side-effects, long-term safety concerns, and combinations thereof (Johnson et al., Hum Reprod, 2013).

Recently, the use of YAZ Flex (comprising 20 µg ethinylestradiol and 3 mg DRSP intended for use in a flexible extended-cycle oral contraceptive regimen) for endometriosis-associated pelvic pain was studied (clinicaltrials.gov, study identifier NCT03126747) and proven to be effective to manage endometriosis-associated pain.

Nevertheless, there remains an unmet need for improved innovative strategies for the management of the disease, especially for those that provide a safe and effective reduction of endometriosis-induced pain to further improve the quality of life of a subject afflicted by endometriosis and having less side-effects than the existing products.

SUMMARY

As evidenced by the examples which illustrate certain representative embodiments of the invention, the inventors have found that a composition comprising from 13.5 mg to 16.5 mg estetrol (E4) and from 2.5 mg to 3.5 mg drospirenone (DRSP) is particularly suited for relieving a subject from endometriosis-associated pain. Unexpectedly, this composition was observed to be superior to existing hormonal endometriosis therapies for relieving pain, such as a composition comprising ethinylestradiol (EE) and drospirenone (DRSP), especially in subjects that report, or are considered to have, a high degree of pain (i.e. a high Visual Analogue Scale score) caused by said endometriosis. This improvement could also be observed in subjects suffering from adenomyosis and/or uterine fibroids in addition to endometriosis. Hence, in a more general context the composition specified herein is particularly suited to alleviate endometriosis and endometriosis symptoms.

More specifically, a similar decrease of the VAS for the most severe endometriosis-associated pelvic pain was observed between the treatment group (E4/DRSP) and the control group (YAZ Flex; EE/DRSP). Surprisingly, E4/DRSP was shown to be significantly more effective than the control group in suppressing pain during the non-withdrawal bleeding period particularly in patients with a pre-administration baseline VAS value of 70 mm or more. In combination with the general excellent estetrol safety profile that has been described at numerous occasions throughout the art when compared to other estrogens, it may therefore be concluded that endometriosis subjects with a baseline VAS of 70 mm or greater should ideally use the tested E4/DRSP composition instead of other hormonal compositions that are used to date in order to manage endometriosis pain during the non-withdrawal bleeding period.

The disclosure therefore provides the following statements:

Statement 1. A pharmaceutical composition comprising from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone, for use in relieving pain associated with endometriosis in a subject and/or for use in treating endometriosis in said subject.

Statement 2. A pharmaceutical composition comprising from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone for use in treating a subject suffering from pelvic pain and/or for use in treating endometriosis in said subject.

Statement 3. A pharmaceutical composition comprising from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone, for use in relieving pain associated with endometriosis in a subject and/or for use in treating endometriosis in said subject, wherein the use comprises a step of determining whether the patient has pelvic pain prior to administration defined by a Visual Analogue Scale (VAS) score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm.

Statement 4. Use of a composition comprising from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone, for the manufacture of a medicament for relieving pain associated with endometriosis in a subject or for the manufacture of a medicament for treating endometriosis.

Statement 5. Use of a composition comprising from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone for the manufacture of a medicament for treating a subject suffering from pelvic pain.

Statement 6. Use of a composition comprising from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone for the manufacture of a medicament for relieving pain associated with endometriosis in a subject or for the manufacture of a medicament for treating endometriosis in said subject, wherein the use comprises the step of determining whether the patient has pelvic pain prior to administration as defined by a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm.

Statement 7. A method of relieving pain associated with endometriosis in a subject or for treating endometriosis in said subject, comprising administration of a composition comprising from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone to said subject.

Statement 8. A method of treating a subject suffering from pelvic pain, comprising administration of a composition comprising from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone to said subject.

Statement 9. A method of relieving pain associated with endometriosis in a subject or of treating endometriosis in said subject, comprising a first step of determining whether the patient has pelvic pain defined by a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm, and comprising a further step of administrating a composition comprising from about 13.5 mg to about 16.5 mg estetrol and from about 2.5 mg to about 3.5 mg drospirenone to said subject.

Statement 10. The pharmaceutical composition for use according to any one of statements 1 to 3, the use according to any one of statements 4 to 6, or the method according to any one of statements 7 to 9, wherein the estetrol is estetrol monohydrate.

Statement 11. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the pain in the subject is relieved (i.e. reduced) during the non-withdrawal bleeding period.

Statement 12. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the pain in the subject is relieved during the period not related to the withdrawal bleeding period, preferably during a period up to two days before the onset of the withdrawal bleeding.

Statement 13. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the pain in the subject is relieved during a period of from two days before the onset of the withdrawal bleeding to the onset of the withdrawal bleeding, preferably during a period of from one day before the onset of the withdrawal bleeding to the onset of the withdrawal bleeding.

Statement 14. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the pain in the subject is relieved from about 48 hours prior to onset of the withdrawal bleeding until the onset of the withdrawal bleeding, preferably wherein the pain in the subject is relieved from about 36 hours, more preferably from about 24 hours prior to onset of the withdrawal bleeding until the onset of the withdrawal bleeding.

Statement 15. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the pain in the subject is relieved on hormone-free days that mark the end of an administration cycle of a hormonal contraceptive, preferably wherein the pain in the subject is relieved on days prior to day 25 (first day of the hormone-free interval) in a typical hormonal contraceptive treatment schedule.

Statement 16. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the subject is not considered to have or not diagnosed to have primary dysmenorrhea, or wherein the anamnesis of the subject resulted in exclusion of primary

dysmenorrhea in said subject, or wherein the subject is a subject wherein primary dysmenorrhea is excluded by the anamnesis of said subject.

Statement 17. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the subject has pelvic pain as defined by a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm prior to administration.

Statement 18. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the subject is suffering from pelvic pain associated with endometriosis having a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm prior to administration.

Statement 19. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the subject is suffering from pelvic pain induced by endometriosis having a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm prior to administration.

Statement 20. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the pain is resulting from endometrial tissue engrafts outside the uterine cavity in the pelvis.

Statement 21. The pharmaceutical composition for use, the use, or the method according to statement 20, wherein the pain is resulting from endometrial tissue engrafts located on the ovaries, fallopian tubes, tissues that hold the uterus in place (ligaments), outer surface of the uterus, vagina, cervix, vulva, bowel, bladder, rectum, or any combination thereof.

Statement 22. The pharmaceutical composition for use, the use, or the method according to statement 20 or 21, wherein said pain is resulting from endometrial tissue engrafts located on the ovaries, fallopian tubes, tissues that hold the uterus in place (ligaments), outer surface of the uterus, or any combination thereof.

Statement 23. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein said pain is chronic pelvic pain, pelvic pain such as lower abdominal pain and/or low back pain, defecation pain and sexual intercourse pain, or pain caused by adhesion of endometrium in the Douglas pouch.

Statement 24. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the use results in an improvement of the CGI-I Scale (Clinician Global Impressions – Improvement Scale) of at least about 10%, preferably at least about 20%, more preferably of about 28.9%.

Statement 25. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the use results in an improvement graded "significantly satisfied or more" of the PGI-I Scale (Patient Global Impressions – Improvement Scale) of at least about 10%, preferably at least about 20%, more preferably of about 24%.

Statement 26. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the use results in a responder proportion of at least about 40%, preferably at least about 50%, more preferably of at least about 60%.

Statement 27. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the use results in a decrease of CA125, preferably wherein the use results in a decrease of CA125 serum levels to below 35 U/ml..

Statement 28. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the subject is diagnosed as having endometriosis by laparotomy/laparoscopy, and/or as having ovarian chocolate cysts as assessed by Transvaginal Ultrasound (TVUS) and/or Magnetic Resonance Imaging (MRI).

Statement 29. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the subject has adenomyosis and/or uterine fibroids in addition to endometriosis.

Statement 30. The pharmaceutical composition for use, the use, or the method according to statement 29, wherein the subject has adenomyosis which affects about 25% or less of the uterine corpus (mild adenomyosis), or from about 25% to about 50% of the uterine corpus (moderate adenomyosis), or more than about 50% of the uterine corpus (severe adenomyosis).

Statement 31. The pharmaceutical composition for use, the use, or the method according to statement 29, wherein the subject has uterine fibroid(s) classified as pedunculated, submucosal, intramural, subserosal, or any combination thereof.

Statement 32. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein the composition is used in cycles of 21 to 28 daily active dosage units of said composition.

Statement 33. The pharmaceutical composition for use, the use, or the method according to statement 32, wherein the composition is used in cycles of 24 daily active dosage units of said composition.

Statement 34. The pharmaceutical composition for use, the use, or the method according to statement 32 or 33, wherein said cycle comprises an administration-free interval of 7 days, preferably an administration-free interval of 4 days.

Statement 35. The pharmaceutical composition for use, the use, or the method according to any one of statements 32 to 34, wherein use of the composition results in a decrease in VAS score from prior to administration to after the second or third administration cycle.

Statement 36. The pharmaceutical composition for use, the use, or the method according to statement 35, wherein use of the composition results in a decrease in VAS score of at least about 10%, preferably at least about 20%, more preferably at least about 30%, more preferably at least about 40%, most preferably at least about 50% from prior to administration to after the second or third administration cycle.

Statement 37. The pharmaceutical composition for use, the use, or the method according to statement 36, wherein said decrease is maintained substantially stable after the second or third administration cycle.

Statement 38. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein use of the composition results in improvement in the severity of Douglas induration, restriction of uterine mobility and/or pelvic tenderness, reduced size and/or number of ovarian chocolate cysts as assessed by TVUS or MRI.

Statement 39. The pharmaceutical composition for use, the use, or the method according to statement 38, wherein the use of the composition results in an improvement in the severity of at least about 10%, preferably at least about 20%, more preferably at least about 30%, more preferably at least about 40%, most preferably at least about 50%.

Statement 40. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein use of the composition results in less TEAE than use of an EE 20 µg / DRSP 3 mg, fixed dose combination tablet.

Statement 41. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, wherein said subject has reduced Treatment Emergent Adverse Events (TEAE) selected from the group consisting of: intermenstrual bleeding, headache, nausea and heavy menstrual bleeding.

Statement 42. The pharmaceutical composition for use, the use, or the method according to any one of the preceding statements, for reducing endometriosis-associated sleep disturbance.

In an aspect, there is provided use of a composition in the manufacture of a medicament for relieving pain induced by endometriosis in a subject, wherein said composition comprises from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone, and wherein said pain in said subject is pain during the non-withdrawal bleeding period.

In another aspect, there is provided use of a composition in the manufacture of a medicament for treating pelvic pain in a subject, wherein said composition comprises from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol, and from about 2.5 mg to about 3.5 mg drospirenone, and wherein said pelvic pain in said subject is pelvic pain during the non-withdrawal bleeding period.

In another aspect, there is provided use of a composition in the manufacture of a medicament for relieving pain induced by endometriosis in a subject, wherein said composition comprises from about 13.5 mg to about 16.5 mg estetrol or estetrol monohydrate and about 2.5 mg to about 3.5 mg drospirenone, wherein prior to administration of the composition, the patient is to be determined for pelvic pain defined by a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm, and wherein said pain in said subject is pain during the non-withdrawal bleeding period.

As defined herein, said dosage unit may be presented as a kit-of-parts containing a packaging unit, e.g. a blister pack, containing the daily oral dosage units comprising the estetrol and drospirenone. The skilled person will additionally know that, within the scope of the present disclosure, each packaging unit, e.g. blister pack, may be numbered or otherwise marked. In a particular example of the kit-of-parts, the packaging unit comprises 28 containers or a

multitude of 28 containers, such as 2 to 12 times 28 containers. In a preferred example, the packaging unit comprises 3 or 6 times 28 containers. Within the scope of the disclosure, each packaging unit may be a sealed blister pack with a cardboard, paperboard, foil plastic backing and enclosed in a suitable cover.

Also as defined herein are packaging units such as bottles. The material of the bottle is not particularly limiting. In preferred examples, the bottle is a glass bottle characterized by a color capable of reducing or preventing degradation of the contents of the bottle by e.g. UV light while maintaining a degree of transparency that allows for visual inspection of the contents of said bottle. Suitable colors include without limitation amber, cobalt, or vintage green.

The above and further statements or aspects and preferred embodiments of the disclosure are described in the following sections and in the appended claims. The subject matter of the appended claims is hereby specifically incorporated in this specification.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. (A) Individual VAS values and Spline curves. X-axis: relative day from the first treatment day; Y-axis: VAS value (mm). (B) Mean VAS values. X-axis: days; Y-axis: VAS value (mm). "FSN-013" corresponds to the 15 mg E4/ 3 mg DRSP group.

Figure 2. Definition of Responders. Responder: VAS reduced by more than 70 mm in 80% or more days of evaluated period. Evaluated period: non-withdrawal bleeding period between days 29-84.

Figure 3. CGI-I and PGI-I improvement in the responder and non-responder (E4/DRSP + Yaz Flex). Left panel: CGI-I; right panel: PGI-I. Diagonally striped: Responder, right sample group of each histogram. Solid grey filled: Non-Responder, left sample of each histogram.

Figure 4. Proportion of the responder in E4/DRSP and Yaz Flex groups. FSN-013 group corresponds to 15 mg E4/ 3 mg DRSP group.

Figure 5. (A) Gynecologic objective findings following 6 cycle treatment - proportion of subjects who were improved, stable or worsened: induration of cul-de sac ($p = 0.002$, Fisher's exact), limitation of uterine mobility ($p = 0.005$, Fisher's exact), pelvic tenderness ($p = 0.022$, Fisher's exact). (B) Stratified analysis with or without adenomyosis in alteration of gynecologic objective findings following 6 cycle treatments.

DETAILED DESCRIPTION

As used herein, the singular forms "a", "an", and "the" include both singular and plural referents unless the context clearly dictates otherwise.

CLAIMS

1. Use of a composition in the manufacture of a medicament for relieving pain induced by endometriosis in a subject, wherein said composition comprises from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol and from about 2.5 mg to about 3.5 mg drospirenone, and wherein said pain in said subject is pain during the non-withdrawal bleeding period.

2. Use of a composition in the manufacture of a medicament for treating pelvic pain in a subject, wherein said composition comprises from about 13.5 mg to about 16.5 mg estetrol or hydrates of estetrol, and from about 2.5 mg to about 3.5 mg drospirenone, and wherein said pelvic pain in said subject is pelvic pain during the non-withdrawal bleeding period.

3. The use according to claim 1 or 2, wherein the pain or the pelvic pain of the subject is measured using the VAS (Visual Analogue Scale), preferably wherein the subject has pelvic pain defined by a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm prior to administration.

4. The use according to any one of claims 1 to 3, wherein the subject is suffering from pelvic pain induced by endometriosis having a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm prior to administration, preferably wherein the subject is suffering from pelvic pain induced by endometriosis having a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm prior to administration.

5. The use according to any one of the preceding claims, wherein said pain or pelvic pain is resulting from endometrial tissue engrafts outside the uterine cavity in the pelvis.

6. The use according to any one of the preceding claims, wherein said pain or pelvic pain is chronic pelvic pain, pelvic pain such as lower abdominal pain and/or low back pain, defecation pain and sexual intercourse pain, or pain caused by adhesion of endometrium in the Douglas pouch.

7. The use according to any one of the preceding claims, wherein the use results in an improvement of the CGI-I Scale (Clinician Global Impressions – Improvement Scale), preferably wherein the use results in an improvement of the CGI-I Scale of about 28.9%.

8. The use according to any one of the preceding claims, wherein the use results in an improvement graded “significantly satisfied or more” of the PGI-I Scale (Patient Global Impressions – Improvement scale), preferably wherein the use results in an improvement graded “significantly satisfied or more” of the PGI-I Scale of about 24%.

9. The use according to any of the preceding claims, wherein the use results in a responder proportion of about 60%.

10. The use according to any of the preceding claims, wherein the subject is diagnosed as having endometriosis by laparotomy/laparoscopy, and/or as having ovarian chocolate cysts as assessed by Transvaginal Ultrasound (TVUS) and/or Magnetic Resonance Imaging (MRI).

11. The use according to any of the preceding claims, wherein the composition is used in cycles of 21 to 28 daily active dosage units of said composition, preferably wherein the composition is used in cycles of 24 daily active dosage units of said composition.

12. The use according to claim 11, wherein said cycle comprises an administration-free interval of 7 days, preferably an administration-free interval of 4 days.

13. The use according to claim 11 or 12, wherein use of the composition results in a decrease in VAS score from prior to administration after the second or third administration cycle, preferably wherein said decrease is maintained substantially stable after the second or third administration cycle.

14. The use according to any of the preceding claims, wherein use of the composition results in improvement in the severity of Douglas induration, restriction of uterine mobility and/or pelvic tenderness, reduced size and/or number of ovarian chocolate cysts as assessed by TVUS or MRI.

15. The use according to any of the preceding claims, wherein use of the composition results in less TEAE than use of an EE 20 µg / DRSP 3 mg, fixed dose combination tablet, preferably wherein the TEAE are selected from the group consisting of: intermenstrual bleeding, headache, nausea and heavy menstrual bleeding.

16. The use according to any one of the preceding claims, wherein the subject has adenomyosis and/or uterine fibroids, in addition to endometriosis.

17. Use of a composition in the manufacture of a medicament for relieving pain induced by endometriosis in a subject, wherein said composition comprises from about 13.5 mg to about 16.5 mg estetrol or estetrol monohydrate and about 2.5 mg to about 3.5 mg drospirenone, wherein prior to administration of the composition, the patient is to be determined for pelvic pain defined by a VAS score of greater than about 40 mm, about 50 mm, about 60 mm, or about 70 mm, and wherein said pain in said subject is pain during the non-withdrawal bleeding period.