A randomized, double-blind study on efficacy and safety of sepranolone in premenstrual dysphoric disorder

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ABSTRACT

Women with *premenstrual dysphoric disorder (*PMDD) experience mood symptoms related to the increase in progesterone and the neuroactive steroid allopregnanolone. Our hypothesis is that allopregnanolone is the symptom provoking factor. The rationale for the present study was to treat PMDD patients with the GABA$_A$ receptor modulating steroid antagonist, sepranolone (isoallopregnanolone). Patients (n = 206) with PMDD from 12 European centers were randomized in a parallel double-blind study and treated with placebo, sepranolone 10 mg and 16 mg. Patients administered sepranolone subcutaneously every 48 h during the 14 premenstrual days of three consecutive menstrual cycles. After obtaining informed consent, the PMDD diagnosis was confirmed according to DSM-5 and verified with two menstrual cycles of daily symptom ratings using the Daily Record of Severity of Problems (DRSP) scale in an eDiary. Inclusion and exclusion criteria stipulated that the women should be essentially healthy, not pregnant, have no ongoing psychiatric disorder or take interfering medications, and have regular menstrual cycles. The study's primary endpoint was the Total symptom score (Sum21, the score for all 21 symptom questions in the DRSP). In the prespecified statistical analysis the average score of the 5 worst premenstrual days in treatment cycles 2 and 3 were subtracted from the corresponding average score in the two diagnostic cycles. The treatment effects were tested using analysis of variance in a hierarchal order starting with the combined active sepranolone treatments vs. placebo. The prespecified analysis of Sum21 showed a large treatment effect of all three treatments but no statistically significant difference to placebo. However, the ratings of distress showed a significant treatment effect of sepranolone compared to placebo (p = 0.037) and the ratings of impairment showed a trend to greater treatment effect of sepranolone compared to placebo. Many women with PMDD had symptoms during a longer period than the late luteal phase. It has previously been shown that 9 premenstrual days may be more representative for comparison of PMDD symptom periods than the 5 worst premenstrual days. A post hoc analysis was undertaken in the per protocol population investigating the treatment effect during 9 premenstrual days in the third treatment cycle. The Sum21 results of this analysis showed that the sepranolone 10 mg was significantly better than placebo (p = 0.008). Similar significant treatment effects were found for the impairment and distress scores. A significantly larger number of individuals experienced no or minimal symptoms (Sum21 <42 points) with the 10 mg sepranolone treatment compared to placebo (p = 0.020). The results indicate that there is an attenuating effect by sepranolone on symptoms, impairment, and distress in women with PMDD especially by the 10 mg dosage. Sepranolone was well tolerated, and no safety concerns were identified.

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1. Introduction

*Premenstrual dysphoric disorder (*PMDD) (APA, 2013) and the less severe condition premenstrual syndrome (PMS) (ACOG, 2001) are considered to be sex steroid driven, menstrual cycle related conditions (Nevatte et al., 2013; DeVane, 1991). PMDD is included in the international classification of disorders, ICD-11, as a gynecological disease with its own gynecological classification code, GA34.41 (Reed et al., 2019; WHO, 2020) and in the Diagnostic and Statistical Manuel (DSM) for Mental Disorders, fifth edition (APA, 2013; Epperson et al., 2012) under the category of depressive disorders (625.4) PMDD is a well-defined clinical condition although the pathogenesis is still not fully understood. Symptoms start at the time of ovulation and the severity increases in parallel with the rise in serum progesterone and allopregnanolone (Bäckström et al., 2014; O'Brien et al., 2011). The negative symptoms reach a maximum during the premenstruum and disappear within day 3–4 of the next menstrual cycle. During the pre-ovulatory phase there is a period of wellbeing (Bäckström et al., 1983). In addition, the cyclicity of the symptoms disappears in anovulatory menstrual cycles, when steroids from the corpus luteum are not produced, indicating that a symptom provoking factor is produced in the corpus luteum of the ovary (Hammarbäck and Bäckström, 1988; Hammarbäck et al., 1991). Progesterone administration leads to resurgence of symptoms in women with PMDD who have undergone ovarian suppression with gonadotropic releasing hormone (GnRH) agonist (Schmidt et al., 1998) and in postmenopausal women taking estrogen (Andreen et al., 2006) suggesting that progesterone, and presumably allopregnanolone trigger PMDD symptoms. Generally, progesterone/allopregnanolone serum concentrations across the menstrual cycle are similar in women with and without PMDD (Nevatte et al., 2013). However, compared to controls women with PMDD show altered gamma amino-butyric acid (GABA) type A (GABA$_A$) receptor sensitivity to allopregnanolone- with greater sensitivity associated with more severe PMDD symptoms (Timby et al., 2016; Sundström et al., 1998). Administration of GnRH agonist or a 5α reductase inhibitor results in decreases in allopregnanolone, leading to a significant alleviation of premenstrual symptoms in women with PMDD (Nyberg et al., 2007, Martinez et.al, 2016).

The objective of this study was to test the compound sepranolone, a GABA$_A$ receptor modulating steroid antagonist (GAMSA) in the treatment of PMDD symptoms in naturally cycling women. Sepranolone is identical to the compound isoallopregnanolone (3β-hydroxy5α-pregnan-20-one), a naturally occurring metabolite of progesterone (Corpechot et al., 1993) and a stereoisomer of allopregnanolone. Iso-allopregnanolone is formed in parallel with progesterone and allopregnanolone in women during the luteal phase of the menstrual cycle. Unlike progesterone, isoallopregnanolone lacks classical hormonal effects (Jewgenow et al., 1998; Hedström et al., 2009) and has no effect per se on the GABA$_A$ receptor but works as an antagonist to positive GABA$_A$ modulating steroids e.g., allopregnanolone (Birzniece et al., 2006; Lundgren et al., 2003).

In pre-clinical studies, sepranolone has been shown to inhibit the effect of allopregnanolone on GABA-stimulated chloride uptake on the GABA$_A$ receptor in vitro (Lundgren et al., 2003) and, in rats sepranolone inhibited allopregnanolone-induced anaesthesia (Bäckström et al., 2005). The ability of sepranolone to antagonise allopregnanolone-induced effects has also been demonstrated in women, by detecting effects on sedation in a pharmacodynamic model of GABA$_A$ receptor activation (Bengtsson et al., 2015). In a first explorative clinical phase I/II study patients with well-characterized PMDD, luteal phase sepranolone administration reduced premenstrual symptoms and impairment of daily life (Bixo et al., 2017).

The study described herein is an extension of previous research with sepranolone to test the hypothesis that sepranolone is more effective than placebo in reducing PMDD symptoms, presumably through sepranolone-induced inhibition or blockade of allopregnanolone action

at the GABA$_A$ receptor in women with PMDD (Bäckström et al., 2011). A secondary hypothesis is that sepranolone has a good safety and tolerability profile.

2. Methods

2.1. Design of the study and study participants

This study was a parallel double-blind, randomized controlled trial design. The primary objective was to evaluate the effect and secondary objective to evaluate safety and tolerability of repeated subcutaneous administration of sepranolone. Women with DSM-5 confirmed PMDD from 12 European medical centers were recruited to participate in a randomized double-blind, placebo-control study to test the effectiveness, safety, and tolerability of two doses of subcutaneously administered sepranolone (10 mg/dose or 16 mg/dose) in the treatment of PMDD symptoms. Participants self-administered the study medication at home every second day during the luteal phase of 3 menstrual cycles, starting 14 days prior to the next estimated onset of menstruation, for a maximum of 7 doses per cycle (Fig. 1). This treatment regimen aimed to provide an isoallopregnanolone plasma level that was 2–3 times higher than the endogenous luteal phase allopregnanolone levels in those receiving active drug (Bixo et al., 2017).

Written informed consent was obtained from each patient and ethics permission was given by the governing institutional review board or ethics committee of each investigational center prior to the start of the trial. The study complied with the ethical principles of Good Clinical Practice (GCP) and was made in accordance with the current version of the Declaration of Helsinki with the EudraCT number 2017–000822–37.

The patients were asked to record daily ratings of premenstrual symptoms using a validated diary (Daily Record of Severity of Problems, DRSP; Endicott et al., 2006) during the study. The ratings were recorded in an electronic diary, and the recordings were accessible to the investigators during the diagnostic period but blinded during treatments. The DRSP recordings during diagnosis verification constituted baseline data and the same system was used to capture symptoms during treatment with active substance or placebo.

2.2. Inclusion criteria

Inclusion criteria included: Be between 18 and 45 years of age, have PMDD by history and verified cyclical symptom changes according to DSM-5 in two menstrual cycles by prospective symptom ratings, including minimal or absent preovulatory symptoms and presence of significant premenstrual symptoms (APA, 2013). Have a regular menstrual cycle of 24–35 days. Use an acceptable method of non-hormonal contraception. Be able to understand the procedures and agree to participate in the study by signing the informed consent and intend to comply with the requirements of the study.

2.3. Exclusion criteria

Patients <u>could not</u>: Have a body mass index (BMI) > 35, have any steroid hormonal treatment during the previous 3 months prior to the first study visit. For injectable medroxyprogesterone acetate, a 6-month wash-out period was required. For hormonal implants, a wash-out period resulting in at least one menstrual cycle with normal length was required. Have been treated with any psychopharmaceuticals during the previous 3 months, except SSRI where a 1-month wash-out time was acceptable. During the previous 3 months have used any over-the-counter or prescription drug for PMS symptoms. Use spironolactone, gabapentin, oral corticosteroids, or daily topical corticosteroids. Use GnRH-agonist injections; a wash-out of one menstrual cycle with normal length was needed before inclusion. Have a significant ongoing medical condition, including any psychiatric disease (M.I.N.I, International Neuropsychiatric Interview) with a relapse in the past year. Have or
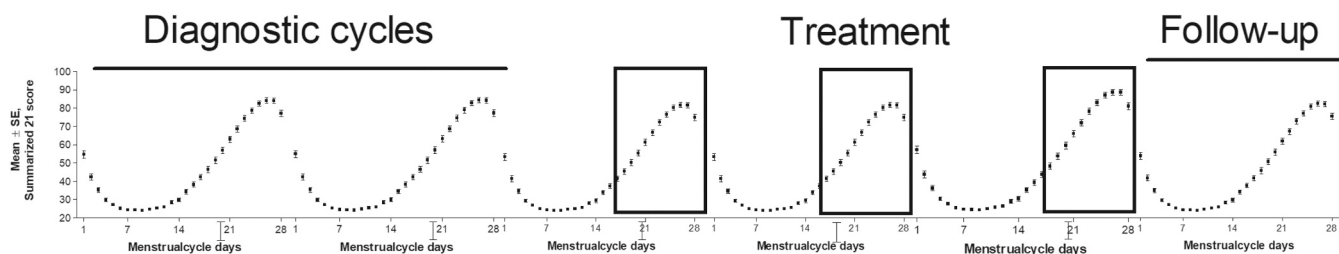
Fig. 1. Overview of the study design including two diagnostic cycles, three treatment cycles and one follow-up cycle. The Y-axis illustrates presence of symptoms in women with premenstrual dysphoric disorder (PMDD).

have had a history of an acute or chronic severe condition. Have ongoing or have a history during the last 2 years of drug or alcohol misuse or dependency. Be pregnant, have given birth within the last 4 months, be breastfeeding, or intending to become pregnant. Have a clinically relevant finding on the physical examination or blood testing. Be hypersensitive to any of the components in the active or placebo preparations. Be working night shifts on a regular basis. Be participating within the last 3 months in another clinical trial.

2.4. Test products, dose and mode of administration

Sepranolone (Asarina Pharma AB, Lot: 18900023), is an investigational product for subcutaneous use, provided prefilled (0.4 mL) in single-use syringes suspended in an oily vehicle. In the present study individuals were randomized to receive sepranolone 10 mg/dose, sepranolone 16 mg/dose or placebo, given every 48 h starting 14 days prior to the next estimated menstruation and stopping with the onset of menstruation. Drug administration continued in this manner for three menstrual cycles. Participants were limited to 7 doses per cycle. The study medication was administered as subcutaneous injections to avoid the extensive first pass hepatic metabolism known to occur with the isoallopregnanolone molecule. The placebo used in this study was diluted Intralipid® which is an aqueous solution with a similar appearance as the active study medication, prefilled in the same device as the active drug. Participants were trained to self-administer the study drug.

2.5. Criteria for evaluation

2.5.1. Collection of effect data

The primary endpoint of the study was the total symptom scores of 21 questions (Sum21) on the validated daily rating scale DRSP (Endicott et al., 2006) containing the required symptoms in DSM-5 for diagnosis of PMDD. This was followed by three questions on impairment of functioning. In addition, patients reported in one question on menstrual bleeding. In the ICD-11, GA34.41 it is stated that for PMDD diagnosis "The symptoms are severe enough to cause significant distress or significant impairment in personal, family, social, educational, occupational or other important areas of functioning and do not represent the exacerbation of a mental disorder" (WHO, 2020) therefore a question distress was rated daily. All ratings (except menstrual bleeding) were captured in a Likert scale ranging from 1 to 6, with 1 as absence of a symptom, $2 =$ minimal, $3 =$ mild, $4 =$ moderate, $5 =$ severe and $6 =$ extreme severity of the symptom. Corresponding numbers for Sum21 scores are 21 for no symptoms, 42, 63, 84, 105 and 126 for extreme symptoms (Fig. A1). A 4-step scale was used for the daily recording of bleedings (no bleeding, spotting, moderate flow, significant flow). During drug administration patients also reported daily if study drug was taken (yes or no).

The patients' daily ratings were captured in an eDiary system, using a smartphone (patient's own or a loaned device). During the diagnostic period, the symptom ratings were visible for the site staff on a secure web tool. After randomisation, symptom rating was blinded to the site staff and the clinical research assistant (CRA) except for menstrual bleeding and injections to enable control of compliance to daily ratings and treatment. The system included automatic text message reminders to the patients if they had not submitted ratings in the specified time.

2.5.2. Safety and tolerability

Safety and tolerability were assessed by adverse events reporting (AE/SAE recording), physical examination, including observation of injection sites, standard clinical chemistry, and hematology, check of menstrual cycles (length and bleeding pattern) and mid-luteal phase progesterone blood concentration to verify ovulation.

2.5.3. Bioanalyses

Blood samples were taken from the patients at pre-defined time intervals to assess exposure of isoallopregnanolone and allopregnanolone in patients before and during treatment luteal phase progesterone to diagnose ovulation. No bioanalytical results from the analyses were disclosed until after closing of the database. allopregnanolone and isoallopregnanolone were analysed by validated methods using UPLC-MS/ MS, Lablytica, Uppsala Sweden.

2.6. Work up of the data and statistical methods

2.6.1. Estimation of sample size

The power analysis was based on the results from the earlier phase I/ II studies (Bixo et al., 2017). With a power of 90% and alpha level 5%, the total sample size was calculated to 150 for a 1:2 ratio based on a two-sided Mann-Whitney independent group test i.e., 50 patients per group but to compensate for dropout's recruitment was set to 75 per treatment group.

2.6.2. Efficacy

The Total symptom score, summarized 21 symptoms (Sum21), was determined per day for each woman during the study. In the predefined analysis, a maximal luteal phase score (LmaxSum21) was generated from the average of ratings during the worst 5 consecutive days assessed during Day -6 to Day $+1$ of the menstrual cycle. A minimal follicular phase score (FminSum21) was generated from the average of ratings during the best 5 consecutive days assessed during Day 5 to Day 12 of the menstrual cycle. For the predefined primary analysis, the difference in baseline LmaxSum21 scores (average of two cycles) minus treatment (the average of the two last treatment cycle) was compared between the treatment groups. The scores in the first treatment cycle were not used as they were considered an adaptation to the treatment situation. Only ovulatory cycles were used for assessment of treatment effects. The predefined analysis was made in hierarchical order, first analyzing the combined treatment, and stopped there if the result was not significant. The secondary DRSP-derived score Impairment, and the Distress score, were calculated in a corresponding manner. To be part of the intent-to-treat (ITT) population women needed to have completed at least one ovulatory treatment cycle 2 or 3, with 4 doses of study medication taken and have evaluable data, i.e., at least 4 days with reported ratings during the assessment period. In the per protocol (PP) population the women

needed to have evaluable data in ovulatory treatment cycle 2 or 3 with at least 4 doses taken in these cycles. For participation in the post-hoc analysis the patient had to have complete data and fulfill the above criteria for treatment cycle 3. For within-subject differences non-parametric tests were applied (e.g., Mann-Whitney, Friedman's test, Wilcoxon test or Fisher's exact test as applicable) on an ITT base (not substantially deviated from protocol). All-patient-treated (APT) was used for the safety and tolerability variables.

Many women with PMDD experience significant symptoms before the last week of the menstrual cycle and it has previously been found that a period of nine (9) days is most optimal in diagnosing menstrual cycle linked mood changes (Hammarbäck et al., 1989). Hence, in a post-hoc analysis, nine consecutive premenstrual days (Day −9 to Day −1) were used for the primary and secondary measures and the effects in the third treatment cycle were compared between treatments using repeated measures analysis of variance (ANOVA) followed by a least significance difference test. Summarized scores and change in summarized scores from baseline to treatment cycles in the sepranolone dose groups separate and combined were compared to the same period in the placebo group.

3. Results

The first and final participant was enrolled in April 2018 and in February 2020, respectively. In total, 475 women were enrolled (Fig. 2) and of these women, 206 were eligible and were randomized to one of the three study arms. The population for safety analyses consisted of 202 women as four women never started study drug administration. Ten

women either withdrew from the study or did not have at least one ovulatory and evaluable cycle, hence the ITT population consisted of 192 women. The PP population was made up of 166 women (placebo=58, 10 mg = 56 and 16 mg = 52). There were 143 women with an ovulatory cycle and evaluable data in the 3rd treatment cycle (placebo n = 44, 10 mg n = 50 and 16 mg n = 49) constituting the analyzed PP-population in the post-hoc analysis.

Baseline characteristics for the ITT-population are shown in Table 1. The number of women with a previous depressive disorder in the ITT population showed a trend (p = 0.086) to be more prevalent in the 16 mg group compared to the placebo group. Otherwise, there were no differences between the treatment groups in baseline characteristics. Baseline characteristics for the PP-population used in the post-hoc analysis are shown in the appendix Table A1.

3.1. Safety results, n = 202

Twenty-one women terminated study during treatment by withdrawal of consent, 9 individuals in the placebo group, 8 in the 16 mg group and 4 in the 10 mg group. A total of 14 subjects discontinued the study due to a treatment-emergent adverse event (TEAE): 3 subjects (4.5%) in the placebo group, 5 subjects in the sepranolone 10 mg group (7.4%), and 6 subjects (8.9%) in the sepranolone 16 mg group. More administration site related AEs were observed in the sepranolone groups compared with the placebo group. The most prevalent AE was injection site pain, affecting 8 out of 68 subjects (11.8%) in the sepranolone 16 mg group 59 events (5.8% of the total number of injections). In the 10 mg and the placebo groups injection site pain occurred in 3% and 4%,
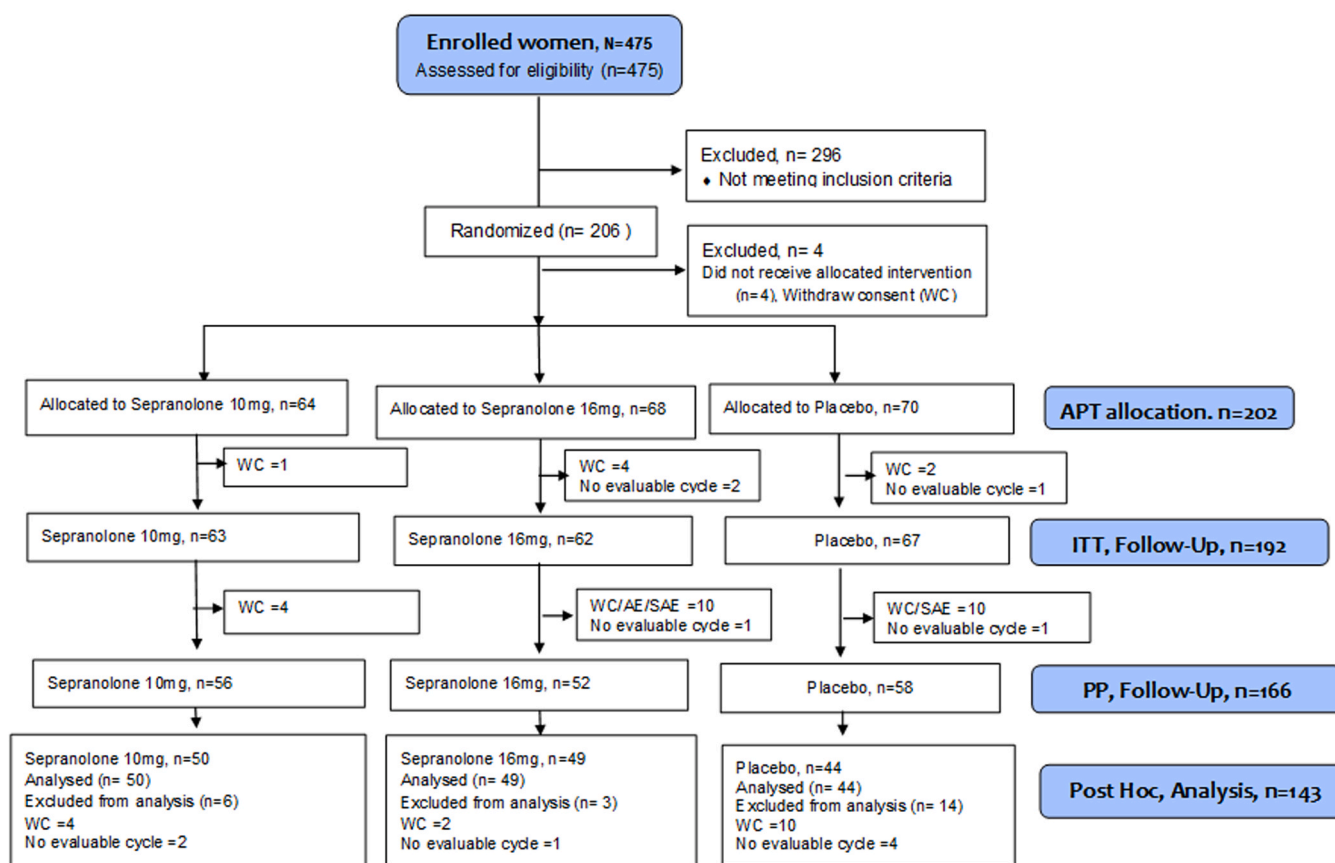

Fig. 2. Consort flow-chart and distribution of patients between the different populations. APT=all patients treated, ITT=intent-to-treat; PP=per protocol. Post hoc analysis=PP population in the third treatment cycle. AE= adverse event, SAE = Serious adverse event, WC=withdraw consent, no evaluable cycle=according to criteria described in "Methods".

Table 1
Baseline characteristics in the ITT population, n = 192.

	Sepranolone 10 mg N = 63	Sepranolone 16 mg N = 62	Placebo N = 67
Age, years median (min-max)	32.7 (23–45)	33.0 (20–43)	35.5 (22–45)
BMI, kg/m², median (min-max)	23.6 (19–35)	24.0 (17–35)	23.9 (18–34)
Non-smokers, %	54.0	64.5	56.7
PMDD diagnosis history, %	17.5	16.1	23.9
PMDD symptoms in patients with a history, median (min-max), years	8(2–27)	7(2–22)	9(1–30)
Previous use of PMDD treatment, %	27.0	32.3	25.4
Previous depressive disorder, %	17.4	29.0	16.4
CGI-S[a], not at all ill, %	1.6	1.6	4.5
Mildly ill, %	11.1	14.5	10.4
Moderately ill, %	31.7	24.2	34.3
Markedly ill, %	23.8	37.1	26.9
Severely ill, %	28.6	21.0	22.4
Extremely ill, %	3.2	1.6	1.5
Concomitant medication any time, %	66.7	69.4	73.1
Length of menstrual cycle at diagnosis, days, median (min-max)	28(24–35)	28(24–36)	27(24–35)

[a] CGI-S = Clinical Global Impression - Severity of Illness.

respectively. No clinically significant findings regarding vital signs, physical examinations, electro-cardiac function (QTc) or other safety observations were seen in this study. Treatment with sepranolone did not have any effect on menstrual cycle length, ovulation frequency or any of the luteal phase hormone levels (progesterone, FSH and LH, data not shown). There were no deaths during the study period. Two subjects experienced an SAE, but neither was 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 benign gastrointestinal stromal tumour.

3.2. Summarized symptom scores during the diagnostic cycles

Sum21 per day (average of two diagnostic cycles) of the ITT population is shown in figure A2. Baseline LmaxSum21 was 81.4, 88.5 and 83.7 points in the 10 mg, 16 mg and placebo groups, respectively. The ratings in the diagnostic cycles of the post-hoc PP population are shown in Fig. 2. In the graph's symptoms are depicted as mean±SE for each treatment group. The data are centralized around the first day of bleeding (Day 1) 14 days before and 14 days after including day 1 (±14 days) and then plotted into a cycle with 28 days. Sum21 during the diagnostic cycles (baseline) was similar in the three treatment groups (Figure A2, Table A2). The variation between the two diagnostic cycles was small and non-significant. LmaxSum21 (mean ± SE) during the nine premenstrual days was 74.4 ± 1.61 points.

3.3. Summarized symptom scores during the treatment cycles

In the predefined analysis the LmaxSum21 scores of the five worst premenstrual days decreased by 30.6, 31.0 and 25.8 points in the 10 mg, 16 mg and placebo groups, respectively, with no statistically significant difference between the three treatment groups (Table A3). In a responder analysis a large proportion of women experienced a > 75% or > 50% change in LmaxSum21 scores but no significant difference between active treatment and placebo. The decrease in impairment or the "PMDD core symptoms" during the five worst days Lmax(Q22–24)

showed no significant difference between the groups. However, in the ITT population the distress variable, showed a significant improvement during the five worst days in the change from baseline to the treatment period (sepranolone 10 mg and 16 mg combined group) compared to the placebo group (p = 0.037, Table A4). For the PP population the corresponding improvement with sepranolone treatment compared to placebo was even stronger (p = 0.016). In the ITT population LmaxSum21 show a trend of an average greater placebo response in cycle T2 than in T3 (Figure A3), however not significant.

3.4. Post-hoc analyses in the PP population

3.4.1. Summarized 21 symptom scores during the third treatment cycle

The summarized scores in treatment cycle 3 show a clear effect of all three treatment modalities compared to pre-treatment (Fig. 3A,3B). When comparing Sum21 during nine premenstrual days between the groups, there was a statistically significant difference between placebo and the combined active doses (p = 0.027). This improvement was predominant for treatment with 10 mg sepranolone, showing a clear statistically significant improvement compared to placebo (Fig. 3A, ANOVA (1,92)= 7.80; p = 0.006), effect size 0.58 (Hedge's g) over 9 luteal phase days. When comparing the 16 mg treatment with placebo the mean score in the 16 mg group was lower than in the placebo group during the last 9 days of the menstrual cycle but no significant difference in effect was noted (Fig. 3B).

3.4.2. Treatment effect on impairment scores

A total daily score was calculated by summarizing the points of the three questions with a minimum score of 3 and maximum score of 18 points (Figs. 3C,D). The mean summarized impairment score during the baseline nine premenstrual days was 11.3 points. The treatment effect on summarized impairment scores during the nine premenstrual days in treatment cycle 3 shows a significant effect of sepranolone 10 mg compared to placebo (F(1,92)= 8.77;P = 0.004), giving an effect size of 0.61 (Hedge's g) over 9 premenstrual days) while the effect of sepranolone 16 mg treatment was not significant.

The effect on work performance was analyzed separately. During the nine premenstrual days in the baseline cycles of the PP population 116 out of 143 patients (81%) showed more than a moderate impairment (mean score above 3 points), for work performance. During treatment cycle 3, 20/44 (45.5%) of the women in the placebo group still had an impairment of work performance. In the sepranolone 10 mg group 10/50 (20.0%, p = 0.008 vs placebo) had some work impairment and thus about 80% did no longer have any work impairment. In the sepranolone 16 mg group 12/49 (24.5%, p = 0.034 vs. placebo) had some work impairment while 75.5% did not.

3.4.3. Treatment effect on PMDD distress symptoms

In the third treatment cycle, the sepranolone effect on distress ratings (combined active dose groups) was superior to placebo (F(1,141)= 13.10;p < 0.000) and when the effect of the treatment doses were investigated separately, only sepranolone 10 mg showed a significant treatment effect vs. placebo (F(1,92)= 20.06;p < 0.000, Fig. 3E, Hedge's effect size g= 0.862) whereas the effect by the sepranolone 16 mg dosage (Fig. 3F) was lower showing a borderline significance (F(1,91)= 3.92;p = 0.051).

3.4.4. Treatment effect on change in Sum21 PMDD symptoms

The mean ± SE improvement in Sum21 scores during nine premenstrual days from baseline to treatment cycle 3 was calculated as the treatment cycle 3 Sum21 score minus the baseline Sum21 score per day for the respective patients. A repeated measures ANOVA gave F (1,92) = 7.297; p = 0.008 for treatment with 10 mg sepranolone compared to placebo. Neither the 16 mg treatment group, nor the combined active treatment groups 10 mg and 16 mg showed an effect significantly superior to placebo (p = 0.184), see Fig. 4.
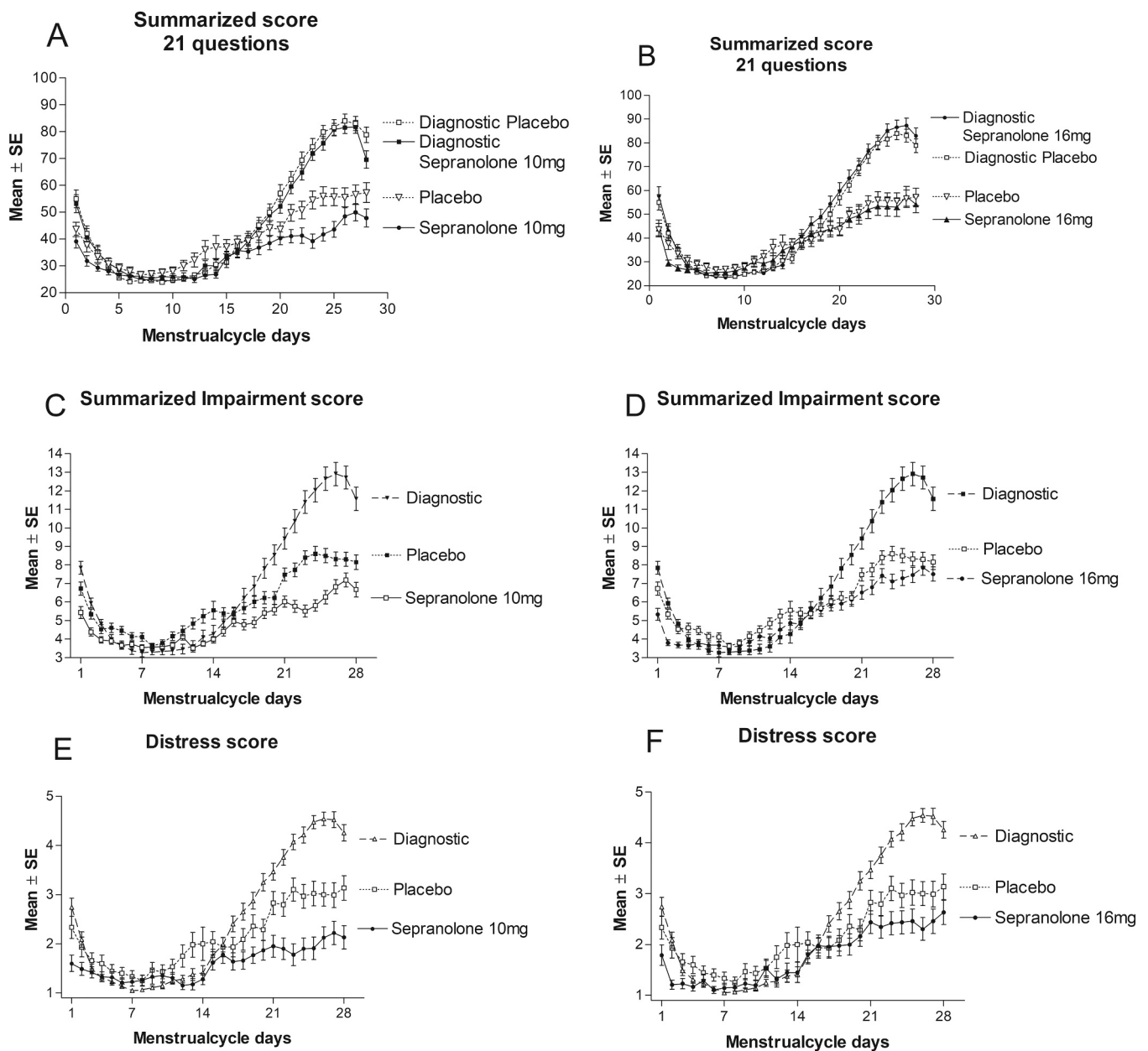
Fig. 3. Effect of sepranolone on symptom scores (mean±SE) in the PP population with an ovulatory and evaluable treatment cycle 3 (n = 143). Symptoms are centered around the 1st day of menstrual bleeding ±14 days. Top panel (A-B): An average of the Sum21 score during the two diagnostic cycles and treatment cycle 3 are shown for women treated with placebo, sepranolone 10 mg (3 A) or 16 mg (3B). Diagnostic cycles shown separately for each treatment group. Score 21 =absence of symptoms. Middle panel (C-D): Effect on summarized impairment scores in the PP population during diagnostic cycles and treatment cycle 3 is shown with placebo, sepranolone 10 mg (3 C) and 16 mg (3D) separated. Score 3 = no impairment and maximal impairment could be 18. Bottom panel (E-F): The effect on distress scores in the PP population during diagnostic cycles and treatment cycle 3 is shown (placebo+sepranolone 10 mg (3E) and placebo+ 16 mg (3 F). Score 1 means absence of distress and maximal distress could be 6.

3.4.5. Responder analysis for treatment cycle 3

A responder analysis was made by calculating the number of patients that became symptom free during 9 premenstrual days of treatment, (mean Sum21 <30 points §2.6.2). In this analysis treatment with 10 mg sepranolone was superior compared to placebo (Table 2) as well as the number of individuals with mean minimal symptom score (<43 points) during the 9 premenstrual days. Treatment with sepranolone 16 mg showed a trend towards an effect.

3.4.6. Treatment effect on PMDD core symptoms

Summarized negative mood score (anger/irritability, depression, anxiety, and lability) show the same pattern as total symptom score with significant improvement compared to placebo with 10 mg (p = 0.008) but not with 16 mg. Depression and irritability are two main mood symptoms in PMDD. In both symptoms sepranolone 10 mg has a clear treatment effect compared to placebo during the 9 premenstrual days (p = 0.013 and p = 0.005). However, Sepranolone 16 mg did not show significant effects compared to placebo even though the mean symptom score showed lower mean level compared to placebo. Summarized physical symptoms (Breast tenderness + bloating) did not show a significant difference compared to placebo even though 10 mg was numerically better than placebo.
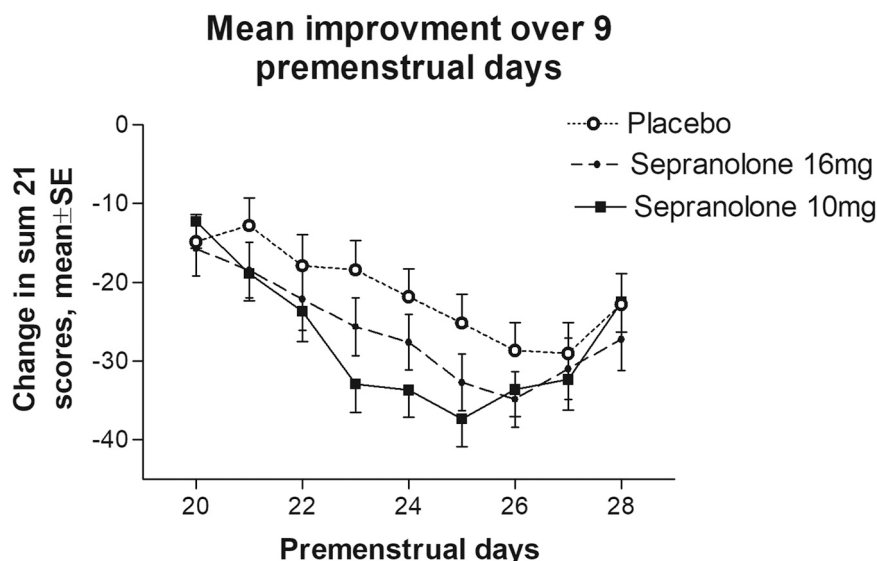
Fig. 4. Change in Sum21 during nine luteal phase days from baseline to the 3rd treatment cycle in the PP population. Comparison between women treated with sepranolone, 10 mg or 16 mg, or placebo.

Table 2
Number of individuals becoming symptom free (i.e. mean<30 points) or having minimal symptoms (≤42 points) on the DRSP scale (figure A1) during nine premenstrual days in treatment cycle 3. Test = chi-sq, n = 143.

Less than mean 30 p during treatment	Yes	No	Total	P-value vs. placebo
Placebo	3	41	44	
Sepranolone 10 mg	12	38	50	0.023
Sepranolone 16 mg	10	39	49	0.059, NS
Less than mean 43 p during treatment	Yes	No	Total	P-value vs placebo
Placebo	15	29	44	
Sepranolone 10 mg	29	21	50	0.020
Sepranolone 16 mg	22	27	49	NS

3.5. Plasma concentrations of allopregnanolone and isoallopregnanolone at baseline and during treatment cycles

Plasma concentrations of allopregnanolone and isoallopregnanolone are presented in appendix (Fig. A4). The concentrations of allopregnanolone were essentially the same at baseline and in the groups treated with sepranolone 10 mg or 16 mg. A full pharmacokinetic analysis of isoallopregnanolone has not been undertaken. The isoallopregnanolone concentration for the 16 mg treatment group was somewhat higher than for the 10 mg group and showed a greater variability than that of the lower dose. Results are consistent with results from the previous study and confirm that repeated doses of 10 mg and 16 mg results in an average isoallopregnanolone plasma concentration ranging between 2 and 10 nmoles/L.

4. Discussion

The present study was a phase II study using sepranolone 10 mg and 16 mg as luteal phase treatment for PMDD in a randomized, parallel-group, placebo-controlled design. In the present study using the pre-defined endpoint, five worst late luteal phase days, distress scores were significantly improved by sepranolone treatment compared to placebo. However, in the other predefined primary and secondary endpoints no significant effect over placebo could be recorded. Many women have a longer symptom duration than the five late luteal phase days used as predefined in the protocol. In a post hoc analysis, nine luteal phase days were used instead. The efficacy results in the PP population and the change from baseline to treatment in cycle 3 showed that sepranolone 10 mg reduced PMDD symptoms significantly more than placebo (Fig. 3). This reduction in symptoms by sepranolone could be expressed as a shift from severe to mild/minimal-absence scores on the DRSP scale (Figures A1 and Table 2). The post hoc analysis revealed that the magnitude of effect by sepranolone 10 mg treatment was similar or better than shown in an earlier study with sepranolone (Bixo et al., 2017) and treatments with SSRIs or drosperinone-containing oral contraceptives (Cohen, 2002, Halbreich, 2002, Pearlstein, 2003, Yonkers, 2005 and Pearlstein, 2005). However, the effect of sepranolone 16 mg dosage did not statistically differ from placebo even though the mean symptom ratings were numerically lower compared to the placebo group. This was surprising and is further discussed below.

The placebo effect is often large in treatment studies of PMDD (Cohen et al., 2002) and the placebo effect was about 30% higher in the present study compared to the previous phase 2a study with sepranolone (Bixo et al., 2017). The higher placebo effect in this study may be due to the self-administration of the injections but was also slightly lower in the third compared to the second treatment cycle indicating a declining placebo effect over time. That may teach us that studies on PMDD should be longer than three cycles or that the effect of 10 mg and 16 mg were similar but that the power of the 16 mg group was too low given greater variance of measurements to render a statistical difference.

In conformity with previous studies, the present study used the average symptom score for the five worst late luteal phase days as a predefined measure whereas a period of nine premenstrual days was used in a post hoc analysis for assessing the effect of treatment. A study by Hammarbäck et al. (1989) found that nine premenstrual days was the optimal number of days for PMDD diagnosis. Therefore, nine days was chosen to compare effects in this post hoc analysis. Many women do have severe symptoms and impairment during a longer premenstrual period than only five days. Therefore, the nine days statistical testing of symptoms, impairment and distress scores are presented in the result part of the present report.

The present study is performed in accordance with the recommendations of the ISPMD consensus group examining two untreated cycles for diagnosis and using three treatment cycles for the study of effect (O'Brien et al., 2011). The rating scale used for the assessment of treatment effects (DRSP, Endicott et al., 2006) has been used in earlier studies where treatment effects of sepranolone, SSRIs and oral contraceptives were investigated. The Sum21 score was consistently used as primary measure in these studies (Cohen et al., 2002; Yonkers et al., 2005; Bixo et al., 2017). The DRSP rating scale was approved by the FDA

(US agency Food and Drug Administration) and therefore, the DRSP rating scale and the Sum21score was used in this study. In the diagnostic cycles of the present study the Sum21 was somewhat higher than in previous studies (Bixo et al., 2017; Cohen et al., 2002; Yonkers et al., 2005) and the preovulatory follicular phase showed consistently low scores (Fig. 3 and A2). This shows that the recruitment and diagnostic procedures were valid in this study and that the criteria for PMDD in DSM-5 were fulfilled (APA, 2013). In addition, the criteria for PMDD in WHO's International Classification of Diseases, ICD-11 (code GA34.41) were also fulfilled (Reed et al., 2019; WHO, 2020). In ICD-11 PMDD is included as a gynecological disease and requirements for diagnosis are: "The symptoms are severe enough to cause significant distress or significant impairment in personal, family, social, educational, occupational or other important areas of functioning and do not represent the exacerbation of a mental disorder". It was considered important to also fulfil the ICD-11 demands and by adding the variable "distress" to the daily ratings during the diagnostic and treatment cycles the demands of the ICD-11 were also fulfilled. The PMDD diagnosis was however made according to DSM-5.

The treatment effects on impairment and distress gave a similar picture as the Sum21 score results. Notable is that in the diagnostic cycles of the PP population 81% of the women showed a premenstrual reduction of work performance but during sepranolone 10 mg treatment only 20% had a work impairment and in the 16 mg group 24.5% had a work impairment while in the placebo group about 45.5% had a work impairment. A responder analysis showed that sepranolone 10 mg gave a significantly higher responder rate compared to placebo. However, sepranolone 16 mg showed only a trend compared to placebo towards a curing effect. The core PMDD symptoms showed similar pattern as total symptoms with an effect of 10 mg but not 16 mg compared to placebo. Interesting is that for physical symptoms no significant improvement was noted compared to placebo.

A statistical analysis was also performed using the combined sepranolone treatment groups. In the combined treatment the effect was reduced due to a lower response rate in the 16 mg group and the significance against placebo was reduced compared to sepranolone 10 mg. However, a rating of distress showed a robust treatment effect also noted in the combined 10 mg and 16 mg groups compared to placebo.

The smaller treatment effect by the 16 mg treatment was surprising as the mean plasma level of isoallopregnanolone was about the same or slightly higher in the 16 mg group compared to the 10 mg group. One could have imagined that the metabolism to allopregnanolone would be higher in the 16 mg group, but the allopregnanolone levels were not different between the dosage groups (Fig. A4). The reason for why the higher dosages is less effective compared to the 10 mg dose is not known but one can speculate. In the 16 mg group there is a trend ($p = 0.08$) of a higher frequency of individuals with previous depressive disorder. This might be of importance as women with a previous depression are more sensitive to negative mood effects of oral contraceptives and this might be the case for steroids in general (Bengtsdotter et al., 2018). Another possibility is that there exists a pharmacodynamic similarity between isoallopregnanolone and positive GABA$_A$ receptor modulators (PAM). With PAM it is well known that the effect can wain off with higher dosages and that there exists a biphasic dosage-response effect documented in numerous biological, toxicological, and pharmacological investigations (Calabrese, Baldwin, 2001, Baldi, 2005, Bayer et al., 2018, Srinivasan et al., 1999; Mehta and Ticku, 1998, Bäckström et al., 2011, Pinna et al., 2006, Miczek et al., 2003). A biphasic effect has been shown in humans regarding mood in relation to allopregnanolone plasma concentration (Andreen et al., 2006). Normal luteal phase concentrations, induce more severe mood than both higher and lower levels indicating a biphasic effect of allopregnanolone on mood (Andreen et al., 2006; Hommer et al., 1986). In women with PMDD, premenstrual mood improves when serum levels of allopregnanolone decrease (Nyberg et al., 2007; Martinez et al., 2016). If a biphasic dose-response curve exists for the isoallopregnanolone effect is not known. However, in

a pharmacodynamic study of the allopregnanolone effect on saccadic eye velocity the antagonizing effect of isoallopregnanolone in a higher dosage was not more effective compared to the effect of a lower dosage (Bengtsson et al., 2015).

In the secondary objective the study demonstrates that sepranolone given subcutaneously during the luteal phase is a safe and well tolerated treatment. Very few side-effects were noted, and the only adverse event of higher frequency was injection site reactions. Even so, only a few patients discontinued the study because of injection site discomfort. No disturbance occurred in vital signs or in menstrual cycle parameters like menstrual cycle length. No effects were noted in hormonal measurements. This favorable safety profile for sepranolone contrasts with that of treatments using selective serotonin reuptake inhibitors (SSRIs) and oral contraceptives, where side-effects are common and even some potential harm (e.g., thromboembolism) exists. Compliance to SSRI treatment is low, and many PMDD patients end their treatment due to adverse effects (Sundstrom-Poromaa et al., 2000).

5. Conclusion

Although the predefined statistical analyses could not differentiate the effect of sepranolone from the large placebo effect, there is a signal in the results that during ovulatory luteal phases in women with PMDD 10 mg sepranolone could ameliorate negative mood symptoms and improve distress and impairment occurring in the premenstrual phase to a greater degree than placebo. Sepranolone was well tolerated, and no safety concerns were identified.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105426.

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