements are provided in 8.

Screening Phase (Visit 0)

The following will be performed during the Screening Visit including:

- review inclusion/exclusion criteria for eligibility
- collect demographics
- collect medical, social, sexual, and medication history
- perform diagnostic screening for HSDD
- perform vital signs assessment (systolic and diastolic BP, heart rate, temperature)
- perform comprehensive physical examination
- perform 12-lead ECG
- collect blood and urine for clinical laboratory tests including:
  - hematology
  - serum chemistry
  - urinalysis
  - FSH, LH, oestradiol, progesterone, prolactin, dehydroepiandrosterone sulphate (DHEAS), androstenedione & testosterone

  - urine pregnancy test
  - DNA analysis (if patient consents) to assess for novel genes implicated in the aetiology of HSDD
- have subject complete questionnaires/assessments such as:
  - PHQ-9
  - BSS
  - Decreased Sexual Desire Screener (DSDS) (Clayton et al., 2009)
  - FSFI
  - FSDS-DAO
  - MMAS
- schedule study visits for participants who are eligible and available for the duration of the study
- advise participants to consume a normal breakfast on day of study and abstain from sexual activity, alcohol, caffeine and tobacco from midnight before their study visits
- MRI safety questionnaire

7.2.1 Intervention Phase (Visits 1 and 2)

Visit 1

Visit 1 will occur after Screening (Visit 0), on **day 1-7** of the menstrual cycle. Subjects will be randomised and the following procedures will be performed:

- On arrival
  - review and confirm study eligibility
  - perform vital signs assessment (systolic and diastolic BP, heart rate, temperature)
  - perform symptom-driven physical examination
  - collect blood and urine for clinical laboratory tests (haematology, serum chemistry, urinalysis)
  - perform urine pregnancy test
  - review concomitant medications
  - MRI safety questionnaire
- Prior to intervention
  - remove intervention autoinjector from assigned study kit; warm to room temperature
  - collect arousal/psychometric data using behavioral potentiometer (including the Visual Analogue Scale (VAS), the State-Trait Anxiety Inventory (STAI Y1 and

Y2), the Sexual Arousal and Desire Inventory (SADI) and the Positive and Negative Affect Schedule (PANAS) at the end of scanning component of session (see Appendices E to I).

- Post-intervention assessments:
  - administer intervention based on randomisation assignment
  - collect blood at time-points: -15, 0 (SC injection), 15, 45, 60, 75, 90, 120, 150, 180, 210, 240, 270, 300 (14 timepoints total). A maximum of 12ml will be taken at each time-point. The total volume of blood collected over both study visits will not exceed 340ml.
  - During SS1:
    - perform fMRI in accordance with Imaging Manual instructions (including functional MRI scan **(**commencing t=45mins) and anatomical MRI scan)
    - Exposure to visual erotic stimuli as well as other tasks designed to elicit brain responses related to emotional, sensory, or cognitive functions.
    - collect psychometric data using behavioral potentiometer alongside session (arousal handheld device in scanner and psychometric/behavioral potentiometer questionnaires including the Visual Analogue Scale (VAS), the State-Trait Anxiety Inventory (STAI Y2), the Sexual Arousal and Desire Inventory (SADI) and the Positive and Negative Affect Schedule (PANAS) at the end of scanning component of session (see Appendices E to I).
  - During SS2:
    - perform fMRI (and anatomical scan) in accordance with Imaging Manual instructions (commencing t=240mins)
    - Exposure to stimuli as per SS1.
    - collect psychometric data using behavioral potentiometer alongside session (arousal handheld device in scanner and psychometric/behavioral potentiometer questionnaires including the Visual Analogue Scale (VAS), the State-Trait Anxiety Inventory (STAI Y2), the Sexual Arousal and Desire Inventory (SADI), the Positive and Negative Affect Schedule (PANAS) and the D2 Test of Attention at the end of scanning component of session (see Appendices E to I).

Visit 2

This will occur on **day 1-7** of a subsequent menstrual cycle, to allow for the study to be carried out in the same part of the menstrual cycle on each visit.

The following procedures will be performed:

- On arrival
  - As described for Visit 1
- Prior to intervention
  - As described for Visit 1

- Post-intervention assessments
    - As described for Visit 1

Follow-up

Participants will be sent a short questionnaire 24 hours after the study to assess the perceived duration of effect of BMT (see Appendix J).

7.3. Subject Discontinuation and Criteria for Withdrawal

7.3.1 Subject Withdrawal

All participants are free to withdraw at any time without giving reasons and without prejudicing future treatment.

8. STUDY ASSESSMENTS AND MEASUREMENTS

8.1. Vital Signs

Systolic and diastolic BP, heart rate, and temperature will be performed at Screening and at Visits 1 and 2 before administration of the intervention and before/after each SS.

8.2. Physical Examination

A comprehensive physical examination including height, weight, BMI, and assessment of all body systems will be performed at Screening. Subsequent physical examinations at Visits 1 and 2 will be symptom-driven based on any AEs, subject complaints about physical state, or subject reported changes in physical state.

8.3. 12-Lead Electrocardiogram

A 12-lead ECG will be performed at Screening and reviewed by a qualified clinician designated by the Principal Investigator to read and interpret the results. Any anomalies will be managed as clinically appropriate and the GP of the patient informed.

8.4. Clinical Laboratory Tests and Visit Assessments

Urine pregnancy tests will be conducted at Screening and at the start of each study visit. Clinical laboratory tests will be performed by a clinical laboratory.

Subjects will be fully informed that the study is evaluating sexual desire brain activity patterns. In conjunction with each fMRI scan, subjective desire will be measured with a behavioral potentiometer.

8.4.1 Safety Assessments

Safety will be monitored with the following assessments: incidence of AEs, vital signs, clinical laboratory tests, and physical examination.

8.5 MRI scans

Prior to the first functional MRI scan, an anatomical MRI scan will be performed. These anatomical scans will be reviewed by a qualified neuroradiologist and if any abnormalities are detected, the patient's GP will be informed, with their consent. They will be withdrawn from the study, in the case of abnormalities that would affect the study.

9. SAFETY MONITORING AND RISK MANAGEMENT

9.1. Safety Events and Reporting

During the study:

Any potential adverse events of the study will be reviewed regularly by the Chief Investigator, Professor Dhillo, and the other investigators. The safety of the subjects is of the highest importance throughout the study. An internal audit will be completed at the end of the study. Study progress and safety will be regularly reviewed in fortnightly meetings. A formal monitoring committee is not deemed necessary as the MC4R agonist (BMT) has been administered safely previously. If any subjects come to harm as a result of taking part in this research study the study will be terminated.

Adverse Events:

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement will be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, will also be considered serious.

Reporting Procedures:

All adverse events will be reported. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to Professor Waljit Dhillo in the first instance.

Non serious AE's

All such events, whether expected or not, will be recorded.

Serious AE's

An SAE form will be completed and faxed to Professor Waljit Dhillo within 24 hours. However, relapse and death due to unrelated pre-existing conditions, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the local REC committee where in the opinion of the Chief Investigator, Professor Waljit Dhillo, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator, Professor Waljit Dhillo, becoming aware of the event, using the National Research Ethics Service (NRES) SAE form for non-IMP studies.

Local investigators will report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

All AE's/SAE's must be reported during the study, regardless of relationship to study intervention or clinical significance.

9.1.1 Pregnancy

In the unlikely event that a female subject becomes pregnant at any time during the study, the Investigator must notify the Sponsor (Imperial College Healthcare NHS Trust) immediately (within 24 hours) so as to facilitate discussion and implementation of necessary follow-up measures and to enable the Sponsor to submit necessary reports to the ethics committee. The Investigator will be required to follow the subject and pregnancy through delivery (or earlier loss/termination) and report any congenital anomalies or birth defects. Additional information may be requested to meet regulatory reporting requirements.

9.2. Unblinding Procedures

Only in the case of an emergency, when the identity of the study intervention is essential for the clinical management or welfare of the subject, can an Investigator request unblinding of a subject's intervention assignment.

10. STATISTICAL PLAN

10.1. Analysis Populations

This study will include the following analysis populations:

- Randomised Population: all subjects who are assigned an intervention sequence via randomisation in the Intervention Phase
- Intent-to-Treat (ITT) Population: all randomised subjects who receive any study intervention in the Intervention Phase
- Completer Population: all randomised subjects who complete both Visit 1 and 2 in the Intervention Phase
- Per-Protocol Population: all randomised subjects who complete both Visit 1 and 2 in the Intervention Phase and have no major protocol deviations that would confound results
- Safety Population: all subjects who receive any study intervention in the Intervention Phase

Subject allocation to analysis populations, including the review of major protocol deviations and assignment to the Per-Protocol Population, will be based on a blinded review prior to database lock.

10.2. Statistical Methods

10.2.1 General Considerations

All individual subject data for all individual subjects randomised to an intervention sequence will be presented in data listings.

Data collected in this study will be presented using summary tables and data listings. Continuous variables will be summarised using descriptive statistics, such as the number of subjects (n), mean, median, standard deviation (SD), standard error (SE), minimum, and maximum. Categorical variables will be summarised by frequencies and percentages when appropriate. All statistical tests will be two-sided at the 5% significance level, unless otherwise noted.

10.2.2 Demographics and Baseline Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, and other background characteristics will be summarised.

10.2.3 Endpoint Analyses

Endpoint analyses (see section 5 for endpoints) will be performed on populations as above. Analyses will be performed based on randomised intervention (Completer and Per-Protocol Populations as appropriate).

The MRI data will be processed and analysed using current best practice methods, which will include (but may not be limited to) application of the General Linear Model (GLM) for neuroimaging data. Robust methods of correcting for multiple comparisons (e.g. permutation testing) will be used for statistical analysis and thresholding of the statistical brain images.

Brain activation patterns will be presented by intervention and analysed by whole-brain and region of interest (including amygdala, thalamus, posterior cingulate cortex and entorhinal region.

Correlations will be explored between brain activation and behavioral data, corrected for visit order as appropriate (including Pearson and Partial Correlation testing).

10.2.4 Safety Analyses

Safety analyses will be performed on the Safety Population; all analyses will be performed based on intervention received. Clinical laboratory results, vital signs, and 12-lead ECG results will be summarised using descriptive statistics (n, mean, SD, SE, median, minimum, and maximum values, as appropriate) by intervention and time point, and all data will be listed.

10.3. Sample Size Justification

The final projected sample size (approximately 30) has been determined by appropriate power calculation and is in line with the recommended n number required for neuroimaging clinical studies to be powered appropriately to be able to observe significant changes in fMRI brain activation patterns (Murphy and Garavan, 2004).

10.3.1 Power calculation

There are no previous functional magnetic resonance imaging (fMRI) studies examining the role of the melanocortin-4 receptor (MC4R) in hypoactive sexual desire disorder (HSDD). However, data from a previous fMRI study (Comninos et al., 2017) examining a similar scenario (kisspeptin hormonal administration effects on fMRI sexual brain activity) can be used to estimate requirements for the current study. The amygdala is an important structure involved in the processing of sexual stimuli in healthy participants as well as patients with HSDD and so is an appropriate reference point. (Woodward et al., 2013). This study shows that kisspeptin enhances blood oxygen level dependent (BOLD) signal change in the amygdala by mean 0.74% and standard deviation 0.38% compared to vehicle (mean 0.48%, standard deviation 0.51%).

We are anticipating a similar response in this study and have performed sample size calculations for the study using these data. With a 5% significance level, and 80% power, and assuming a correlation between Bremelanotide (an MC4R agonist) and vehicle means of 0.4, a sample size of 31 patients is calculated. To allow for natural variation in responses, drop-out and exclusion rate (e.g. a priori head movement > 2mm) of 20%, it is planned to recruit a total of approximately 40 patients to the study.

11. REGULATORY ISSUES

11.1 Ethical Approval

The Principal Investigator will obtain approval from the … Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

11.2 Confidentiality

The Chief Investigator, Professor Waljit Dhillo is the data custodian. He will preserve the confidentiality of participants taking part in the study under the Data Protection Act 2018. Their data will only be accessed by members of the research team. All samples will be coded by the research team, and these codes will only be accessible to researchers directly involved with the study. Details stored on Imperial College London computers will be password-encrypted and will only be accessed by the researchers involved in the study. Written confidential patient notes will also be kept at Imperial College London, which will contain personal information and medical history of participants. All records will be stored in secure containment for 5 years after the study on the Hammersmith Hospital campus, Imperial College London, under the authority of Professor Dhillo

If participants are to be enrolled in the study, we will ask their consent to view their medical records. If they are not registered with Imperial College Healthcare NHS Trust (ICHT), a set of ICHT notes will be created. Personal addresses and contact details are required for communication with the participants during the study. This information is held solely for communication between the researchers and participants.

Information held on NHS computers is solely for the purpose of hospital booking, routine sample collection and analysis (e.g. for the screening visit). This information is password−encrypted, in a similar manner to that of other hospital patients. Written confidential patient notes will also be kept, which will contain personal information and medical history of participants.

Personally Identifiable Information (PII) will be entered into Invicro's Patient Information Management System which assigns them a unique six-digit ID. This six-digit ID is used within the Radiology Information System (RIS) for the purposes of verifying the identity of participants immediately prior to the scans. The six-digit participant identification code is the only identifier subsequently used when acquiring the imaging data. The imaging data (and any ancillary data generated) is therefore pseudo-anonymised (code is kept in case of need to un-break blinding). Invicro operates under a highly-secure and enterprise-class computing environment, and fully complies with Good Clinical Practice (GCP) guidelines and Data Protection Act (2018) directives with regard to participant PII. Invicro pseudo-anonymised data will be stored indefinitely. Invicro also holds the study file and consent forms, which are archived indefinitely in a secure off-site document storage facility.

AMAG Pharmaceuticals, Inc. will receive anonymised data relating to this study.

11.3 Indemnity

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and Insurance cover with NHS resolution for NHS Trusts in England, which apply to this study.

Separate insurance is held by Invicro for the conduct at their site.

11.4 Funding

AMAG Pharmaceuticals Inc are funding this study. Participants will receive £150 per completed study visit to cover expenses including travel costs, time off work and lost earnings, in keeping with NIHR guidelines.

11.5 Audits

The study may be subject to inspection and audit by Imperial College Healthcare NHS Trust under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

11.6 Sample storage

At the end of the study, the data will be kept in locked storage in the Department of Investigative Medicine on the Hammersmith Hospital campus, Imperial College London, under the authority of Professor Dhillo. On a day−to−day basis, data will be managed by the department's senior administrative manager. Only the researchers will have access to the data. Samples will be stored for 5 years.

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Appendix A: STUDY FLOWCHART

Variables	Screening (Visit 0)	Intervention phase (Visit 1)	Intervention Phase (Visit 2)
Informed Consent Form (ICF)	X		
Review inclusion/exclusion criteria	X	X	X
Demographics	X		
Medical, social and sexual history	X		
Review medications	X	X	X
Perform diagnostic screening for HSDD	X		
Perform baseline screening questionnaires: PHQ-9, BSS, FSFI, FSDS-DAO, MMAS	X		
Vital signs	X	X	X
12-lead ECG	X		
Urine pregnancy test	X	X	X
Physical exam	X	X	X
Clinical laboratory tests	X	X	X
Randomisation		X	
Continued eligibility assessment		X	X
Administer intervention BMT/placebo		X	X
fMRI & behavioral potentiometer (including handheld device and questionnaires such as VAS, STAI Y1 and Y2, SADI, PANAS, D2 Test of Attention)		X	X
Review adverse events		X	X

APPENDIX B: Diagnostic Screening Guide For HSDD

INSTRUCTIONS: *This guide is designed to facilitate the diagnostic assignment of possible cases of female sexual dysfunction (FSD) into one of three categories: hypoactive sexual desire disorder (HSDD) (ie, HSDD Distinct); HSDD with arousal problems (ie, HSDD Mixed (HSDD/female sexual arousal disorder [FSAD]); or neither condition present. The questions reflect the diagnostic criteria in Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and those proposed in DSM-5. The guide is intended as an outline for you to follow in making your diagnostic decision.*

Introduction: Ask various questions to make the subject feel comfortable and also to gain some insight into the subject's life, such as:

- *Tell me a little about yourself please. Then, if the conversation falters a bit, provide her with some leading questions, such as:*
  - *Do you work? What job do you have? What is your typical day like?*
  - *Do you have children? If yes, what are their ages? How are they doing?*
- *Why are you participating in this study?*
  - *Does your partner know you are participating in a study?*
  - *Is the partner supportive of your being here?*

1) Please briefly describe your current relationship.
   a) How long have you been together? How long have you been sexually intimate?
   b) Do you feel positively about your relationship with your partner?
   c) Do you believe that your partner feels positive about your relationship?
   d) Are there any major issues troubling you regarding the relationship (for example, trust issues, resentments)?
   e) Do you feel you can talk to your partner about these issues?
2) Are you currently experiencing any sexual difficulties? If yes, what are they?
3) Was there any time in your life when you experienced personal desire for sexual activity (for example, positive sexual thoughts/fantasies about having sexual activities)?
4) Was there a time in your life that you were you able to become sexually aroused or excited when you engaged in sexual activities?
5) Was there a time with your current partner that you had desire for sexual activity and routinely became aroused?
6) Have you sometimes initiated sexual activity with your partner in the past, prior to your current sexual problems?

HSDD Screen:

7) Would you say that, for at least the past 6 months, your desire for sexual activity has decreased compared to what it was previously?

8) Has the number or intensity of your sexual thoughts/daydreams decreased over this time?

9) How do you feel about this change in desire?

   a) Are you worried about this decrease?

   b) Does it distress you?

   c) Does it distress your partner?

10) When did you first notice this decrease? Was the onset gradual or sudden?

Screen for Comorbid Arousal Problems:

11) During the past 6 months, when you engaged in sexual activity did you have difficulty becoming or staying mentally aroused or excited?

12) How do you feel about this change? Are you concerned about this difficulty with becoming mentally aroused?

13) How long have you experienced this problem with mental arousal?

Lubrication:

14) Would you say that, for at least the past 6 months, you have had difficulty experiencing adequate vaginal lubrication or other arousal difficulties during sexual activity (for example, genital swelling and tingling, nipple sensitivity)?

15) How long have you experienced this problem with lubrication?

16) How do you feel about this change? Does this problem concern you?

Orgasmic Difficulties:

17) During the past 6 months have you been having any problems with having orgasms?

18) How long have you experienced this problem achieving an orgasm?

19) Does this orgasmic problem concern you?

Pain:

20) Would you say that, for at least the past 6 months, you have had difficulty or problems with pain (either vaginally or elsewhere) during sexual activity?

21) How long have you experienced this pain problem?

22) Does the pain interfere with sexual activity? What impact has the pain had on your sexual life?

23) Does this pain problem concern you?

NOTE: If there is an absence of a formal diagnosis of sexual dysfunction, skip the section below on Mitigating Factors.

Mitigating Factors (SKIP THIS SECTION if there is no formal diagnosis of sexual dysfunction)

Now let me take a few minutes to review some factors that may have contributed to your current sexual problems. Please let me know if you feel any of the following issues have made a significant contribution to your sexual difficulties.

a.) Medical Condition:

b.) Life Stress:

c.) Medications:

d.) Surgery:

e.) Relationship Issues:

DIAGNOSIS:

PART A: FOR ALL SUBJECTS

Please place a check in the box below that most accurately describes the subject's diagnostic status.

HSDD **without decreased arousal**	**HSDD** **with decreased arousal**	**No HSDD**

For how long prior to Screening has the subject had HSDD (with or without decreased arousal)?	

PART B: FOR ALL SUBJECTS WITH SEXUAL DYSFUNCTION

Circle the appropriate choice which describes their sexual dysfunction.
LIFELONG OR ACQUIRED
GENERALISED OR SITUATIONAL

PART C: SUPPLEMENTARY QUESTION

For what percentage of your sexual encounters do you have absent/reduced sexual excitement/pleasure during sexual activity? (in identified situational contexts or, if generalised, in all contexts) (Write answer in box to the right or indicate NA for not applicable)	

NOTES:

DSM-5 CHECKLIST

Female Sexual Interest and Arousal Disorder (SI/AD) – Diagnostic Criteria*		**Yes**	**No**
A. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following:			
	1) Absent/reduced interest in sexual activity.		
	2) Absent/reduced sexual/erotic thoughts or fantasies.		
	3) No/reduced initiation of sexual activity and typically unreceptive to a partner's attempts to initiate.		
	4) Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately 75% to 100%) sexual encounters (in identified situational contexts or, if generalised, in all contexts).		
	5) Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual)		
	6) Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (approximately 75% to 100%) sexual encounters (in identified situational contexts or, if generalised, in all contexts).		
B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.			
C. The symptoms in Criterion A cause clinically significant distress in the individual.			
D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.			

Specify whether:	**Circle the Appropriate Choice:**
1) **Lifelong**: The disturbance has been present since the individual became sexually active **Acquired**: The disturbance began after a period of relatively normal sexual function.	Lifelong Acquired
2) **Generalised**: Not limited to certain types of stimulation, situations, or partners **Situational**: Only occurs with certain types of stimulation, situations, or partners	Generalised Situational
3) Severity of distress associated with symptoms in Criterion A	Mild Moderate Severe

	Circle the Number that Corresponds to How Relevant the Specifier is for the Diagnosis:					
	Not					Extremely
4) Partner factors (partner's sexual problems, partner's health status)	0	1	2	3	4	5
5) Relationship factors (for example, poor communication, relationship discord, discrepancies in desire for sexual activity)	0	1	2	3	4	5
6) Individual vulnerability factors (for example, depression or anxiety, poor body image, history of abuse experience)	0	1	2	3	4	5
7) Cultural/religious factors (for example, inhibitions related to prohibitions against sexual activity)	0	1	2	3	4	5
8) With medical factors relevant to prognosis, course, or treatment	0	1	2	3	4	5

*Text in the checklist is taken from the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition, DSM-5™, American Psychiatric Association, 2013

APPENDIX C: FEMALE SEXUAL FUNCTION INDEX (FSFI) QUESTIONNAIRE

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 ("turned 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.

D. Ferguson and R. Rosen, 2000

APPENDIX D: FEMALE SEXUAL DISTRESS SCALE - DESIRE/AROUSAL/ORGASM (FSDS-DAO) QUESTIONNAIRE

INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST 30 DAYS INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: **Personal responsibility for your sexual problems?**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1.	Distressed about your sex life	0	1	2	3	4
2.	Unhappy about your sexual relationship	0	1	2	3	4
3.	Guilty about sexual difficulties	0	1	2	3	4
4.	Frustrated by your sexual problems	0	1	2	3	4
5.	Stressed about sex	0	1	2	3	4
6.	Inferior because of sexual problems	0	1	2	3	4
7.	Worried about sex	0	1	2	3	4
8.	Sexually inadequate	0	1	2	3	4
9.	Regrets about your sexual functioning	0	1	2	3	4
10.	Embarrassed about sexual problems	0	1	2	3	4
11.	Dissatisfied with your sex life	0	1	2	3	4
12.	Angry about your sex life	0	1	2	3	4
13.	Bothered by low sexual desire	0	1	2	3	4
14.	Concerned by difficulties with sexual arousal	0	1	2	3	4
15.	Frustrated by problems with orgasm	0	1	2	3	4

APPENDIX E: Visual Analogue Scale

Please place a vertical mark along the line according to how you are feeling

Example: 

How hungry do you feel right now?

NOT AT ALL EXTREMELY

How sick (or nauseous) do you feel right now?

NOT AT ALL EXTREMELY

How pleasant would it be to eat right now?

NOT AT ALL EXTREMELY

How much do you think you could eat right now?

NOTHING A LARGE AMOUNT

How full do you feel right now?

NOT AT ALL EXTREMELY

How sleepy do you feel right now?

NOT AT ALL EXTREMELY

APPENDIX F: State-Trait Anxiety Inventory Y-1 and Y-2

SELF-EVALUATION QUESTIONNAIRE STAI Form Y-1

Please provide the following information:

Name_____Date_____S_____

Age_____ Gender (*Circle*) **M F** T_____

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-2

Name_____ Date_____

DIRECTIONS

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

APPENDIX G: The Sexual Arousal and Desire Inventory (SADI)

Sexual Arousal is defined as the **physiological responses that accompany or follow sexual desire**. For example, when you feel sexually aroused, your heart might beat faster or your palms may get sweaty. Men may experience penile erection, and women may feel a moistness of the vagina. Sexual Arousal involves the more physiological aspects of wanting sex. **Sexual desire is defined as an energizing force that motivates a person to seek out or initiate sexual contact and behaviour.** You can think of it as a hunger or a sexual 'drive' that leads you to seek out sexual contact. Sexual desire involves the more psychological aspects of wanting sex.

Keep in mind the definitions of sexual arousal and sexual desire. Following is a list of words that might **describe how you feel currently**. Different people experience sexual arousal and desire in distinct, individual ways. There is no 'right' or 'wrong' answer. Please indicate to what extent each word describes how you feel **RIGHT NOW**, by placing the number that describes the feeling most accurately.

0	1	2	3	4	5
does not describe it at all			describes it moderately well		describes it perfectly

Anticipatory____
Tingly all over____
Restrained____
Anxious____
Driven____
Frigid____
Sensitive to touch____
Sluggish____
Urge to satisfy and/or be satisfied____
Enthusiastic____
Unhappy____
Wet (women only)____
Hard (men only)____
Resistant____
Warm all over____

Frustrated____
Lustful____
Entranced____
Aversion____
Hot____
Tempted____
Passionate____
Fantasize about sex____
Repressed____
Disturbed____
Flushed____
Impatient____
Sensual____
Breathe faster/pant____
Displeasure____

Excited____
Tingling in genital area____
Uninterested____
Pleasure____
Heart beats faster____
Happy____
Angry____
Attractive____
Powerful____
Naughty____
Alluring____
Lethargic____
Horny____

Stimulated____
Tingling sensation in gut____
I forget about everything else____
Repulsion____
Sexy____
Quivering sensations____
Insensible____
Seductive____
Genitals reddish____
Unattractive____
Good____
Throbs in genital area____

APPENDIX H: The Positive and Negative Affect Schedule (PANAS)

PANAS Questionnaire

This scale consists of a number of words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. **Indicate to what extent you feel this way right now, that is, at the present moment *OR* indicate the extent you have felt this way over the past week (circle the instructions you followed when taking this measure)**

1	2	3	4	5
Very Slightly or Not at All	A Little	Moderately	Quite a Bit	Extremely

_____ 1. Interested	_____ 11. Irritable
_____ 2. Distressed	_____ 12. Alert
_____ 3. Excited	_____ 13. Ashamed
_____ 4. Upset	_____ 14. Inspired
_____ 5. Strong	_____ 15. Nervous
_____ 6. Guilty	_____ 16. Determined
_____ 7. Scared	_____ 17. Attentive
_____ 8. Hostile	_____ 18. Jittery
_____ 9. Enthusiastic	_____ 19. Active
_____ 10. Proud	_____ 20. Afraid

APPENDIX I: D2 Test of Attention

d2 Test of Attention

Rolf Brickenkamp & Eric A. Zillmer

Name: ____________________

Age: ______ Sex: ☐ male ☐ female

Handedness: ☐ L ☐ R

Years of education: ____________________

Occupation: ____________________

Examiner: ____________________ Date: ____________

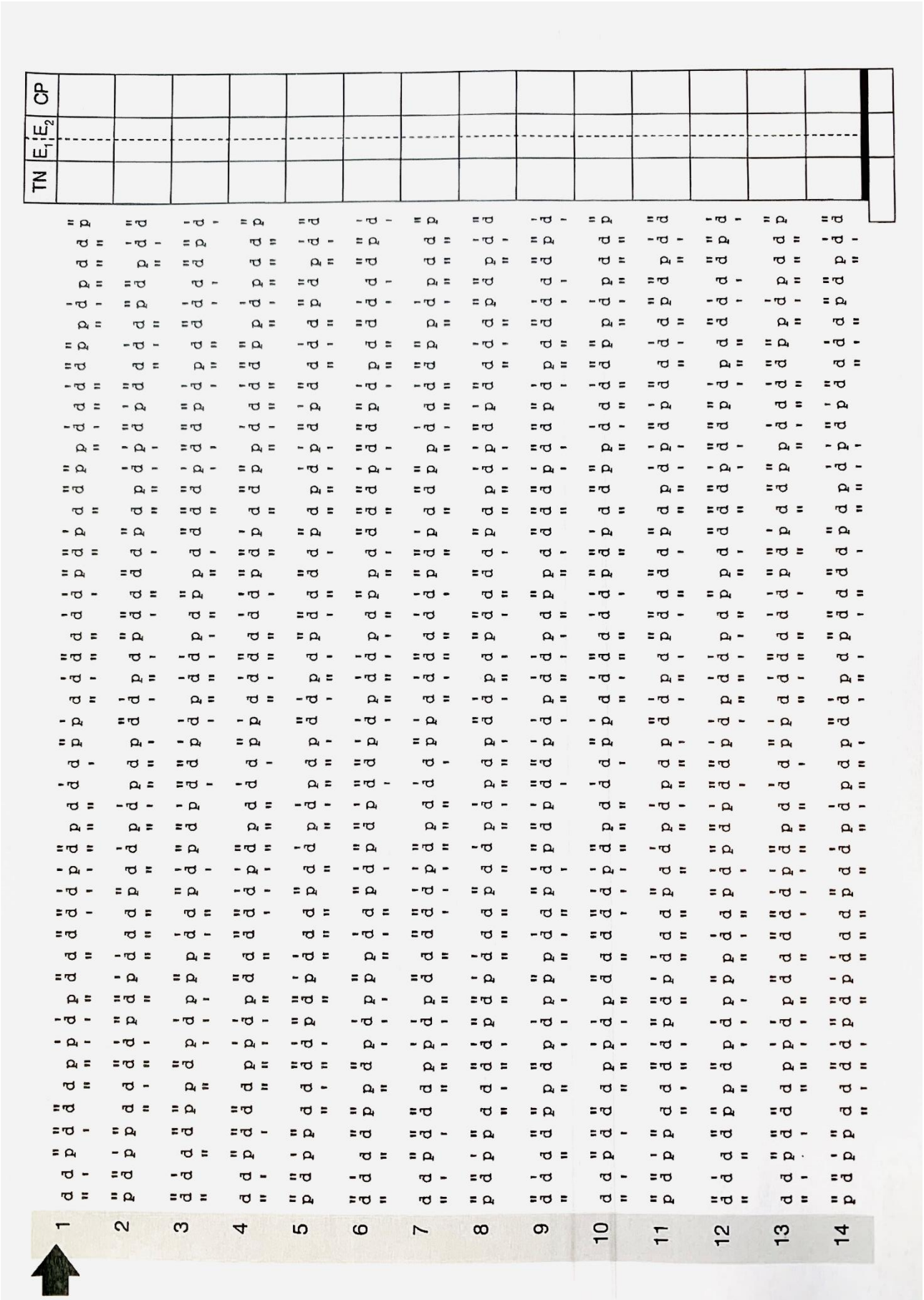
Example: d d d

Practice line:

d	p	d	d	d	d	p	d	d	p	d	d	d	d	p	p	d	d	d	p	d	d
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22

	Raw Score	Percentage	Percentile Rank	Standard Score
TN (total number)				
Omissions: E1				
Commissions: E2				
E (errors)				
TN-E (total-errors)				
CP (concentration performance)				
FR (fluctuation rate)				

S-Syndrome: ☐


TN
E1 E2
CP
1
2
3
4
5
6
7
8
9
10
11
12
13
14

APPENDIX J: Follow-up Questionnaire

1. Did you feel an increase in sexual desire after administration of study drug? YES/NO

2. If yes, how long after study drug administration did the increase in sexual desire last?

   0-2 hrs
   >2-4 hrs
   >4-8 hrs
   >8-12 hrs
   >12-18 hrs
   >18-24 hrs

   Thank you