CLINICAL STUDY REPORT

A phase II, randomised, double-blind, placebo-controlled, parallel group, multicentre study investigating efficacy and safety of Sepranolone (UC1010) in patients with PMDD

Protocol Number:	UM203
EudraCT number:	2017-000822-37
Investigational Medicinal Product:	Sepranolone (UC1010)
Indication:	Premenstrual dysphoric disorder (PMDD)
Phase:	II
Sponsor:	Asarina Pharma Clinical Research & Development c/o COBIS, Ole Maaloes Vej 3 2200 Kobenhavn N, Denmark
Principal/Coordinating Investigator	Prof Shaughn O'Brien, DSc MD FRCOG Professor of Obstetrics and Gynaecology, Keele University School of Medicine Consultant Obstetrician and Gynaecologist, Royal Stoke University Hospital +44 7971 868 401
First Patient, First Visit:	20 April 2018
Last Patient, Last Visit:	25 February 2020
Date of Report and Version:	23 October 2020, Final Version 1.0

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements, including the archiving of essential documents.

Clinical Study Report Approval

Study Title: A phase II, randomised, double-blind, placebo-controlled, parallel group, multicentre study investigating efficacy and safety of Sepranolone (UC1010) in patients with PMDD

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Sponsor Medical Representative

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26/10 2020
Date

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Date

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2020-10-26
Date

2. SYNOPSIS

Name of Company: Asarina Pharma	**Volume:** (For national authority use only)
Name of Finished Product: Sepranolone Injection	**Page:**
Name of Active Ingredient(s): Sepranolone (UC1010)	
Title of Study: A phase II, randomised, double-blind, placebo-controlled, parallel-group, multicentre study investigating the efficacy and safety of Sepranolone (UC1010) in patients with PMDD	
Protocol Number: UM203	
Study Period:	**Study Phase:** Phase II
Date of first patient, first visit: 20 Apr 2018	
Date of last patient, last visit: 25 Feb 2020	
Principal Investigator: Professor Shaughn O'Brien, DSc MD FRCOG **Other Investigators:** Dr Axel Schaefer, Dr Christian Deckert, Dr Heike Benes, Dr Julia Chevts, Dr Kerstin Sturm, Dr Irma Schoell, Prof Klaus-Christian Steinwachs, Dr Bozena Gornikiewicz-Brzezicka, Dr Bartomiej Golanski, Dr Mariusz Kiecka, Prof Roman Smolarczyk, Pro Angelica Linden Hirschberg, Dr Paula Briggs, Dr Radha Inusekhar, Mr Nick Panay.	
Study Centres: Medizentrum Essen Borbeck, Essen, Germany; Klinische Forschung Hamburg GmbH, Hamburg, Germany; Somni Bene Institut for Medical Research and Sleep Medicine, Schwerin, Germany; Klinische Forschung Karlsruhe GmbH, Karisruhe, Germany; Emovis GmbH, Berlin, Germany; Zentrum für Klinische Forschung Dr. Med. I. Schöll, Bad Homborg, Germany; Praxis Dr. Steinwachs, Nürnberg, Germany; Centrum Kliniczno-Badawcze J. Brzezicki. B. Górnikiewicz-Brzezicka Lekarze Spółka Partnerska, Elbląg, Poland; Pro Creative, Kraków, Poland; Centrum Medyczne Angelius Provita, Katowice, Poland; 'Szpital Kliniczny im. ks. Anny Mazowieckiej, Warsaw, Poland; Karolinska University Hospital, Stockholm, Sweden; Liverpool Women's NHS, Liverpool, UK; Royal Stoke University Hospital, Stoke-on-Trent, UK; Imperial College London, London, UK.	
Publication(s): Not applicable	
Objectives: The primary objective was to evaluate: • The efficacy of sepranolone on premenstrual symptoms in patients with defined PMDD The secondary objective was to evaluate: • The safety and tolerability of sepranolone	
Study Design: This was a multicentre, randomised, double-blind, placebo-controlled study with a parallel group design, with 2 active doses of sepranolone and placebo given during 3 luteal phases to women with defined PMDD.	
Number of Patients (planned and analysed): 225-250 treated patients planned (equally divided between study groups): 206 patients from 12 centres were randomised in this study.	

Diagnosis and Main Criteria for Inclusion:

In order to be eligible, the patients must:

1. Be a woman between 18 and 45 years of age (at Visit 1),
2. Have PMDD by history and verified according to DSM-5[a] in two menstrual cycles* by prospective symptom ratings, including minimal or absent preovulatory symptoms and presence of significant premenstrual symptoms,
3. Have a regular menstrual cycle of 24-35 days, in the opinion of the Investigator,
4. Use a highly effective or acceptable method of contraception[†] (e.g. male or female condom, non-hormonal IUD, be truly sexually abstinent, or subject or her partner has been surgically sterilised, including bilateral occlusion). Contraception must be used for the entire duration of the study,
5. Be able to understand the procedures and agree to participate in the study by signing the informed consent; in the Investigator's option, the patient must clearly be able and intend to comply with the requirements of the study.

[a] Diagnostic and Statistical Manual of Mental Disorders, 5th edition

* For the diagnosis of PMDD, patients were asked to record daily ratings of premenstrual symptoms using a validated diary (DRSP, see below) during at least two menstrual cycles. The rating results were recorded in a system accessible to the Investigators to enable assessment of the patient's chance to meet the PMDD criteria on an on-going basis during these diagnostic screening cycles. This includes a minimum or absence of symptoms preovulatory and presence of significant menstrual symptoms as specified in Appendix 16.4.

† To further clarify regarding contraceptive protection, if a woman only has one partner and he is vasectomised, this is accepted as an adequate method, whereas the use of spermicide (which is not available in Sweden, one of the participating countries in this study) without barrier protection is not considered an adequate method. A female condom and a male condom should not be used together as friction between the two can result in either produce failing. True sexual abstinence is considered a highly effective method, if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Exclusion criteria:

Patients must not:

1. Have a BMI >35 kg/m^2.
2. Have any steroid hormonal treatment (including oral contraceptive, hormonal IUD, vaginal ring, cream or dermal patch) during the previous 3 months prior to the first study visit. For the injectable Depot-provera (medroxyprogesterone acetate) a 6-month wash-out period is required prior to first study visit. For implanted contraceptive a wash-out from withdrawal of implant resulting in at least one menstrual cycle with normal length is required before inclusion.
3. Have been treated with any psychopharmaceuticals* during the previous 3 months before the first study visit, unless for SSRI where a 1-month wash-out time is acceptable (unless it is a slow-acting SSRI).
4. Have treatment during the previous 3 months before the first study visit with any over-the-counter or prescription drugs for PMS symptoms including bioidentical hormones and naturopathic preparations, e.g., St John's wort, evening primrose oil or Agnus castor.
5. Use spironolactone, gabapentin, oral corticosteroids, or daily topical corticosteroids group 2-4 steroids used on vaginal mucosa.
6. Use of Depot GnRH-agonist injections; following withdrawal of 1-month injectable, sufficient wash-out time is needed to result in at least one menstrual cycle with normal length before inclusion. For a 3-month injectable, sufficient wash-out is required to result in at least two menstrual cycles with normal length before inclusion.
7. Have a significant medical condition ongoing in the opinion of the Investigator, including any chronic psychiatric disease (according to MINI) with a relapse in the past year[†].
8. Currently have or have a history of acute or chronic severe conditions, e.g., seizure disorder, eating disorder, intracranial mass lesion, severe pulmonary, hepatic or renal disease, unstable endocrine, metabolic or haematologic disease, cancer, or HIV.
9. Have ongoing or have a history during the last 2 years of drug or alcohol misuse or dependency.

Name of Company: Asarina Pharma	**Volume:**	(For national authority use only)
Name of Finished Product: Sepranolone Injection	**Page:**	
Name of Active Ingredient(s): Sepranolone (UC1010)		

10. Be pregnant, given birth within the last 4 months before the first study visit, be breastfeeding, or intending to become pregnant during the study period.
11. Have a clinically relevant finding on the physical examination or blood testing.
12. Be hypersensitive to any of the components in the active or placebo preparations (soybean oil, egg yolk phospholipids or egg protein).
13. Be working night shifts on a regular basis.
14. Is or has been participating within the last 3 months prior to the first study visit in another clinical trial.

As guidance, common conditions that can be accepted, unless poorly controlled, are allergies, asthma, thyroid disease, migraine, hypertension, dysmenorrhoea, and cervical dysplasia.

† Occasional suicidal thoughts are common among patients with PMDD, and hence, a patient showing such ideation should not be excluded unless, in the opinion of the Investigator, it is considered severe. If the patient has a history of active suicide attempts in recent years, the patient should not be included in the study. Patients with signs of suicidal ideation should be followed up during the study.

Test Product, Dose and Mode of Administration, and Lot Number(s): Lot #: 18900023

Sepranolone Injection 10 mg and 16 mg per dose, given every 48 hour with start 14 days prior to the next estimated menstruation start, and continue until menstruation starts, but maximum 7 doses per cycle, i.e. intermittent treatment, during three menstrual cycles.

Reference Therapy, Dose and Mode of Administration, and Lot Number(s): Lot #: 18900023

Placebo (0.4 mL diluted Intralipid®) given every 48 hour with start 14 days prior to the next estimated menstruation start, and continue until menstruation starts, but maximum 7 doses per cycle, i.e. intermittent treatment, during three menstrual cycles.

Duration of Study: Total study duration per patient was approximately 7-8 months, depending on the patient's menstrual cycle length and scheduling of visit in line with the cycle.

Name of Company:	**Volume:**	(For national authority use only)
Asarina Pharma		
Name of Finished Product: Sepranolone Injection	**Page:**	
Name of Active Ingredient(s): Sepranolone (UC1010)		

Criteria for Evaluation:

Efficacy:

The primary endpoint of the study was mood and symptom assessment using a validated daily rating scale (DRSP) containing the demanded symptoms in DSM-5 for diagnosis of PMDD including severity assessment.

The DRSP scale (Daily Ratings of Severity of Problems)* includes separate items of psychological and physical symptoms as well as impairment of functioning caused by the symptoms. The ratings are captured in a Likert scale ranging from 1-6, with 1 as compete absence of a particular symptom, and 6 as the extreme severity of the symptom.

In addition, patients were asked to report menstrual bleeding in a 26th question, and following randomisation, dosing was reported by the patients in a 27th question.

* Endicott et al, Arch Womens Ment Health, 2006;9:41-9.

Safety:

Safety and tolerability were assessed by:

- AE/SAE recording,
- Physical examination, including observation of injection sites,
- Standard clinical chemistry and haematology,
- Check of menstrual cycles (length and bleeding pattern) and mid-luteal progesterone blood concentration to verify ovulation.

Pharmacokinetic:

Blood samples were taken from the patients at pre-defined time intervals to assess exposure of sepranolone and allopregnanolone in patients before and during treatment. No results from the analyses were intended to be made available until after closing of the database and results are not included in this report.

Name of Company:	**Volume:**	(For national authority use only)
Asarina Pharma		
Name of Finished Product: Sepranolone Injection	**Page:**	
Name of Active Ingredient(s): Sepranolone (UC1010)		

Statistical Methods:

Efficacy:

Primary analysis was change from baseline in late luteal phase Total symptom score (Lmax Sum21) as determined by the average sum score of all 21 questions (Q) recorded during the worst 5 consecutive days during Day -6 to Day 1.

The DRSP variables were calculated as the difference between the average of two diagnostic cycles (D) and the average of the two last treatment cycles in the sepranolone-treated (A), and in the placebo-treated (P) patients, i.e. LmaxSum21 (D_A-A versus D_P-P).

Only ovulatory cycles were used for assessment of treatment effects.

The patients' daily ratings were captured in an ePRO system, using a smartphone (patient's own or a provided borrowed device if she did not have one of appropriate standard). During the diagnosis period the symptom ratings were visible in near real-time on a secure web tool. During the treatment, symptom rating was not visible to the site or CRAs, but menstrual bleeding reporting and reporting of injections were visible to enable checking of rating and treatment compliance. The system included automatic text message reminders to the patients if they had not submitted ratings in the specified time.

Secondary end-points:

The corresponding Lmax for the Impairment score, Lmax (Q22-24) was calculated accordingly.

The corresponding Lmax for the PMDD cardinal symptom score, Lmax (Q1-Q8) including depression, anxiety, lability and anger/irritability scores were calculated accordingly.

Symptom severity was assessed using the CGI-S (severity) scale, and change in symptom severity from baseline to after completion of the three treatment cycles was assessed using the CGI-I (impairment) scale where patients with a score of 1 (very much improved) or 2 (much improved) were defined as responders.

Safety

Safety and tolerability were monitored and assessed by

- AE/SAE recording
- Physical examination, including observation of injection sites
- Standard clinical chemistry and haematology.
- Check of menstrual cycles (length and bleeding pattern) and verify ovulation.

Name of Company: Asarina Pharma	**Volume:**	(For national authority use only)
Name of Finished Product: Sepranolone Injection	**Page:**	
Name of Active Ingredient(s): Sepranolone (UC1010)		

Efficacy Results:

- There were no statistically significant differences in the primary endpoints of change in Lmax Total symptom DRSP score (Lmax Sum21) from baseline through treatment between the groups.
- As a secondary analysis, the responder numbers were assessed. More subjects in the active treatment groups experienced >75% change in Lmax Total Symptom Score from baseline compared to placebo, but it was not a statistically significant difference. A corresponding analysis using 50% improvement as the definition of a responder also showed no statistically significant differences between the groups.
- There were no statistically significant differences in change in impairment score Lmax (Q22-24) from baseline through treatment between the groups.
- There were no statistically significant differences in change in corresponding scores for the "PMDD cardinal symptoms" of irritability, depression, tension and lability, i.e. the Lmax (Q1-Q8) from baseline between the groups.
- There were no statistical differences in the number of responders (defined as a subject who by the Investigator experienced either "very much improved" or "much improved" CGI-I) between the groups. In the ITT population, approximately half of all subjects in the sepranolone 10 mg and sepranolone 16 mg groups were considered responders, compared with slightly under half in the placebo group (58.5%, 51.9%, and 47.5%, respectively). A larger percentage of subjects in the placebo group experienced "very much improved" symptom improvement, compared with either of the sepranolone treatment groups.
- Investigators reported more subjects in the placebo group showing marked improvements in the CGI-E than in either of the sepranolone treatment groups. However, more subjects in both sepranolone treatment groups showed moderate beneficial changes in CGI-E compared with the placebo group. One subject in the sepranolone 16 mg group had side-effects that significantly interfered with her physical function or outweighed the therapeutic effect according to the Investigator's assessment.
- In the ITT population there was a statistically significant improvement in Distress Score, Lmax (Q25) between the combined active treatment groups (sepranolone 10 mg plus sepranolone 16 mg) and placebo (p=0.0365).
- For the respective Individual symptoms and Individual impairment variables, there were no statistically significant improvement between either the combined or individual active treatment groups (sepranolone 10 mg and/or sepranolone 16 mg) compared with placebo. In addition, the were no improvement for any of the variables assessed as Lmax-Fmin scores.
- The results for the primary and secondary endpoints in the PP population (N=166) did not show any statistically significant differences between the treatment groups except for Distress, Lmax (Q25) p=0.0160).
- EQ-5D scores were comparable across all three treatment groups, with no significant differences for any of the categories.

Name of Company: Asarina Pharma	**Volume:**	(For national authority use only)
Name of Finished Product: Sepranolone Injection	**Page:**	
Name of Active Ingredient(s): Sepranolone (UC1010)		

Safety Results:

- There were no deaths in this study.
- Two subjects experienced an SAE: neither was considered to be treatment-related. One subject from the sepranolone 16 mg treatment group was diagnosed with breast cancer and a second subject, from the placebo group, was diagnosed with a gastrointestinal stromal tumour.
- A total of 14 subjects discontinued the study due to a TEAE: 3 subjects in the placebo group, 5 subjects in the sepranolone 10 mg group, and 6 subjects in the sepranolone 16 mg group.
- Four subjects experienced a TEAE due to injection site reactions that resulted in study drug discontinuation: 1 subject in the sepranolone 10 mg group, and 3 subjects in the sepranolone 16 mg group. Differences in injection site-related AEs were not unexpected due to the different vehicles used for IMP versus placebo; sepranolone is suspended in an oily vehicle and placebo is an aqueous solution.
- No clinically significant findings in vital signs, physical examinations, electrocardial function (QTc) or other safety observations were seen in this study.
- Treatment with sepranolone appeared to have little effect on menstrual cycle length or any of the luteal levels of hormones (progesterone, FSH and LH).

Conclusions:

The primary efficacy analysis was to evaluate the effect of sepranolone on premenstrual symptoms using the change in Lmax Total symptom DRSP score from baseline and during the diagnostic period. There was no statistically significant difference between either of the sepranolone treatment groups and the placebo group.

There was no statistically significant difference between treatment groups in the secondary endpoint of numbers of responders, using either >75% change or 50% improvement in Lmax Total Symptom Score from baseline. In addition, there was no statistically significant difference in change in impairment score Lmax (Q22-24) from baseline through treatment between the treatment groups. Furthermore, there was no statistically significant difference between the treatment groups in change in corresponding scores for the PMDD cardinal symptoms Lmax (Q1-Q8) from baseline. There was no statistically significant difference between the treatment groups in terms of responders, as defined by CGI-I.

In the exploratory analyses, there was a statistically significant improvement in Distress Score, Lmax (Q25) between the combined active treatment groups (sepranolone 10 mg plus sepranolone 16 mg) compared with placebo. There were no statistically significant differences between treatment groups for all other exploratory analyses.

Sepranolone at both 10 mg and 16 mg was generally safe and well tolerated in this population with PMDD.

Date of Report, version: 23 October 2020, Final