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(54) Title: USE OF COMBINED ORAL CONTRACEPTIVES CONTAINING NOMEGESTROL ACETATE AND ESTRADIOL

(57) Abstract: Provided is the use of compositions comprising nomegestrol acetate (NOMAC) and estradiol or an ester thereof. The compositions are for use in reducing the risk of unintended pregnancy as a result of contraceptive failure associated with use of combined oral contraceptive (COC).

# USE OF COMBINED ORAL CONTRACEPTIVES CONTAINING NOMEGESTROL ACETATE AND ESTRADIOL

## FIELD OF THE INVENTION

The present invention relates to the use of compositions comprising nomegestrol acetate (NOMAC) and estradiol or an ester thereof. The compositions are for use in reducing the risk of unintended pregnancy as a result of contraceptive failure associated with use of combined oral contraceptive (COC).

## BACKGROUND TO THE INVENTION

Combined oral contraceptives (COCs), also known as combined hormonal contraceptives (CHCs), are used to control the menstrual cycle of women. COC use in women typically prevents ovulation, and is thus a means to prevent pregnancy. COCs are a popular form of birth control and are taken by over 100 million women worldwide. COCs are also used in a clinical setting to treat a range of disorders or conditions linked to menstruation and fertility. Examples include the reduction of heavy menstrual bleeding, regulation of the menstrual cycle, alleviation of dysmenorrhea, treatment of polycystic ovary syndrome, treatment of hirsutism and treatment of premenstrual syndrome (Carey and Allen, *The Obstetrician & Gynaecologist* 2012; 14: 223-228).

COCs typically include an estrogen and a progestogen. A variety of different combinations of estrogens and progestogens are used in different COCs. Examples of different progestogens used in COCs currently on the market are levonorgestrel, norethisterone, desogestrel, gestodene, cyproterone acetate, drospirenone, dienogest and nomegestrol acetate. Examples of different estrogens used in COCs currently on the market are ethinylestradiol, mestranol, estradiol valerate and estradiol.

Although COCs are a popular form of birth control, failure of contraception and unintended pregnancy remains a problem. The causes of contraception failure are likely multifactorial, including the estrogen and progestogen compounds used in the COC, as well as behavioural factors such as compliance, as well as the capability of a particular COC regimen to cope with variation in compliance. There therefore remains a need to identify COCs with a reduced risk of contraceptive failure and unintended pregnancy. The present invention addresses this need.

## SUMMARY OF INVENTION

One example of a COC already in clinical use is "NOMAC-E2", a COC marketed by Theramex HQ UK Limited as ZOELY®. NOMAC-E2 is a monophasic oral contraceptive containing a fixed dose of nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg). NOMAC-E2 pills are typically taken by women for 24 days followed by 4 days of placebo.

The progestogen contained in NOMAC-E2, nomegestrol acetate or "NOMAC", is a derivative of 19-norprogesterone and is thus structurally very similar to the naturally-occurring progesterone produced by the human body. It has a strong affinity for the progesterone receptor and has strong anti-gonadotropic activity and progesterone receptor-mediated anti-estrogenic activity. It also has moderate anti-androgenic activity, and is devoid of estrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

The estrogen contained in NOMAC-E2 is 17β-estradiol or "E2". E2 is a synthetically produced estrogen but is identical to the natural estrogen - 17β-estradiol – produced by the human body; it is classified as a "bio-identical" hormone.

The present application reports the results of a study in which NOMAC-E2 was found to reduce the risk of contraception failure and unintended pregnancy compared to other COCs. The comparator COCs contained the synthetic progesterone levonorgestrel (LNG) and the synthetic estrogen ethinylestradiol. NOMAC-E2 has been in clinical use for some time without any serious health concerns. The present application reveals, for the first time, the opportunity to use COCs containing NOMAC and estradiol to significantly reduce the risk of unintended pregnancy for women using such COCs, compared to comparator COCs such as those containing levonorgestrel.

In a first aspect, the present invention provides a method for reducing the risk of unintended pregnancy during a period of combined oral contraceptive use by a woman, the method comprising administering a combined oral contraceptive (COC) composition to the woman, wherein the COC composition comprises nomegestrol acetate and estradiol or an ester thereof.

In a second aspect the invention provides a method for reducing the risk of contraceptive failure during a period of combined oral contraceptive use by a woman, the method comprising administering a combined oral contraceptive (COC) composition to the woman, wherein the COC composition comprises nomegestrol acetate and estradiol or an ester thereof.

In a further aspect the invention provides use of a composition comprising nomegestrol acetate and estradiol or an ester thereof in a method according to the first aspect or second aspect.

The invention also provides a composition for use in a method according to the first or second aspects of the invention

In preferred embodiments of all aspects of the invention described herein, the composition comprises nomegestrol acetate and 17β-estradiol.

## BRIEF DESCRIPTION OF DRAWINGS

**Figure 1** shows an overview of cohorts included in the clinical study categorised according to age group.

**Figure 2** shows the incidence of serious adverse effects (SAEs) observed in the study – according to COC or contraceptive used.

**Figure 3** shows the incidence of unintended pregnancy according to COC or contraceptive cohort. The incidence rates per 100 WY and 95% confidence intervals per (sub)-cohort are shown. The box shows the crude and adjusted hazard ratio for unintended pregnancy between cohorts receiving COC NOMAC-E2 and $COC_{LNG}$. Adjusted hazard ratio is adjusted for age, BMI, gravidity, and education.

**Figure 4** shows the incidence of unintended pregnancy according to COC or contraceptive cohort by age, where (A) is women less than 35 years of age and (B) is women of 35 years of age or greater. The incidence rates per 100 WY and 95% confidence intervals per (sub)-cohort are shown.

**Figure 5** shows the incidence of unintended pregnancy according to COC or contraceptive cohort by education level, where (A) is women having an education level of less than or equal to university entrance level, and (B) is women having an education level greater than university entrance level. The incidence rates per 100 WY and 95% confidence intervals per (sub)-cohort are shown.

**Figure 6** shows the incidence of unintended pregnancy according to COC or contraceptive cohort for women using the administered contraceptive composition solely for contraceptive

purposes. The incidence rates per 100 WY and 95% confidence intervals per (sub)-cohort are shown.

## DETAILED DESCRIPTION

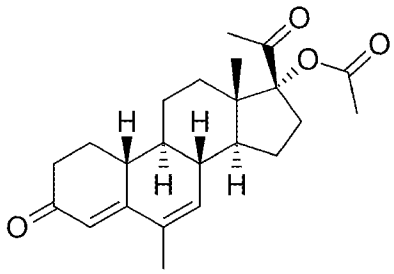
### A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one skilled in the art in the technical field of the invention.

**"Combined oral contraceptive" (COC)** – as used herein a "combined oral contraceptive" or "COC" refers to a hormonal combination treatment for women that includes an estrogen and a progestogen. Combined oral contraceptives are also referred to in the literature as "combined hormonal contraceptives" or "CHCs". A variety of different combinations of estrogens and progestogens are known to be used in different forms of COCs. The COCs for use according to the present invention comprise nomegestrol acetate (NOMAC) as the progestogen and estradiol or an ester thereof as the estrogen.

"**Progestogens**" – as used herein the term "progestogens" refers to a class of synthetic steroid hormones which produce similar or equivalent effects to progesterone – the naturally occurring progestogen. Progestogens are also referred to as "gestagens". Progestogens possess antiestrogenic and antigonadotropic properties. Many examples of progestogens are derivatives or metabolites of the naturally-occurring progesterone.

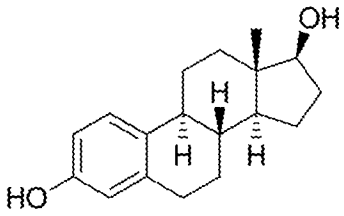
**"Nomegestrol acetate"** – as used herein "nomegestrol acetate" or "NOMAC" or "NOMAc" refers to a kind of progestogen as represented by the formula:




NOMAC is also known as 17α-acetoxy-6-methyl-δ6-19-norprogesterone or as 17α-acetoxy-6-methyl-19-norpregna-4,6-diene-3,20-dione. It is a derivative of progesterone belonging to the 19-norprogesterone and 17α-hydroxyprogesterone groups.

"**Estrogens**" – as used herein the term "estrogens" (also written as "oestrogens") refers to a class of steroid hormones of which the endogenous or naturally-occurring forms are estrone (E1), estradiol (E2), estriol (E3) and estetrol (E4). Estrogens perform a multitude of functions within the human body including regulation of the menstrual cycle, ovulation and fertility.

"**Estradiol**" – as used herein the term "estradiol" or "E2" refers to the estrogen as represented by the formula:




This compound is also known as "17β-estradiol" or "beta-estradiol". Estradiol is the predominant estrogen produced by the human body during a woman's reproductive years.

"**Woman of child-bearing age**" – as used herein this term refers to a post-pubescent and pre-menopausal woman. A woman of child-bearing age is a woman who is most likely to use the compositions described herein as a means of contraception.

"**Period of combined oral contraceptive use**" – as used herein this term refers to a period of time in which a woman is taking a combined oral contraceptive as a means of contraception.

"**Means of contraception**" – as used herein this term refers to the use of a composition as described herein for the prevention of pregnancy.

"**Hazard Ratio**" (**HR**) – as used herein the "hazard ratio" or "HR" is the ratio of unintended pregnancy or contraception failure risk in a first group of subjects versus the risk in a second group of subjects. The HR as described herein typically represents the risk associated with women receiving compositions as described herein (comprising NOMAC and estradiol or an ester thereof) as compared with the risk associated with women receiving a different COC. HRs may be calculated and expressed in crude form - by simply comparing the incidence of pregnancy between two groups of subjects. HRs may also be calculated and expressed in an adjusted form, whereby the HR is adjusted to take into account other known risk factors such as age, body mass index (BMI) at baseline, gravidity, duration of use of COCs and education status, in the two groups of subjects.

**"Plain tablet"** as used herein the term "plain tablet" refers to a solid composition that is compressed or otherwise formed into a defined shape and quantity.

**"Film-coated tablet"** – as used herein the term "film-coated tablet" refers to a tablet encapsulated by a polymer-based coating. The coating may be used to prevent the tablet from degrading in the stomach.

**"Sugar-coated tablet"** – as used herein the term "sugar-coated tablet" refers to a tablet encapsulated by a mono-, di-, oligo- or poly-saccharide coating. The coating may be used to mask the flavour of particularly unpalatable drugs. The coating can also be used to prevent light or moisture from entering the tablet, which could prevent a drug from breaking down prematurely.

**"Soft gelatin capsule"** – as used herein the term "soft gelatin capsule" refers to a dosage form in which a liquid or semi-solid centre (inner fill) is encapsulated by a solid capsule (outer shell). The outer shell may comprise, for example, a combination of gelatin, water, opacifier and a plasticizer such as glycerin and/or sorbitol(s).

**"Cachets"** or "**wafer capsules"** – as used herein, these terms refer to a seal-shaped capsule or wafer made of flour for enclosing powders of disagreeable taste. The sealed dosage form is wetted and swallowed.

**"Pill"** – as used herein this term refers to any solid form of medication.

**"Powder"** – as used herein this term refers to a mixture of solid non-compressed, active drug (e.g. NOMAC-E2) and excipients.

**"Excipient"** – as used herein this term refers to a compound that is generally safe, non-toxic and neither biologically nor otherwise undesirable. The excipient is substantially inert.

**"Oral administration"** – as used herein this term means that the dosage form is taken by mouth and is thereby delivered into the gastrointestinal tract.

**"Monophasic"** – as used herein this term means that a fixed quantity or dosage of the estrogen and/or the progestogen in the COC is administered throughout a treatment cycle. For example, if a treatment cycle consists of 24 daily doses of the COC, a fixed quantity or dosage of the estrogen and/or the progestogen is administered to the woman each day of the 24-day

period. The NOMAC-E2 compositions described herein may be administered as monophasic oral contraceptives. For example, a fixed dosage of 2.5 mg and 1.5 mg E2 may be administered daily for a period of 24 days.

"**Multiphasic**" – as used herein this term means that the quantity or dosage of the estrogen and/or the progestogen varies throughout a treatment cycle. For example, if a treatment cycle consists of daily doses of a COC over a period of several days, the amount of estrogen and/or progestogen administered to the woman on different days of the treatment cycle can vary.

"**Acne**" – as used herein this term refers to a long-term skin disease that occurs when dead skin cells and oil from the skin clog hair follicles. Typical features of the condition include blackheads or whiteheads, pimples, oily skin, and possible scarring.

"**Ovarian cysts**" – as used herein this term refers to fluid-filled sacs that develop in or on the ovaries. Typically, an ovarian cyst only causes symptoms if it ruptures, is very large or blocks the blood supply to the ovaries. Symptoms associated with ovarian cysts are pelvic pain, pain during sex, difficulty emptying the bowels, a frequent need to urinate, heavy periods, irregular periods, lighter periods than normal, bloating or a swollen stomach, feeling very full after only eating a little and difficulty getting pregnant.

"**Polycystic ovary syndrome**" **(PCOS)** - as used herein this term refers to a condition in which the ovaries contain a large number of follicles. The follicles are underdeveloped sacs in which eggs develop, which means that these sacs are often unable to release an egg. PCOS can result in a lack of ovulation and problems with fertility. Symptoms of PCOS include irregular periods or no periods at all, difficulty getting pregnant, excessive hair growth (hirsutism), (particularly on the face, chest, back or buttocks), weight gain, thinning hair and hair loss from the head, oily skin or acne.

"**Premenstrual syndrome**" **(PMS)** - as used herein this term refers to a recurring, cyclical disorder involving behavioural, emotional, social and physical symptoms (Steiner et al., Annu. Rev. Med. (1997) 48: 447-455). Symptoms may include, irritability, mood swings, depression, hostility and social withdrawal. Physical symptoms include, bloating, breast tenderness, myalgia, migraines, headaches, or fatigue.

"**Endometriosis**" - as used herein this term refers to a condition where tissue similar to the lining of the womb starts to grow elsewhere in the reproductive system, such as the ovaries and fallopian tubes. Symptoms may include any one or more of: abdominal pain, back pain, period

pain, pain during or after sex, pain during defecation or urination, feeling sick, constipation, diarrhoea, blood in the stool, difficulty getting pregnant, heavy periods or depression.

**"Premenstrual dysphoric disorder" (PMDD)** - as used herein this term refers to a disorder possessed by a subgroup of women with PMS. PMDD is considered a severe form of PMS. Symptoms can include any one or more of: mood swings, feeling upset or tearful, feeling angry or irritable, feelings of anxiety, feeling hopeless, feelings of tension or being on edge, difficulty concentrating, feeling overwhelmed, lack of energy, less interest in activities normally enjoyed, suicidal feelings, breast tenderness or swelling, pain in your muscles and joints, headaches, feeling bloated, changes in appetite or sleep problems.

**"Menstrual cycle regulation"** – as used herein this term refers to the regulation of the menstrual cycle using hormonal treatment. Hormonal treatments may be used to regulate the menstrual cycle in women who exhibit problems including but not limited to menstrual cycles of differing length, painful menstruation, very heavy bleeding at menstruation.

**"Placebo"** – as used herein refers to a dosage form containing no active ingredient.

**B. Methods for reducing the risk of unintended pregnancy**

As discussed herein, the use of COCs is associated with a certain risk of contraceptive failure, resulting in unintended pregnancy occurring in some individuals. The present inventors hypothesise contraceptive failure may be multifactorial in cause, including factors such as the estrogen and progestogen compounds in the particular COC, the level of compliance of the individual taking the COC, and the ability of the COC in question to mitigate the effects of lapses in regimen compliance.

As reported herein, it has unexpectedly been found that women taking a COC containing NOMAC and estradiol exhibit a reduced risk of contraceptive failure and thus unintended pregnancy. This reduction in risk was seen relative to women taking other COCs containing different forms of progestogen and estrogen. Women taking a COC containing NOMAC and estradiol experienced an unintended pregnancy at a rate of 0.15 per 100 women years (WY). In contrast, women taking a COC containing levonorgestrel ($COC_{LNG}$) experienced an unintended pregnancy at a rate of 0.41 per 100 WY. Furthermore, women taking other forms of COC containing different estrogens and/or progestogens exhibited unintended pregnancy at a rate of 0.26 per 100 WY.

Taking into account the above, in a first aspect, the invention provides a method for reducing the risk of unintended pregnancy during a period of combined oral contraceptive use by a woman, the method comprising administering a combined oral contraceptive (COC) composition to the woman, wherein the COC composition comprises nomegestrol acetate and estradiol or an ester thereof.

In a further aspect, the invention provides a method for reducing the risk of contraceptive failure during a period of combined oral contraceptive use by a woman, the method comprising administering a combined oral contraceptive (COC) composition to the woman, wherein the COC composition comprises nomegestrol acetate and estradiol or an ester thereof.

All embodiments described herein are equally applicable to the methods according to these aspects of the invention unless indicated to the contrary.

*(i) Reducing the risk of unintended pregnancy*

The methods of the invention are aimed at reducing the risk of contraceptive failure and thus unintended pregnancy during a period of contraceptive use, where the contraceptive is a COC. As detailed herein, a significant decrease in the incidence of unintended pregnancy was observed in women taking a COC containing NOMAC and estradiol as compared with women taking other forms of COC. The risk of unintended pregnancy associated with the use of COCs is thus clearly reduced in women taking compositions comprising NOMAC and estradiol or esters thereof.

In certain embodiments, administration of a COC composition comprising nomegestrol acetate and estradiol or an ester thereof in accordance with methods of the invention results in a rate of unintended pregnancy or contraception failure in the range of from 0.05 to 0.3 per 100 woman years (WY). In certain embodiments, the resulting rate of unintended pregnancy or contraception failure is in the range of from 0.1 to 0.3 per 100 WY. In certain embodiments, the resulting rate of unintended pregnancy or contraception failure is about 0.2 per 100 WY. In certain embodiments, the resulting rate of unintended pregnancy or contraception failure is about 0.15 per 100 WY.

The risk of unintended pregnancy associated with COC compositions used in accordance with the invention is reduced relative to the risk observed in women taking other COCs i.e. the level of risk associated with the use of COCs generally. In certain embodiments, the risk is reduced as compared with the risk observed in women taking other COCs (of any type) by at least 10%, at least 20%, at least 30%, at least 40%.

In some embodiments, the risk of unintended pregnancy associated with compositions used in accordance with the invention is reduced relative to the risk of unintended pregnancy associated with the use of a particular COC, specifically a different COC. In this regard, a different COC means a COC other than a composition for use in accordance with the invention as defined herein. A different COC will not contain NOMAC and estradiol or an ester thereof.

In some embodiments, the risk of unintended pregnancy is reduced relative to the risk associated with use of a different COC containing different forms of estrogen and/or progestogen as compared with the compositions described herein. The different COC may comprise a synthetic estrogen selected from the group including but not limited to ethinylestradiol, or mestranol. Alternatively or in addition, the different COC may comprise a synthetic progestogen selected from the group including but not limited to levonorgestrel, norethisterone, desogestrel, gestodene, cyproterone acetate, drospirenone, or dienogest.

In some embodiments, the risk of unintended pregnancy associated with compositions used in accordance with the invention is reduced relative to the risk associated with use of a COC containing the progestogen levonorgestrel - also referred to herein as $COC_{LNG}$. In some embodiments, the risk of unintended pregnancy is reduced relative to the risk associated with use of a COC containing levonorgestrel and ethinylestradiol.

In some embodiments, the risk of unintended pregnancy is reduced relative to a monophasic COC containing levonorgestrel. In some embodiments, the risk of unintended pregnancy is reduced relative to a monophasic COC containing levonorgestrel and 20-30 mcg ethinylestradiol. In some embodiments, the risk of unintended pregnancy is reduced relative to a monophasic COC containing levonorgestrel and 20 mcg ethinylestradiol. In some embodiments, the risk of unintended pregnancy is reduced relative to a multiphasic COC containing levonorgestrel. In other embodiments, the risk of unintended pregnancy is reduced relative to a multiphasic COC containing levonorgestrel and 40 mcg ethinylestradiol. The dose of levonorgestrel in the COC may be in the range from 100 mcg to 250 mcg. In certain embodiments, the dose of levonorgestrel in the COC is 150 mcg.

The risk of unintended pregnancy associated with COC compositions used in accordance with the invention is reduced relative to the risk observed in women taking $COC_{LNG}$ in accordance with the embodiments provided herein. In certain such embodiments, the risk is reduced as compared with the risk observed in women taking $COC_{LNG}$ by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%.

The reduction in risk of unintended pregnancy associated with compositions used in accordance with the invention may be expressed as a Hazard Ratio (HR). In some embodiments, the HR associated with use of the COC compositions described herein is 0.3-0.6. In some embodiments, the HR associated with use of the compositions described herein is 0.3-0.5. In some embodiments, the HR is 0.4 or 0.5. In some embodiments, the crude HR ($HR_{crude}$) is 0.4. In other embodiments the adjusted HR ($HR_{adj}$) is 0.5.

As described herein, the crude HR can be adjusted to take into account other known risk factors. These risk factors include, for example, age, BMI at baseline, gravidity, education level in the two groups of subjects. In some embodiments, the adjusted HR takes into account these factors. In these embodiments, the adjusted HR is 0.5.

In some embodiments, the risk of unintended pregnancy is reduced relative to a COC containing levonorgestrel and 20 mcg ethinylestradiol and the $HR_{crude}$ is 0.4. In other embodiments, the risk of unintended pregnancy is reduced relative to a COC containing levonorgestrel and 20 mcg ethinylestradiol and the $HR_{adj}$ is 0.5.

In some embodiments, the risk of unintended pregnancy is reduced by at least 20% in women administered compositions comprising NOMAC and estradiol or an ester thereof as compared with women taking $COC_{LNG}$. In some embodiments, the risk of unintended pregnancy is reduced by at least 25% in women administered compositions comprising NOMAC and estradiol or an ester thereof as compared with women taking $COC_{LNG}$. In some embodiments, the risk of unintended pregnancy is reduced by at least 30% in women administered compositions comprising NOMAC and estradiol or an ester thereof as compared with women taking $COC_{LNG}$. In some embodiments, the risk of unintended pregnancy is reduced by at least 35% in women administered compositions comprising NOMAC and estradiol or an ester thereof as compared with women taking $COC_{LNG}$.

In preferred embodiments, the risk of unintended pregnancy is reduced by at least 40% in women administered compositions comprising NOMAC and estradiol or an ester thereof as compared with women taking $COC_{LNG}$. In further preferred embodiments, the risk of unintended pregnancy is reduced by at least 50% (or at least halved) in women administered compositions comprising NOMAC and estradiol or an ester thereof as compared with women taking $COC_{LNG}$.

*(ii) Administration to women*

In the methods provided herein, combined oral contraceptive (COC) compositions are administered to a woman or women of child-bearing age as a means of contraception. Accordingly, in some embodiments, the compositions are administered to a woman or women aged 12-55. In some embodiments, the woman or women is/are aged 15-55. In some embodiments, the woman or women is/are aged 15-50. In some embodiments, the woman or women is/are aged 15-45.

In some embodiments, a COC composition (e.g. a COC composition comprises nomegestrol acetate and estradiol or an ester thereof as described herein) is administered to a woman or women 35 years of age or above; optionally 36 years of age or above; optionally 37 years of age or above; optionally 38 years of age or above; optionally 39 years of age or above; optionally 40 years of age or above. The composition may be administered to a woman or women having an age of between 35 and 45.

In some embodiments, a COC composition (e.g. a COC composition comprises nomegestrol acetate and estradiol or an ester thereof as described herein) is administered to a woman or women less than 35 years of age; optionally less than 30 years of age; optionally less than 25 years of age; optionally less than 24 years of age or above; optionally less than 23 years of age; optionally less than 22 years of age, optionally less than 21 years of age, optionally less than 20 years of age. The composition may be administered to a woman or women having an age of between 15 and 35.

In some embodiments, a composition as described herein is administered to a woman having an education level of less than or equal to university entrance level.

In some embodiments, a composition as described herein is administered to a woman or women who are categorised as overweight or obese according to one or more measures used in clinical practice.

In some embodiments, the COC composition comprising nomegestrol acetate and estradiol or an ester thereof as described herein is administered to a woman or women who has/have not received a prior COC. In alternative embodiments, a composition as described herein is administered to a woman or women who has/have previously received COC treatment in their lifetime. Such women may be classified as “restarters”. In certain embodiments, such women may have taken a break from COC treatment for a period of 2 months or more, 3 months or more, 4 months or more, 5 months or more, 6 months or more, 12 months or more.

In some embodiments, a COC composition comprising nomegestrol acetate and estradiol or an ester thereof as described herein is administered to a woman or women who has/have previously received a COC that does not contain NOMAC and estradiol or an ester thereof.

As revealed by the data presented herein, administration of a COC composition comprising nomegestrol acetate and estradiol or an ester thereof confers a greatly reduced risk of contraceptive failure and unintended pregnancy compared to other COC compositions. For a woman taking one such other COC composition it is possible for her risk of unintended pregnancy to be reduced by switching to a COC composition comprising nomegestrol acetate and estradiol or an ester thereof.

Accordingly, in certain embodiments of the methods of the first aspect of the invention, the method comprises the steps of

(i) identifying a woman in a period of combined oral contraceptive (COC) use, wherein the woman is taking a first COC and the first COC is other than a COC composition comprising nomegestrol acetate and estradiol or an ester thereof;

(ii) identifying the woman as at increased risk of unintended pregnancy;

(iii) stopping administration to the woman of the first COC and starting administration to the woman of a COC composition comprising nomegestrol acetate and estradiol or an ester thereof,

thereby reducing the risk of unintended pregnancy during the subsequent period of combined oral contraceptive use by the woman.

In certain embodiments of the methods of the second aspect of the invention, the method comprises the steps of:

(i) identifying a woman in a period of combined oral contraceptive (COC) use, wherein the woman is taking a first COC and the first COC is other than a COC composition comprising nomegestrol acetate and estradiol or an ester thereof;

(ii) identifying the woman as at increased risk of contraceptive failure;

(iii) stopping administration to the woman of the first COC and starting administration to the woman of a COC composition comprising nomegestrol acetate and estradiol or an ester thereof,

thereby reducing the risk of contraceptive failure during the subsequent period of combined oral contraceptive use by the woman.

In certain embodiments, the woman is administered the COC solely for the purposes of contraception. That is the woman is not administered the COC for any alternative or additional purpose, for example to treat acne or manage menstrual cycle.

*(iii) COC compositions comprising NOMAC and estradiol or an ester thereof*

The compositions described herein for use in accordance with the invention comprise NOMAC and estradiol or an ester thereof. The compositions for use in accordance with the invention are thus themselves COCs wherein the progestogen active ingredient is NOMAC and the estrogen active ingredient is estradiol or an ester thereof. As described elsewhere herein, these compositions are associated with a reduced risk of contraception failure and thus unintended pregnancy and can thus be used in place of other COCs so as to reduce the risk of unintended pregnancy during a period of COC contraceptive use.

In some embodiments, the NOMAC and estradiol or ester thereof are present in a weight ratio of 5 to 0.5. In some embodiments, the NOMAC and estradiol or ester thereof are present in a weight ratio of 3 to 1. In a preferred embodiment, the NOMAC and estradiol or ester thereof are present in a weight ratio of 1.67 to 1.

In some embodiments, the NOMAC is present in an amount ranging from 1.5 mg to 3.75 mg. In some embodiments, the estradiol or ester thereof is present in an amount ranging from 0.5 mg to 3 mg. In some embodiments, the NOMAC is present in an amount of about 2.5 mg and the estradiol or ester thereof is present in an amount of about 1.5 mg.

In a preferred embodiment, the NOMAC is present in an amount of 2.5 mg and the estradiol or ester thereof is present in an amount of 1.5 mg.

In some embodiments, the compositions for use comprise NOMAC in combination with an estradiol ester. Such estradiol esters include but are not limited to estradiol valerate, estradiol benzoate, estradiol phenylpropionate, estradiol enanthate, estradiol acetate, estradiol cypionate, estradiol dipropionate, estradiol undecylate and polyestradiol phosphate (an estradiol ester in polymeric form).

In preferred embodiments, the composition comprises NOMAC in combination with 17β-estradiol (also referred to herein as E2). In a particularly preferred embodiment, the 17β-estradiol is in hemihydrate form. In preferred embodiments, the composition comprises 2.5 mg NOMAC and 1.5 mg 17β-estradiol.

The compositions for use according to the invention may be formulated so as to comprise one or more pharmaceutically acceptable carriers or excipients. Alternatively or in addition, the compositions for use according to the invention may be formulated as to comprise one or more additional agents selected from but not limited to: binding agents; disintegrants; lubricants; glidants; fillers; and/or diluents.

In some embodiments, the composition comprises one or more additional agents selected from: lactose monohydrate; anhydrous lactose; spray-dried lactose; sifted/sieved/milled lactose; crystalline lactose; sucrose; trehalose; dextrose; fructose; dextrates; dextrin; dextrose anhydrous; sorbitol; mannitol; xylitol; maltitol solution; glucose liquid; and polydextrose.

Alternatively or in addition, the composition may comprise one or more additional agents selected from: microcrystalline cellulose; cellulose powder or derivatives thereof with different molecular weights including other forms such as gel, gum, crystal, cotton, sugar, alpha-grade, paste, guar gum; pre-gelatinised maize starch; croscarmellose sodium; alginic acid; acacia; calcium phosphate (dibasic anhydrous/ dihydrate, tribasic); carboxymethylcellulose sodium; carrageenan; silicified microcrystalline cellulose; cellulose acetate; cellulose acetate phthalate; carbomer; hydroxypropyl cellulose (or low substituted); hydroxypropyl starch; hypromellose (and acetate succinate and phthalate); hydroxyethyl cellulose; hydroxyethylmethyl cellulose; hydroxypropyl cellulose; sodium phosphate (dibasic or monobasic); sodium starch glycolate; maize starch; sucralose; povidone; polyoxyethylen (including alkly ethers, castor oil derivatives, sorbitan fatty acid esters, stearate, glycerides); shellac; sodium alginate; vitamin E polyethylene glycol succinate; calcium sulfate; carbomer (polyacrylic acid, carboxyvinyl polymer, carbopol); carrageenan; chitosan; hydroxypropyl starch; corn starch; pregelatinized starch; dextrates; dextrin; dextrose; glycerol behenate; Novagel® / Avicel ® (such as PH 101, 102, 301, 302); Vivapur ®; Emcocel ®; Comprecel ®; and Microcel®.

Alternatively or in addition, the composition may comprise one or more additional agents selected from: crospovidone; PVP; polyvinyl N-pyrrolidone; povidone, plasdon; polypasdone (including its XL/ XL-10/ INF-10) with differing particle size distribution (standard, fine, superfine, micronized); guar gum; hydroxypropyl betadex; hydroxypropyl starch; sodium starch glycolate; Kollidon® (with full range of K value - PVP K12, PVP K15, PVP K17, PVP K30, PVP K60, PVP K90, bulk density, hydration capacity, and peroxide levels); and croscarmellose sodium.

Alternatively or in addition, the composition may comprise one or more additional agents selected from: talc; magnesium silicate (monoclinic or triclinic); aluminium magnesium silicate; talcum; corn starch; kaolin; saponite; montmorillonite; and titanium dioxide.

Alternatively or in addition, the composition may comprise one or more additional agents selected from: magnesium stearate (generally a mixture of crystalline forms – anhydrate, monohydrate, dihydrate and trihydrate with Mg, Ca, Na); stearic acid; a composition consisting of magnesium stearate to palmitate, and other fatty acid esters, such as palmitic acid, myristic acid, glyceride esters (glyceryl monostearate, glyceryl tribehenate, glyceryl dibehenate or Compritol 888) and sugar esters (sorbitan monostearate and sucrose monopalmitate); sodium stearyl fumarate; hydrogenated vegetable oil; hydrogenated castor oil; sterotex; talc; waxes (such as anionic emulsifying, carnauba, cetyl esters, microcrystalline, nonionic emulsifying, white or yellow); Stear-O-Wet; boric acid; carbowax (PEG) 4000/6000; sodium oleate; sodium benzoate; sodium acetate; sodium lauryl sulfate; and Mg-lauryl sulfate

Alternatively or in addition, the composition may comprise one or more additional agents selected from: colloidal anhydrous silica or silicon dioxide colloidal; Aerosil; Cab-O-Sil; fumed silica; anhydrous silicic acid; silicic anhydride; silicon dioxide fumed; silicon dioxide amorphous; magnesium trisilicate; magnesium silicate; and magnesium aluminium silicate.

In some embodiments, the composition comprises at least one additional agent selected from: lactose monohydrate; microcrystalline cellulose; crospovidone; talc; magnesium stearate; and colloidal anhydrous silica; or any combination thereof.

In some embodiments, the composition comprises the additional agents: lactose monohydrate; microcrystalline cellulose; crospovidone; talc; magnesium stearate; and colloidal anhydrous silica.

In some embodiments, the composition comprises or consists of:

| Constituent | Amount (mg) |
|---|---|
| NOMAC | 1.5-3.5 |
| 17β-estradiol | 0.5-2.5 |
| lactose monohydrate | 15-98 |
| microcrystalline cellulose | 5-90 |
| crospovidone | 1-5 |
| talc | 0.2-2 |
| magnesium stearate | 0.2-2 |
| colloidal anhydrous silica | 0.2-2 |

In preferred embodiments, the composition comprises or consists of:

| Constituent | Amount (mg) |
|---|---|
| NOMAC | 2.5 |
| 17β-estradiol | 1.5 |
| lactose monohydrate | 57.7 |
| microcrystalline cellulose | 14 |
| crospovidone | 2.4 |
| talc | 0.7 |
| magnesium stearate | 0.7 |
| colloidal anhydrous silica | 0.44 |

In preferred embodiments, the composition comprises or consists of:

| Constituent | Amount (mg) |
|---|---|
| NOMAC | 2.5 |
| 17β-estradiol hemihydrate | 1.55* |
| lactose monohydrate | 57.7 |
| microcrystalline cellulose | 14 |
| crospovidone | 2.4 |
| talc | 0.7 |
| magnesium stearate | 0.7 |
| colloidal anhydrous silica | 0.44 |

* Equivalent to 1.5 mg estradiol

In some embodiments, the composition is formulated for oral administration.

In some embodiments, the composition is in the form of plain or film-coated tablets, sugar-coated tablets, soft gelatin capsules, wafer capsules, pills, cachets or powders.

In preferred embodiments, the composition is in the form of a film-coated tablet. In some embodiments, the film-coating comprises one or more of: poly(vinyl alcohol); titanium dioxide; macrogol 3350; and/or talc.

*(iv) Administration schedule*

Administration of the COC compositions comprising nomegestrol acetate and estradiol or an ester thereof in accordance with the invention is, in some embodiments, at a frequency of once per day i.e. daily. In some embodiments, the compositions are administered daily for a period of between 21 and 28 days. In some embodiments, the compositions are administered daily for a period of between 21 and 28 days per cycle. In some embodiments, the compositions are administered for a period of between 21 and 28 consecutive days per cycle. In other embodiments, the compositions are administered for a period of 21 to 28 days intermittently per cycle. In a preferred embodiment, the compositions are administered once a day for a period of 24 consecutive days per cycle.

The compositions may be administered once a day for a period of 24 consecutive days followed by a hormone-free period of 4 consecutive days. The compositions may administered once a day for a period of 24 consecutive days followed by administration of a placebo tablet once a day for a period of 4 consecutive days. The administration of 24 consecutive daily doses of the composition followed by 4 consecutive daily doses of placebo may constitute one cycle. One cycle may be followed directly by one or more consecutive cycles.

In preferred embodiments, the composition is administered as a monophasic composition for the duration of the period of administration.

*(v) Pharmaceutical kits*

In some embodiments, the compositions used in accordance with the methods of the invention, are provided in the form of pharmaceutical kits, optionally wherein the kits contain instructions for use.

A pharmaceutical kit may comprise a plurality of dosage units of compositions as described herein. The pharmaceutical kit may optionally further comprise at least one placebo dosage unit.

In preferred embodiments, the pharmaceutical kits comprise or consist of 24 dosage units of a composition as described herein and 4 dosage units of a placebo.

**C. Uses of COC compositions in methods of the invention**

In another aspect, the invention provides use of a COC composition comprising NOMAC and estradiol or an ester thereof in a method according to the invention provided herein.

In a further aspect, the invention also provides a composition for use in a method according to the invention provided herein, wherein the composition is a COC composition comprising nomegestrol acetate and estradiol or an ester thereof.

All embodiments described herein relating to the composition and methods according to the preceding aspects of the invention (see in particular, Section B) are equally applicable to these further aspects of the invention.

**Incorporation by Reference**

Various publications are cited in the foregoing description and throughout the following example, each of which is incorporated by reference herein in its entirety.

**EXAMPLE**

The invention will be further understood with reference to the following non-limiting example.

**Prospective, controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg) (the PRO-E2 Study)**

**1. Summary**

A large clinical study was conducted to evaluate the safety of a monophasic combined oral contraceptive (COC) containing nomegestrol acetate (NOMAC) and 17β-estradiol. This COC – referred to herein as NOMAC-E2 – has been on the market for some time with no serious health concerns. However, this multinational, non-randomized, controlled, prospective, active surveillance study was conducted so to as monitor the risk of rare serious adverse outcomes in a large cohort of women taking NOMAC-E2 as compared with a large cohort of women taking a a different COC – referred to herein as $COC_{LNG}$. The primary outcome was venous

thromboembolism (VTE), and specifically deep vein thrombosis (DVT) of the lower extremities and pulmonary embolism (PE). The rate of unintended pregnancy was also investigated as a secondary outcome.

The results presented herein are based on 91,313 women (44,559 NOMAC-E2 users and 46,754 $COC_{LNG}$ users) recruited between August 2014 and September 2019. Starters (i.e. those women who had not received COC treatment before) comprised 62.6% of NOMAC-E2 users and 64.4% of $COC_{LNG}$ users. A total of 37.4% of NOMAC-E2 users and 35.6% of $COC_{LNG}$ users were restarters (i.e. women who had received COC treatment previously). During the follow-up phase, sub-cohorts formed as women switched to other COCs or stopped hormonal contraceptive use. These sub-cohorts included: $COC_{Other}$ (i.e. users of COCs other than NOMAC-E2 or $COC_{LNG}$), other hormonal contraceptives (OHC) (e.g. users of progestin-only OCs, vaginal rings, intrauterine devices or implants) and Ex-users (i.e. women not using a hormonal contraceptive).

The NOMAC-E2 cohort had a higher mean age than the $COC_{LNG}$ cohort and the difference was statistically significant (NOMAC-E2: 31.0 years; $COC_{LNG}$: 29.3 years). NOMAC-E2 users and $COC_{LNG}$ users had a similar mean weight (NOMAC-E2: 63.3 kg; $COC_{LNG}$: 63.1 kg) and mean BMI (NOMAC-E2: 23.2; $COC_{LNG}$: 23.3). Gynaecological history and baseline risk factors differed little between the cohorts.

Data from 144,901 women years (WY) of observation have been collected, including 48,846 WY from NOMAC-E2 users and 54,037 WY from $COC_{LNG}$ users. The remaining observation time was contributed by the sub-cohorts which formed during follow-up: $COC_{Other}$ (8,300 WY), OHC (2,364 WY) and ex-users (31,354 WY).Overall, there were 34 VTEs in the main analysis of the primary outcome (DVT of the lower extremities and PE): 9 NOMAC-E2 (2.0 per 10,000 WY; 95% CI, 0.9 – 3.7), 15 $COC_{LNG}$ (3.0 per 10,000 WY; 95% CI, 1.7 – 5.0), 4 $COC_{Other}$ (5.2 per 10,000 WY; 95% CI, 1.4 – 13.4), 1 OHC (4.8 per 10,000 WY; 95% CI, 0.1 – 26.8) and 5 ex-users (1.8 per 10,000 WY; 95% CI, 0.6 – 4.1). The Cox proportional hazards *a priori* expert model (complete case analysis) resulted in a crude hazard ratio ($HR_{crude}$) for NOMAC-E2 versus $COC_{LNG}$ of 0.65 (95% CI, 0.28 – 1.48). After adjusting for age, BMI, family history of VTE and current duration of HC use, the adjusted hazard ratio ($HR_{adj}$) was 0.59 (95% CI, 0.25 – 1.35).

Overall, there were 289 unintended pregnancies in hormonal contraceptive users: 64 in NOMAC-E2 users (0.15 per 100 WY; 95% CI, 0.11 – 0.19), 200 in $COC_{LNG}$ users (0.41 per 100 WY; 95% CI, 0.35 – 0.47), 19 in $COC_{Other}$ users (0.26 per 100 WY; 95% CI, 0.16 – 0.40) and 6 in OHC users (0.28 per 100 WY; 95% CI, 0.10 – 0.61). Unintended pregnancy

was statistically significantly less likely in NOMAC-E2 users compared to $COC_{LNG}$ users ($p<0.0001$).

Further details of this clinical study are provided below.

## 2. List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AMI | Acute Myocardial Infarction |
| AT | As Treated |
| ATE | Arterial Thromboembolism |
| BMI | Body Mass Index |
| COC | Combined Oral Contraceptive |
| $COC_{LNG}$ | Levonorgestrel-containing COC |
| $COC_{LNGMono/20mcg}$ | Monophasic levonorgestrel-containing COC with 20mcg ethinylestradiol |
| $COC_{LNGMono/30mcg}$ | Monophasic levonorgestrel-containing COC with 30mcg ethinlyestradiol |
| $COC_{LNGMulti}$ | Multiphasic levonorgestrel-containing COC |
| $COC_{Other}$ | Combined oral contraceptive other than NOMAC-E2 or $COC_{LNG}$ |
| CT | Computer Tomography |
| CVA | Cerebrovascular Accidents |
| DVT | Deep Venous Thrombosis |
| ECG | Electrocardiogram |
| EE | Ethinylestradiol |
| EURAS | European Active Surveillance (study) |
| LNG | Levonorgestrel |
| MRT | Magnetic Resonance Tomography |
| MRI | Magnetic Resonance Imaging |
| NOMAC-E2 | Nomegestrol Acetate and Estradiol |
| HR | Hazard ratio |
| $HR_{adj}$ | Hazard ratio (adjusted) |
| $HR_{crude}$ | Hazard ratio (crude) |
| OC | Oral Contraceptive |

| | |
|---|---|
| OHC | Other hormonal contraceptive (i.e., progestin-only method, injections, implants, levonorgestrel-releasing intrauterine devices, contraceptive patches) |
| PE | Pulmonary Embolism |
| PIP | Pediatric Investigation Plan |
| SAE | Serious Adverse Event |
| VTE | Venous Thromboembolism |
| WY | Woman-years |

## 3. Rationale and Background

NOMAC-E2 is a monophasic OC containing a fixed dose of nomegestrol acetate (2.5mg) and 17β-estradiol (1.5mg), which is taken for 24 days followed by 4 days of placebo. Nomegestrol acetate has a strong affinity for the progesterone receptor and has strong anti-gonadotropic activity and progesterone receptor-mediated anti-estrogenic activity, moderate anti-androgenic activity, and is devoid of estrogenic, androgenic, glucocorticoid or mineralocorticoid activity. The estrogen contained in NOMAC-E2 is 17β-estradiol, an estrogen identical to the endogenous human 17β-estradiol.

Data from randomized clinical trials has not revealed any serious health concerns for NOMAC-E2. However, the statistical power to detect rare adverse events has been limited in these earlier studies. Based on general public concerns about the safety of COCs, the Prospective Controlled Cohort Study on the Safety of a Monophasic Oral Contraceptive containing Nomegestrol Acetate (2.5mg) and 17β-estradiol (1.5mg), (PRO-E2) Study focused not only on VTE but also on ATE, depressive disorders, cholelithiasis, general hepatobiliary disorders, inflammatory bowel disease, effects on fertility, pregnancy outcomes, weight change and the effect on acne.

The PRO-E2 study was conducted as a required post-authorization safety study in accordance with Article 10a of the EU Regulation 726/2004. The objective of the PRO-E2 Study was to assess the cardiovascular and other health risks associated with the use of NOMAC-E2 compared with the use of $COC_{LNG}$ during standard clinical practice. The study included women who have been newly prescribed NOMAC-E2 or $COC_{LNG}$ (either as first-ever users or as restarters with a COC intake break of at least 2 months). During the follow-up phase, sub-cohorts formed as women switched to other COCs (forming a $COC_{Other}$ sub-cohort), other hormonal contraceptives such as progestin-only methods, injections, implants, levonorgestrel-

releasing intrauterine devices and contraceptive patches (forming an OHC sub-cohort), or stopped hormonal contraceptive use (forming an Ex-user sub-cohort).

As specified in the study protocol dated 5 February 2014, participating countries included Australia, Austria, France, Germany, Hungary, Italy, Poland, Russia and Spain. Subsequent to the approval of the Study Protocol in April 2014, three additional countries (Mexico, Colombia and Sweden) were included in the study (as reflected in the final version of Amendment 1 of the Study Protocol, dated 20 June 2019).

Patient recruitment began in August 2014 in Germany. Thereafter, recruitment began in Australia, Austria, Colombia, France, Hungary, Italy, Mexico, Poland, Russia, Spain and Sweden after country-specific requirements were met.

**4. Research questions and objectives**

The primary objective of the study was to characterize and compare the risks of NOMAC-E2 use with $COC_{LNG}$ use in a study population that is representative of the actual users of the individual preparations. This included an estimate of the absolute risk of rare serious adverse outcomes.

The main clinical outcomes of interest were VTE, specifically:

- DVT of the lower extremities
- PE

Secondary objectives of the study were to measure/describe for NOMAC-E2 users and compare to users of $COC_{LNG}$ during standard clinical practice:

- Pregnancy outcomes
- All VTE, including thromboses of renal, mesenteric, portal and retinal veins
- ATE incidence rate. ATE includes acute myocardial infarction (AMI) and cerebrovascular accidents (CVA)
- Depressive disorders incidence rate (based on the assessment of attending physicians who are specialized in psychiatry and the Three Item Mental Health Inventory)
- Cholelithiasis incidence rate
- Inflammatory bowel disease incidence rate
- Effect on fertility
- Drug utilization pattern and baseline risk for primary and secondary clinical outcomes – in particular cardiovascular outcomes

Additional secondary objectives were to measure/describe the following factors for NOMAC-E2 users and compare to users of $COC_{LNG}$ during standard clinical practice:

- Weight change
- General hepatobiliary disorders
- Effect on acne

## 5. Research Methods

### Study design

The study was a large, multinational, controlled, prospective, active surveillance study that followed two cohorts. The cohorts consisted of new users (starters and restarters) of two different groups of hormonal contraceptives: NOMAC-E2 and $COC_{LNG}$. Starters were first-ever users of any COC. Restarters were users who were restarting hormonal contraceptive use with a COC (same COC as before or a new COC) after a break of at least 2 months. This observational study provides standardized, comprehensive, reliable information on these treatments in a routine clinical practice setting.

Study participants were recruited via an international network of COC-prescribing health care professionals (e.g. gynecologists, general practitioners, midwives). After study entry, study participants were followed for a period of 12 to 24 months for rare serious safety outcomes. Regular, active contact with the study participants provided the necessary information on health-related events or changes in health status. Additional follow-up procedures were used to validate self-reported events.

During the follow-up phase, direct contact with the study participants allowed for almost all relevant clinical outcomes to be captured. However, laypersons often misclassified adverse events (e.g., pneumonia as “pulmonary embolism” or migraine attacks as “stroke” even if modern imaging procedures do not provide any indication of the perceived event). This type of inaccuracy in patient reports required careful validation of the reported events. This was accomplished by contacting the relevant physicians (i.e. the treating physicians) and by reviewing source documents. Under routine medical conditions, clinical outcomes were not always confirmed by diagnostic procedures with high specificity. Therefore, reported serious clinical outcomes were classified as “confirmed” or “not confirmed” by the physicians overseeing this study according to a predefined algorithm. At the end of the study, this classification was verified by blinded independent adjudication.

**Setting**

The PRO-E2 Study was divided into 2 phases: a patient-completed baseline survey, which involved an initial consultation at baseline with a participating physician during routine clinical practice; and a follow-up phase, which included two follow-up contacts with the patient during the first year, and then a follow-up at 24 months after study entry.

**Subjects and study size, including dropouts**

The overall recruitment target was 101,000 study participants (50,500 NOMAC-E2 users and 50,500 $COC_{LNG}$ users) recruited by participating physicians. This was planned to provide approximately 150,000 WY, assuming a drop-out rate of approximately 0.7% per month.

Subjects were considered for enrolment in the PRO-E2 Study after the participating physician and the woman had determined that NOMAC-E2 or $COC_{LNG}$ use was appropriate. There were no specific medical inclusion/exclusion criteria and no age restrictions (to fulfil the pediatric investigation plan (PIP) requirement in the EU). However, women who 1) have been pregnant within 3 months before treatment initiation or 2) have a history of cancer/chemotherapy or an increased genetic risk for VTE at baseline were excluded from the analysis of VTE.

Once enrolled, a study participant could discontinue (and restart) use of hormonal contraception or could switch to another hormonal contraceptive at any time. However, subjects continued to be followed up regardless of whether they remained on the prescribed contraceptive, provided that they did not withdraw their consent.

**Variables**

The following variables were recorded at baseline: ID number; date of birth; age at menarche; problems associated with menstrual period (e.g. irregular bleeding/spotting); hormonal contraceptive use (duration, brand name of most recent hormonal contraceptive, hormonal contraceptive use within the past two months); reason(s) for prescription; previous pregnancies; pregnancy within past three months; number of live births; number of miscarriages, stillbirths, abortions; family history of VTE and ATE; mood over the past four weeks; acne; impact of severe acne on self-esteem; medical history (including DVT, PE, myocardial infarction, stroke, thrombophilia or inherited increased risk of blood clots, depression requiring treatment, diseases of the liver, diseases of the gallbladder or biliary tract, inflammatory bowel disease, cancer, diabetes, high blood pressure, other severe diseases, operations); regular use of concomitant medication; height; weight; smoking status and number of cigarettes smoked per day; level of education; date of completion.

During follow-up, the following variables were recorded: ID number; new SAEs / AEs; hospitalization (planned/unplanned, reason, operation performed); hormonal contraceptive use since last contact (stopped/switched/unchanged, reason for stopping/switching); concomitant medication; pregnancy (occurrence, planned/unplanned, length of time to become pregnant, pregnant despite OC use, possible reasons for contraceptive failure); delivery; serious health issues of the newborn; mood over the past four weeks; acne; impact of severe acne on self-esteem; smoking status and number of cigarettes smoked per day; weight; date of completion; change of personal contact details; name of treating physician in case of SAE/AE.

**Exposure**

**Cohort 1:** NOMAC-E2

**Cohort 2:** Levonorgestrel-containing COCs: 1) monophasic preparations containing 20 - 30mcg of ethinylestradiol; 2) multiphasic preparations containing up to 40mcg of ethinylestradiol

**Outcome**

The primary endpoint was VTE. Specific VTEs – DVT of the lower extremities and PE – were the primary outcomes of interest. Inferential statistics are based on the VTE HR for NOMAC-E2 vs. $COC_{LNG}$.

The secondary endpoints also investigated are described above in the research questions and objectives section.

**Covariates**

In relation to VTE risk, the covariates include age, BMI, duration of current use and family history of VTE.

**Data sources and measurement**

Study participants documented on questionnaires their exposure to hormonal contraceptives and concomitant medications, the occurrence of primary and secondary outcomes and the existence of potential confounding factors and potential effect modifiers. If relevant, recruiting and attending physicians provided further information on additional documentation sheets. Follow-up assessments for each study participant were scheduled at 6 months, 12 months and 24 months after study entry. Questionnaires were provided to the participating women. In some cases, events were reported by the participant or by relatives, friends or attending

physicians between the regular follow-ups. All reports (independent of the source of information) were validated according to a standardized process

The follow-up questionnaires addressed the occurrence of adverse events (in particular, SAEs). If applicable, reasons for COC discontinuation or a switch to another hormonal contraceptive were requested.

**Study Procedures**

Under routine medical conditions, the diagnosis of an SAE is not always confirmed by a diagnostic method with high specificity. Therefore, SAEs were classified as "confirmed" or "not confirmed" according to the following predefined algorithm:

- **Definite Event:**
  Confirmed by diagnostic measures with high specificity (e.g. phlebography for DVT, spiral CT for PE, cerebral MRT for cerebrovascular accidents, electrocardiogram (ECG) with typical ST-segment elevation for acute myocardial infarction, histology for gynecological cancer, two-sided blood pressure measurement with diastolic blood pressure of more than 120 mmHg for hypertensive crisis).

- **Probable Event:**
  Absence of confirmation by a diagnostic measure with high specificity, but clinical diagnosis confirmed by a health professional or supported by diagnostic tests with low specificity (such as D-dimer for VTE or typical ECG/blood gas tests for PE). These cases are usually characterized by a subsequent specific therapy (such as fibrinolysis or long-term anticoagulant therapy). However, if the attending physician confirms that the diagnosis is correct, the event was classified as a probable event even if specific treatment was not given.

- **Event not confirmed:**
  - The diagnosis reported by the patient is excluded by diagnostic procedures.
  - A different medical condition is diagnosed by the attending physician.
  - The participant did not contact a health care professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis.

The exposure data reported by the patients was validated via the prescribing physicians. Definite and probable events were classified as 'confirmed events'.

For the final analysis this classification was verified by means of an independent blinded adjudication process.

**Study size**

The sample size considerations were based on the expected VTE incidence for $COC_{LNG}$. Sample size calculations were based on an incidence rate of 10 VTE per 10,000 WY[1] for $COC_{LNG}$.

The study was powered to test non-inferiority of NOMAC-E2 treatment regarding VTE risk in comparison to $COC_{LNG}$ use. The study was sufficiently powered to exclude a 1.5-fold VTE risk for NOMAC-E2 users compared to $COC_{LNG}$ users in the event that the true VTE risk among NOMAC-E2 users is not higher than among $COC_{LNG}$ users.

The sample size needed for the investigation of the VTE risk was also sufficient for the evaluation of secondary outcomes (with the exception of ATE). Acute myocardial infarction and stroke are very rare in a female population of reproductive age. The study was powered to exclude a 2.5-fold risk of ATE in NOMAC-E2 users compared to $COC_{LNG}$ users. This was sufficient to screen for safety signals and substantial effects.

**Statistical methods**

**Main summary measures**

Incidence rates, crude HRs and adjusted HRs were calculated.

**Main statistical methods**

The study used a non-inferiority design to investigate the VTE risk of NOMAC-E2. The *a priori* assumption was that use of NOMAC-E2 is not associated with an increased risk of VTE compared to $COC_{LNG}$ (i.e. a statistical comparison of NOMAC-E2 and $COC_{LNG}$ is not expected to show a difference).

## 6. Results

**Participants**

A total of 101,498 women were enrolled in the study after having been recruited by 2,413 physicians in Australia, Austria, Colombia, France, Germany, Hungary, Italy, Mexico,

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[1] 'idiopathic' PE and DVT of the lower extremities

Poland, Russia, Spain and Sweden. The results of the analyses presented herein are based on 102,330 women.

**Descriptive data**

Of the 91,313 women in the AT population, a total of 44,559 were NOMAC-E2 users and 46,754 were $COC_{LNG}$ users (48.8% and 51.2% of the study population, respectively). Of the 46,754 $COC_{LNG}$ users, 20,181 (22.1% of the total study population) were users of a monophasic preparation containing 20 mcg of EE, 17,469 (19.1% of the total study population) were users of a monophasic preparation containing 30 mcg of EE and 9,104 (10% of the total study population) were users of multiphasic preparations.

At study entry, the mean age of NOMAC-E2 users was higher (31.0 years) than $COC_{LNG}$ users (29.3 years) and this difference was statistically significant ($p<0.0001$). There were no substantial differences in relation to mean weight (NOMAC-E2: 63.3 kg; $COC_{LNG}$: 63.1 kg) or mean BMI (NOMAC-E2: 23.2; $COC_{LNG}$: 23.3). The distribution of cohorts by age category is displayed in Figure 1. Almost 33% of NOMAC-E2 users and 27% of $COC_{LNG}$ users were aged 35 or older.

As noted above, starters and restarters of COCs are included in the study population. Starters comprised 62.2% of NOMAC-E2 users and 64.4% of $COC_{LNG}$ users. Restarters comprised 37.8% and 35.6% of NOMAC-E2 and $COC_{LNG}$ users, respectively.

Characteristics associated with gynaecological history were largely similar between the cohorts at study entry. This included the mean age at menarche (12.8 years for each cohort), the mean age at first delivery among parous women (NOMAC-E2: 24.3 years; $COC_{LNG}$: 23.7 years), the median number of live births (if ever pregnant) (1.0 in each cohort) and the median number of miscarriages/stillbirths/abortions (if ever pregnant) (1.0 in each cohort). A greater proportion of NOMAC-E2 users reported ever having been pregnant (NOMAC-E2: 57.0%; $COC_{LNG}$: 54.9%).

In this real world observational study, women were asked for the reason(s) for their contraceptive prescription. With regard to the motivating factors behind COC use, 54.9% of NOMAC-E2 users reported seeking a COC prescription for contraceptive reasons only compared to 57.1% of $COC_{LNG}$ users. The proportions of women who reported contraceptive as well as non-contraceptive reasons were 33.9% and 33.1% for NOMAC-E2 and $COC_{LNG}$ users, respectively. Meanwhile, 9.5% of NOMAC-E2 users and 8.6% of $COC_{LNG}$ users reported using COCs exclusively for non-contraceptive reasons (such as cycle control, acne, painful and/or prolonged/heavy bleeding).

The non-contraceptive reasons specified by study participants are displayed in Table 1. Sometimes women reported more than one non-contraceptive reason.

**Table 1 Non-contraceptive reasons for COC prescription reported by patients at study entry, by cohort**

| Reason | NOMAC-E2 (N = 19,329) | | $COC_{LNG}$ (N = 19,482) | | Total (N = 38,811) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Cycle regulation | 8,128 | 42.1 | 9,078 | 46.6 | 17,206 | 44.3 |
| Painful menstrual bleeding | 7,511 | 38.9 | 7,822 | 40.1 | 15,333 | 39.5 |
| Heavy and/or prolonged menstrual bleeding | 5,306 | 27.5 | 4,605 | 23.6 | 9,911 | 25.5 |
| Acne | 1,859 | 9.6 | 1,636 | 8.4 | 3,495 | 9.0 |
| Ovarian cysts | 1,531 | 7.9 | 1,646 | 8.4 | 3,177 | 8.2 |
| Polycystic ovary syndrome (PCOS) | 1,187 | 6.1 | 1,214 | 6.2 | 2,401 | 6.2 |
| Premenstrual syndrome (PMS) | 1,136 | 5.9 | 938 | 4.8 | 2,074 | 5.3 |
| Endometriosis | 1,167 | 6.0 | 777 | 4.0 | 1,944 | 5.0 |
| Bleeding on demand | 495 | 2.6 | 572 | 2.9 | 1,067 | 2.7 |
| Premenstrual dysphoric disorder (PMDD) | 195 | 1.0 | 0.7 | 129 | 324 | 0.8 |
| Other reasons | 1,400 | 7.2 | 1,220 | 6.3 | 2,620 | 6.8 |

Note: Women could report multiple reasons.

At study entry, women were also asked about (i) history of treated depression; and (ii) history of acne. There were no significant differences between the cohorts. Women were also asked about their personal history of disease and regular medication use.

**Outcome data**

**Fatal outcomes**

A total of 30 study participants died during the study. Among the NOMAC-E2 users, 7 deaths were reported: 3 due to accidents, 2 due to cancer (one woman died of end stage lymphoma with metastasis to the liver and the other of vulvar cancer with widespread metastasis), 1 as a result of a systemic herpes infection and 1 due to an unknown cause.

Blinded to the hormonal contraceptive exposure status, the SMAC assessed that in 19 of the deaths there was no relationship to hormonal contraceptive use. One case involving a

NOMAC-E2 user with a history of heart disease who died due to an unknown cause was assessed by the SMAC as having a possible relationship to hormonal contraceptive use because the cause of death was unknown. One case involving an Ex-user who died of an unknown cause was assessed as unlikely to be related to hormonal contraceptive use. In relation to another case involving an Ex-user who died of an unknown cause, the SMAC assessed the relationship with hormonal contraceptive use as 'indeterminate' because insufficient information is known to enable an assessment of a causal relationship.

**SAEs**

There were a total of 3,388 SAEs. An SAE is defined in this study as an adverse event that results in death, a life-threatening experience, inpatient hospitalization, persistent or significant disability/incapacity, or requires medical/surgical intervention to prevent one of these outcomes.

The incidence of SAE was lower in NOMAC-E2 users than in $COC_{LNG}$ users. Figure 2 graphically displays the incidence rates and 95% confidence intervals.

**Main results**

During the reporting period, data from a total of 133,983 WY of observation were collected. In addition to the cohorts at study entry (NOMAC-E2 and $COC_{LNG}$), a number of additional cohorts developed during the follow-up phase as women switched to other forms of contraception or discontinued contraceptive use altogether. Table 2 displays the number of WY within each of the user cohorts.

**Table 2 Number of WY of observation within each (sub)-cohort**

| User (sub-)cohort | Woman years | Percentage of observation time |
|---|---|---|
| NOMAC-E2 | 48,846 | 33.7 |
| $COC_{LNG}$ | 54,037 | 37.3 |
| $COC_{Other}$ | 8,300 | 5.7 |
| Other hormonal contraceptive (OHC)* | 2,364 | 1.6 |
| Ex-user (no hormonal contraceptive use) | 31,354 | 21.6 |
| Total | 144,901 | 100** |

*Progestin-only OC, vaginal ring, injection, intrauterine device, contraceptive patch or implant.
**Discrepancy due to rounding.

**Primary outcome of interest**

**DVT of the lower extremities and PE**

Overall, there have been 34 confirmed VTE (DVT of the lower extremities and PE), excluding all women who reported pre-defined risk factors at study entry (pregnant within 3 months of treatment initiation, have a history of cancer/chemotherapy or an increased genetic risk of VTE (e.g. Factor V Leiden, Protein S or C deficiency). Of the 34 VTE: 9 in NOMAC-E2 users (2.0 per 10,000 WY; 95% CI, 0.9 – 3.7), 15 in $COC_{LNG}$ users (3.0 per 10,000 WY; 95% CI, 1.7 – 5.0), 4 in $COC_{Other}$ users (5.2 per 10,000 WY; 95% CI, 1.4 – 13.4), 1 in an OHC user (4.8 per 10,000 WY; 95% CI, 0.1 – 26.8) and 5 in ex-users (1.8 per 10,000 WY; 95% CI, 0.6 – 4.1) Five women (2 $COC_{LNG}$ users and 3 $COC_{Other}$ users) experienced both a DVT of a lower extremity and a PE.

**Secondary outcomes of interest – unintended pregnancy**

Overall, there were 289 unintended pregnancies in hormonal contraceptive users: 64 in NOMAC-E2 users (0.15 per 100 WY; 95% CI, 0.11 – 0.19), 200 in $COC_{LNG}$ users (0.41 per 100 WY; 95% CI, 0.35 – 0.47), 19 in $COC_{Other}$ users (0.26 per 100 WY; 95% CI, 0.16 – 0.40) and 6 in OHC users (0.28 per 100 WY; 95% CI, 0.10 – 0.61). Unintended pregnancy was statistically significantly less likely in NOMAC-E2 users compared to $COC_{LNG}$ users ($p<0.0001$) (Figure 3).

**Figure 4** shows the incidence of unintended pregnancy according to COC or contraceptive cohort by age, where (A) is women less than 35 years of age and (B) is women of 35 years of age or greater. In both cohorts, unintended pregnancy was less likely in NOMAC-E2 users compared to comparable $COC_{LNG}$ users, with the effect particularly apparent in women under 35.

**Figure 5** shows the incidence of unintended pregnancy according to COC or contraceptive cohort by education level, where (A) is women having an education level of less than or equal to university entrance level, and (B) is women having an education level greater than university entrance level. In both cohorts, unintended pregnancy was less likely in NOMAC-E2 users compared to comparable $COC_{LNG}$ users, with the effect particularly apparent in women having an education level of less than or equal to university entrance level.

**Figure 6** shows the incidence of unintended pregnancy according to COC or contraceptive cohort for women using the administered contraceptive composition solely for contraceptive purposes. In this cohort, unintended pregnancy was significantly less likely in NOMAC-E2 users compared to comparable $COC_{LNG}$ users.

**Interpretation**

These results demonstrate that NOMAC-E2 users are at a lower risk of unintentionally becoming pregnant despite using a COC as a contraceptive, compared to users of other COCs, especially when compared to $COC_{LNG}$ users. That is, NOMAC-E2 users are at a lower risk of contraceptive failure and thus unintended pregnancy.

These results also demonstrate that NOMAC-E2 users are not at higher risk of VTE, ATE, death, SAE, cholelithiasis, inflammatory bowel disease, general hepatobiliary disorders, depressive disorders, mood changes, weight changes or acne changes compared to $COC_{LNG}$ users.

**Generalisation**

The study was designed to reflect routine clinical use of COCs. Study participants were recruited by COC-prescribing healthcare professionals (e.g. gynecologists, general practitioners, midwives) and all new users of COCs could participate in the study. Participation was not limited by medical inclusion and exclusion criteria. Therefore, the ability to generalize the results of this study is high.

## 7. Summary

Baseline characteristics

- NOMAC-E2 users had a higher mean age at study entry compared to $COC_{LNG}$ users. Other baseline characteristics (including cardiovascular risk factors) were similar between the user cohorts. The similarities between the cohorts would indicate that confounding should be minimal.

Primary outcome of interest

- The risk of DVT of the lower extremities and PE (VTE) was lower in the NOMAC-E2 cohort (2.0 per 10,000 WY; 95% CI, 0.9 – 3.7), compared to the $COC_{LNG}$ cohort (3.0 per 10,000 WY; 95% CI, 1.7 – 5.0).
- The $HR_{crude}$ for NOMAC-E2 vs. $COC_{LNG}$ was 0.65 with a 95% confidence interval of 0.28 to 1.48. After adjusting for age, BMI, family history of VTE and current duration of use, $HR_{adj}$ remained 0.6 (95% CI, 0.25 – 1.35).

Secondary outcomes of interest

- The risk of unintended pregnancy was statistically significantly lower in the NOMAC-E2 cohort (0.15 per 100 WY ; 95% CI, 0.11 – 0.19) than the $COC_{LNG}$ cohort (0.41 per 100 WY; 95% CI, 0.35 – 0.47) ($p<0.0001$). The reduction in risk of unintended pregnancy was particularly marked in women under the age of 35 (0.18 per 100 WY; 95% CI, 0.14-0.24 vs 0.49 per 100 WY; 95% CI, 0.42 – 0.57 for the $COC_{LNG}$ cohort), and (independently) in women having an education level of less than or equal to university entrance level (0.21 per 100 WY; 95% CI, 0.16 – 0.28 vs 0.56 per 100 WY; 95% CI, 0.47 – 0.64 for the $COC_{LNG}$ cohort).
- The risk of all VTE was lower in the NOMAC-E2 cohort (2.5 per 10,000 WY; 95% CI, 1.3 – 4.3) compared to the $COC_{LNG}$ cohort (3.7 per 10,000 WY; 95% CI, 2.3 – 5.7).
- The risk of idiopathic VTE was lower in NOMAC-E2 users (2.0 per 10,000 WY; 95% CI, 1.0 3.8) compared to $COC_{LNG}$ users (2.8 per 10,000 WY; 95% CI, 1.6 – 4.6).
- There were no statistically significant differences between NOMAC-E2 users and $COC_{LNG}$ users in relation to the risk of ATE, cholelithiasis, inflammatory bowel disease, general hepatobiliary disorders, depressive disorders, mood changes, weight or acne.

**CLAIMS**

1. A method for reducing the risk of unintended pregnancy during a period of combined oral contraceptive use by a woman, the method comprising administering a combined oral contraceptive (COC) composition to the woman, wherein the COC composition comprises nomegestrol acetate and estradiol or an ester thereof.

2. A method for reducing the risk of contraceptive failure during a period of combined oral contraceptive use by a woman, the method comprising administering a combined oral contraceptive (COC) composition to the woman, wherein the COC composition comprises nomegestrol acetate and estradiol or an ester thereof.

3. A method according to any preceding claim wherein the COC composition comprising nomegestrol acetate and estradiol or an ester thereof is administered to a woman who has not received a combined oral contraceptive for at least 2 months.

4. A method according to any one of the preceding claims, wherein the COC composition comprising nomegestrol acetate and estradiol or an ester thereof is administered to a woman who has not previously received a combined oral contraceptive.

5. A method according to claim 1 or claim 3 dependent on claim 1, wherein the method comprises the steps of:

(i) identifying a woman in a period of combined oral contraceptive (COC) use, wherein the woman is taking a first COC and the first COC is other than a COC composition comprising nomegestrol acetate and estradiol or an ester thereof;

(ii) identifying the woman as at increased risk of unintended pregnancy;

(iii) stopping administration to the woman of the first COC and starting administration to the woman of a COC composition comprising nomegestrol acetate and estradiol or an ester thereof,

thereby reducing the risk of unintended pregnancy during the subsequent period of combined oral contraceptive use by the woman.

6. A method according to claim 2 or claim 3 dependent on claim 2, wherein the method comprises the steps of:

(i) identifying a woman in a period of combined oral contraceptive (COC) use, wherein the woman is taking a first COC and the first COC is other than a COC composition comprising nomegestrol acetate and estradiol or an ester thereof;

(ii) identifying the woman as at increased risk of contraceptive failure;

(iii) stopping administration to the woman of the first COC and starting administration to the woman of a COC composition comprising nomegestrol acetate and estradiol or an ester thereof,

thereby reducing the risk of contraceptive failure during the subsequent period of combined oral contraceptive use by the woman.

7. A method according to any preceding claim wherein the reduction in risk is relative to the risk when the COC used during the period of combined oral contraceptive use is other than a COC composition comprising nomegestrol acetate and estradiol or an ester thereof.

8. A method according to any preceding claim wherein the reduction in risk is relative to the risk when the COC used during the period of combined oral contraceptive use is a COC comprising levonorgestrel, optionally further comprising ethinylestradiol.

9. A method according to any preceding claim wherein administration of a COC composition comprising nomegestrol acetate and estradiol or an ester thereof results in a rate of unintended pregnancy or contraception failure in the range of from 0.05 to 0.3 per 100 woman years (WY), optionally in the range of from 0.1 to 0.3 per 100 WY, optionally about 0.2 per 100 woman years, optionally about 0.15 per 100 woman years.

10. A method according to any preceding claim wherein the reduction in risk is indicated by a hazard ratio of 0.3-0.6, optionally 0.3-0.5.

11. A method according to any preceding claim wherein the woman is less than 35 years of age.

12. A method according to any one of claims 1-10, wherein the age of the woman is 35 years or greater.

13. A method according to any preceding claim, wherein the nomegestrol acetate and estradiol or ester thereof are present in the composition in a weight ratio of approximately 1.67 to 1.

14. A method according to any preceding claim, wherein the nomegestrol acetate is present in the composition in an amount ranging from about 1.5 mg to about 3.75 mg.

15. A method according to any preceding claim, wherein the estradiol or ester thereof is present in the composition in an amount ranging from about 0.5 mg to about 3 mg.

16. A method according to any preceding claim, wherein the estradiol is 17β-estradiol; optionally wherein the 17β-estradiol is in hemihydrate form.

17. A method according to any preceding claim, wherein the nomegestrol acetate is present in the composition in an amount of about 2.5 mg and the estradiol is present in the composition in an amount of about 1.5 mg.

18. A method according to any preceding claim, wherein the COC composition comprising nomegestrol acetate and estradiol or an ester thereof is administered daily for a period of 21 to 28 days; optionally for a period of 24 consecutive days.

19. A method according to any preceding claim, wherein the COC composition comprising nomegestrol acetate and estradiol or an ester thereof is in the form of plain or film-coated tablets, sugar-coated tablets, soft gelatin capsules, wafer capsules, pills, cachets or powders.

20. A method according to any preceding claim, wherein the COC composition comprising nomegestrol acetate and estradiol or an ester thereof further comprises at least one excipient selected from: lactose monohydrate; microcrystalline cellulose (E460); crospovidone (E1201); talc (E553b); magnesium stearate (E572); and colloidal anhydrous silica; or any combination thereof.

21. A method according to any preceding claim wherein the COC composition comprising nomegestrol acetate and estradiol or an ester thereof comprises: 2.5 mg nomegestrol acetate; 1.5 mg 17β-estradiol; 57.7 mg lactose monohydrate; 14 mg microcrystalline cellulose; 2.4 mg crospovidone; 0.7 mg talc; 0.7 mg magnesium stearate, and 0.44 mg colloidal anhydrous silica.

22. A method according to any preceding claim, wherein the COC composition comprising nomegestrol acetate and estradiol or an ester thereof is provided as a pharmaceutical kit comprising a plurality of dosage units and optionally at least one placebo.

23. Use of a composition comprising nomegestrol acetate and estradiol or an ester thereof in a method according to any preceding claim

24. A composition for use in a method of any one of claims 1-22, wherein the composition is a COC composition comprising nomegestrol acetate and estradiol or an ester thereof.

**Fig. 1**

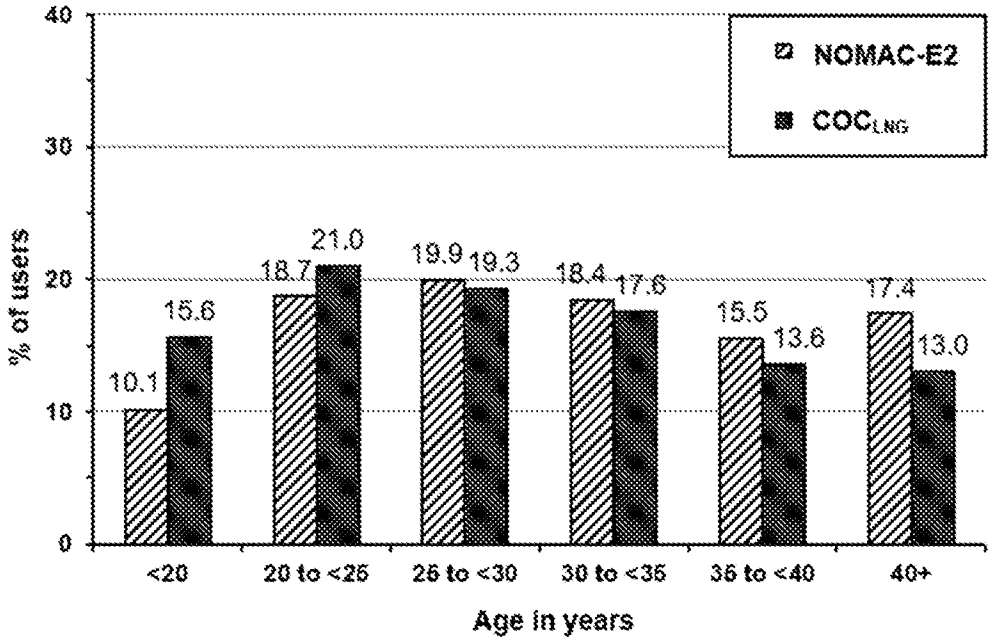

40
30
20
10
0
% of users
NOMAC-E2
COC LNG
10.1
15.6
18.7
21.0
19.9
19.3
18.4
17.6
15.5
13.6
17.4
13.0
<20
20 to <25
25 to <30
30 to <35
35 to <40
40+
Age in years

**Fig. 2**

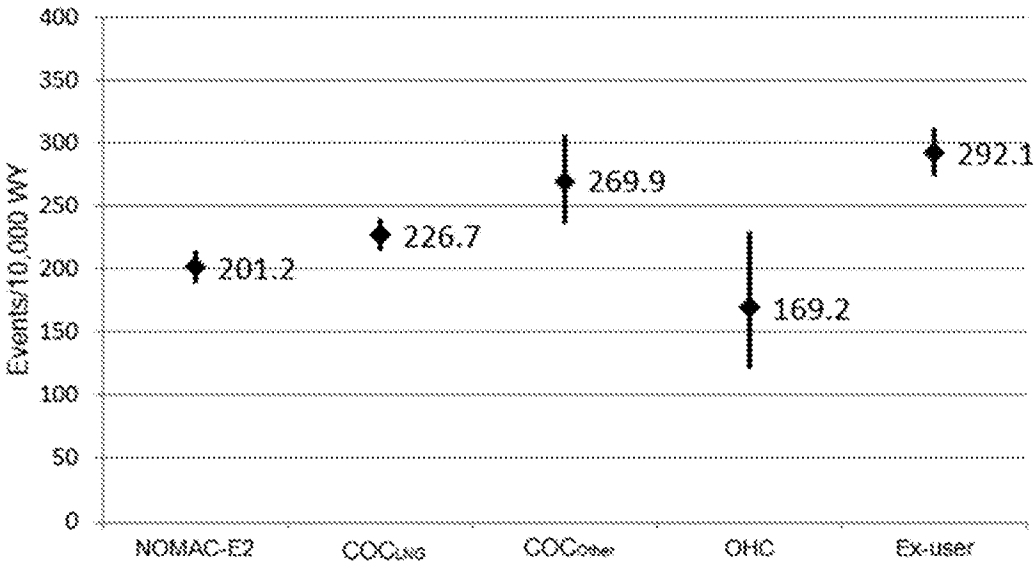

400
350
300
250
200
150
100
50
0
Events/10,000 WY
201.2
226.7
269.9
169.2
292.1
NOMAC-E2
COC$_{LNG}$
COC$_{Other}$
OHC
Ex-user

**Fig. 3**

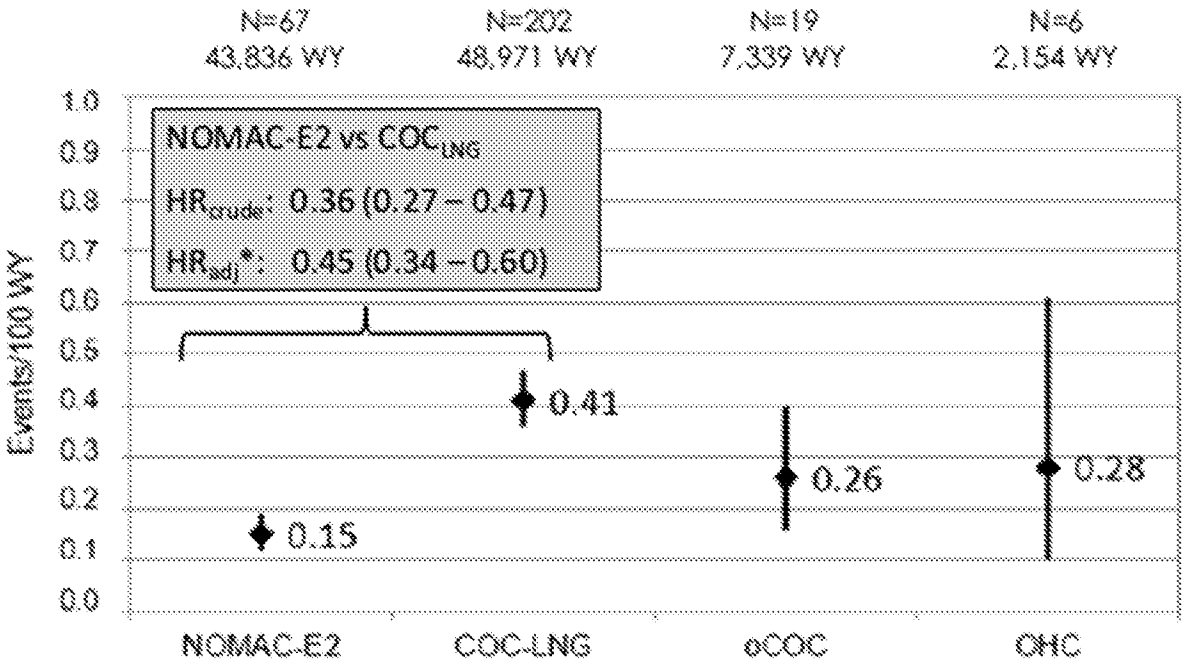
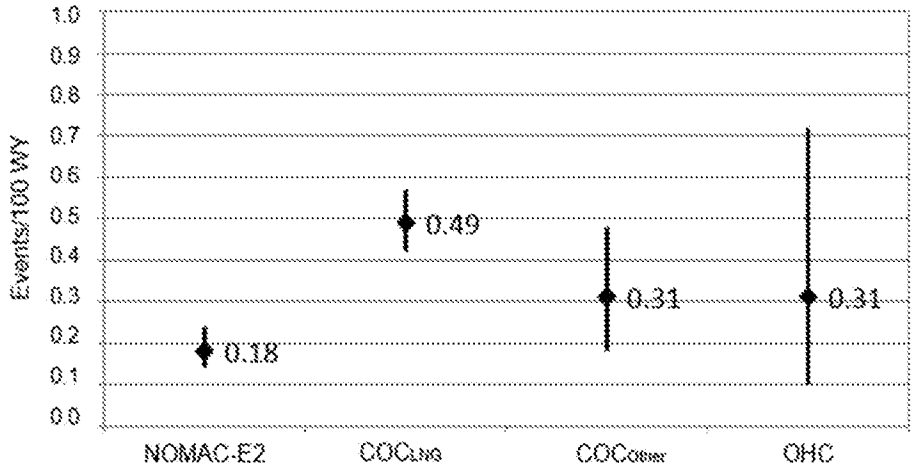

N=67
43,836 WY
N=202
48,971 WY
N=19
7,339 WY
N=6
2,154 WY
NOMAC-E2 vs COC$_{LNG}$
HR$_{crude}$: 0.36 (0.27 – 0.47)
HR$_{adj}$*: 0.45 (0.34 – 0.60)
Events/100 WY
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.41
0.26
0.28
0.15
NOMAC-E2
COC-LNG
oCOC
OHC

Fig. 4

A


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Events/100 WY
0.49
0.31
0.31
0.18
NOMAC-E2
COC$_{LNG}$
COC$_{Other}$
OHC

B

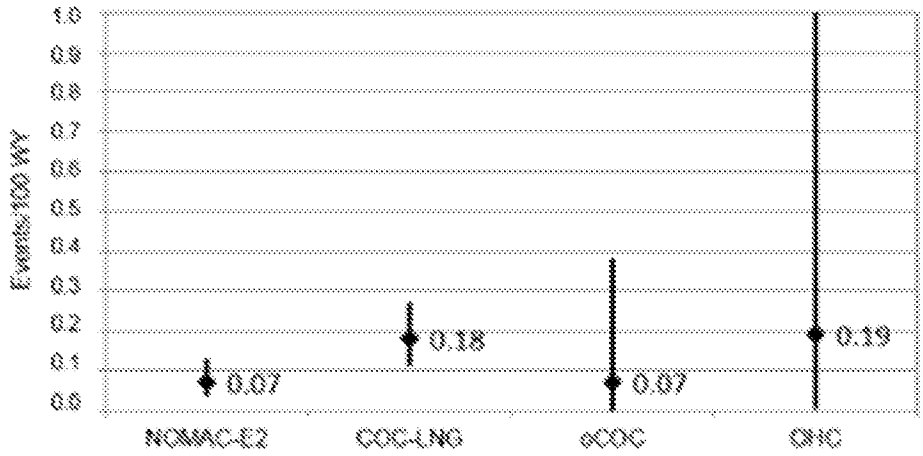
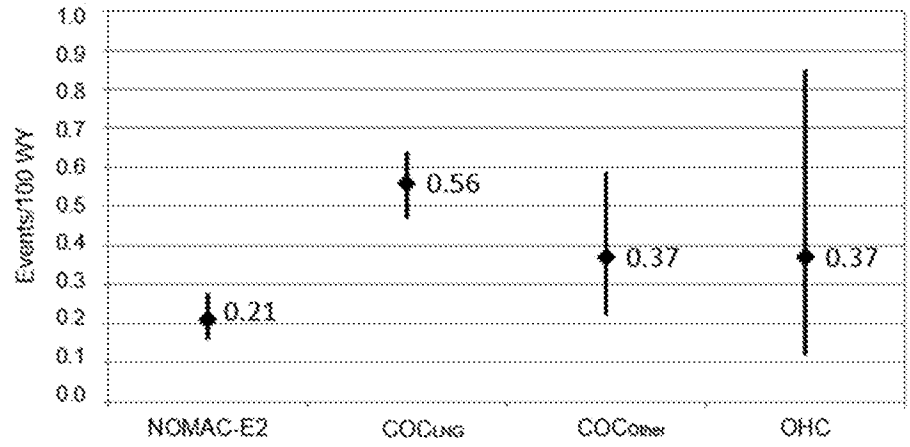

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Events/100 WY
0.18
0.19
0.07
0.07
NOMAC-E2
COC-LNG
eCOC
OHC

Fig. 5

A


Events/100 WY
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.56
0.37
0.37
0.21
NOMAC-E2
COCLNG
COCOther
OHC

B

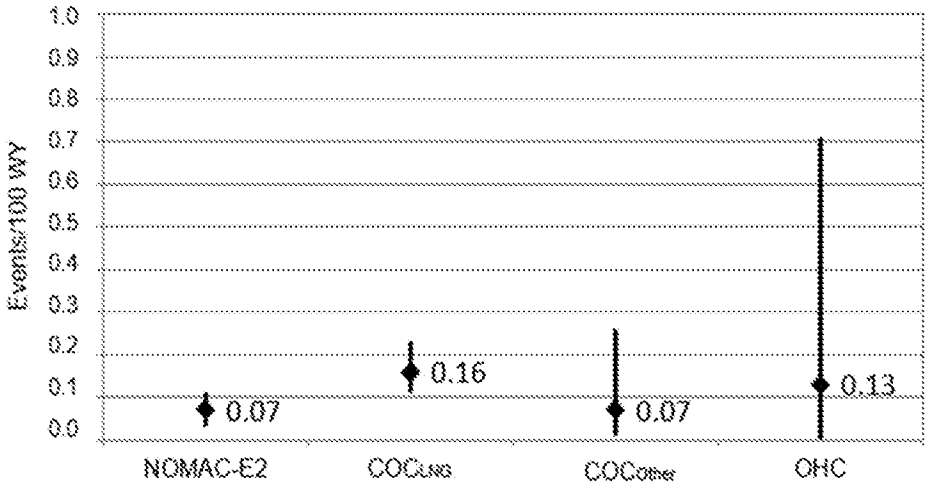
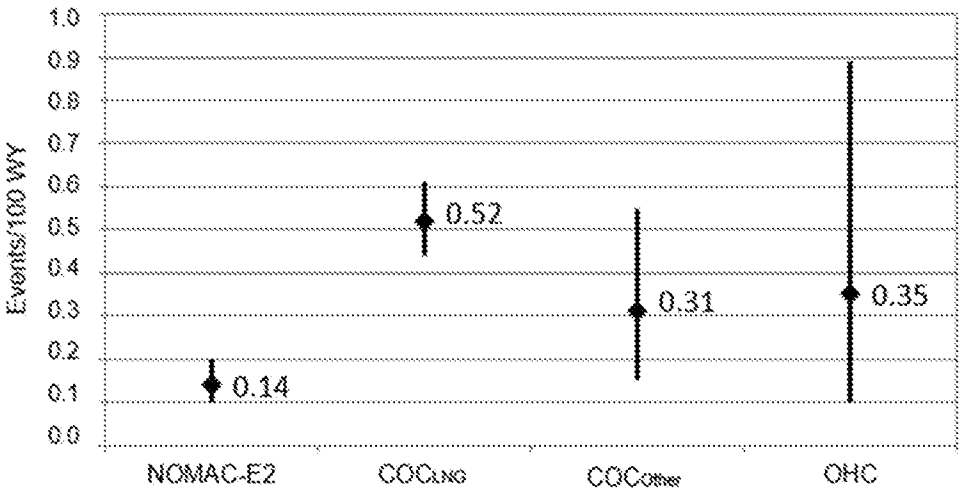

Events/100 WY
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.16
0.13
0.07
0.07
NOMAC-E2
COCLNG
COCOther
OHC

**Fig. 6**


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Events/100 WY
0.14
0.52
0.31
0.35
NOMAC-E2
COCLNG
COCOther
OHC