Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for levonorgestrel / ethinyloestradiol

Proprietary Product Name: Seasonique

Sponsor: Teva Pharma Australia Pty Ltd

September 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviations	Meaning
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under curve
BCM	birth control method
BMD	bone mineral density
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum concentration achieved
CMI	Consumer Medicine Information
COC	combined oral contraceptive
FDA	Federal Drug Administration
FSH	follicle stimulating hormone
HFI	hormone free interval
ITT	intention-to-treat
IVRS	interactive voice response system
LH	luteinising hormone
OCP	oral contraceptive preparation
PD	pharmacodynamic
PI	Product Information
PITT	pregnancy intention-to-treat
PK	pharmacokinetic
RMP	Risk Management Plan
SAE	serious adverse event
SHBG	sex hormone binding globulin
TBM	to be marketed
TVU	transvaginal ultrasound
VTE	venous thromboembolism

1. Introduction

This is an application to register the product Seasonique as an oral contraceptive formulation.

Although this is a new product, the submission is described as a major variation, which covers changes in dosage amount, frequency of use or dosage regimen - as its constituent substances ethinyloestradiol and levonorgestrel are already used together in a number of combined oral contraceptive (COC) formulations currently approved for use in Australia. Altogether there are 21 COCs so registered. All of these are designed for use in a 28 day cycle regimen, imitating the normal human menstrual cycle. The majority employ ethinyloestradiol and levonorgestrel at a dosage of either 30 µg/150 µg or 20 µg/100 µg for 21 days followed by a 7 day hormone free interval (HFI) achieved by either placebo tablets or missed dosage. One preparation uses a dose ratio of 50 µg/125 µg. Three others employ a triphasic dosage regimen of 30 µg ethinyloestradiol and 50 µg levonorgestrel for 6 days, followed by 5 days of 40 mg/75 µg and then 10 days of 30 mg/125 µg, followed by 7 placebo tablets.

The novel aspect of this product with regard to registration in Australia is the use of an extended cycle regimen for this particular combination of synthetic sex steroids. Ethinyloestradiol 30 µg and levonorgestrel 150 µg are given continuously for 84 days followed by 7 days of ethinyloestradiol alone 10 µg, designed to precipitate a withdrawal bleed. The principle of the extended cycle regimen is not novel, and a 91 day cycle product similar to Seasonique but including a 7-day HFI rather than 7 days of ethinyloestradiol 10 µg (Seasonale), has been registered in the USA since 2003 and in Canada since 2007. Also, a formulation containing a different combination of synthetic steroids (ethinyloestradiol 20 µg and drospirenone 3 mg) in a 120 day cycle has been registered in Australia since 2012.

1.1. Drug class and therapeutic indication

Ethinyloestradiol and levonorgestrel are synthetic steroid hormones with predominantly oestrogenic and progestogenic actions respectively.

The proposed indication for Seasonique is: for use as an oral contraceptive.

1.2. Dosage forms and strengths

The submission proposes registration of the two dosage forms and strengths as described above:

- an oral tablet containing the combination of ethinyloestradiol 30 µg and levonorgestrel 150 µg
- an oral tablet containing ethinyloestradiol 10 µg

1.3. Dosage and administration

The tablet containing the combination of ethinyloestradiol 30 µg and levonorgestrel 150 µg is to be taken once daily continuously for 84 days, followed by 7 days administration of the tablet containing ethinyloestradiol alone 10 µg, comprising a 91 day (3 month) cycle. Each supply of the product is sufficient for one cycle, consisting of two blister packs each containing 28 of the combination tablets and a third which contains 28 combination tablets along with the 7 ethinyloestradiol 10 µg tablets.

1.4. Other proposed changes to the PI

Not applicable (new product).

2. Clinical rationale

COCs were originally developed in the 1960s using a 28 day cycle because it was felt appropriate to mimic the physiological ovarian cycle in which menstruation occurs when progesterone levels fall at the end of the luteal phase in the absence of conception having occurred. Typically, 21-22 days of a combined oestrogen/progestogen tablet are given followed by a 6-7 day hormone free interval (HFI) during which withdrawal bleeding occurs. Early COC formulations contained oestrogen doses of or equivalent to ethinyloestradiol in the 50-100 µg range. These were associated with significant side-effects, particularly thromboembolic disorders, and subsequent product development involved lowering the ethinyloestradiol (or equivalent) dose to the 20-30 µg level as in the applicant product.

Following the acceptance of COCs as a safe and effective method of contraception, they came into use also as a means of regulating the menstrual cycle in women with a variety of cycle disorders involving irregular, excessively frequent or infrequent menstruation. The practice then developed of giving COC tablets continuously as a form of medically induced amenorrhoea for women with medical conditions which worsened during menstruation. The principle of using this method for women desiring contraception but without medical indications for menstrual suppression is well summarised by Edelman, who cites the proven safety and acceptability of the approach as encouraging compliance with the contraceptive regimen and having the potential to improve women's quality of life.

The rationale for using 7 days administration of the low 10 µg dose of ethinyloestradiol in place of the HFI is outlined and is based on the hypothesis that this will maintain suppression of the hypothalamic-pituitary-ovarian axis during the HFI, thus limiting the possibility of escape ovulation so that contraceptive efficacy might be improved or at least maintained. It is also postulated that this regimen might reduce the likelihood of hormone withdrawal symptoms during the HFI, and improve the pattern of withdrawal bleeding.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 6 clinical pharmacology studies, including 2 that provided pharmacokinetic data and 4 that provided pharmacodynamic data.
- 1 pivotal efficacy/safety study.
- 4 other efficacy/safety studies.

3.2. Paediatric data

The submission did not include paediatric data. The product is not intended for paediatric use. Note however that data has been submitted in relation to adolescent females (study DR-105-202) and comments on the potential for use in this age group are included in this report.

3.3. Good clinical practice

The submitted studies all state compliance with the required guidelines and appear to have been conducted accordingly.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies are presented. Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Multi-dose	10216207
	Bioequivalence† - Single dose	10416204

† Bioequivalence of clinical trial versus market formulation.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Pharmacokinetics in healthy subjects

The nature of this product as an oral contraceptive requires its administration to healthy subjects. The physicochemical and general PK characteristics of the constituent substances ethinyloestradiol and levonorgestrel are well documented in respect of multiple formulations containing this combination already registered in Australia, as described above. These characteristics are summarised in the draft PI.

PK data included in this submission is restricted to two studies described in the following sections. The second of these covers the particular characteristic of the extended cycle formulation which requires more prolonged continuous administration of the constituent substances.

4.2.1.1. Bioavailability

Bioequivalence of clinical trial and market formulations

Study 10416204 was conducted early in the development program for this product (2004) to establish bioequivalence between the formulation used in clinical trials, including the pivotal efficacy study for this application, and the formulation proposed and subsequently approved for marketing in the USA. These formulations have been described above. The study establishes bioequivalence between them.

Bioavailability during multiple-dosing

PK data were obtained throughout a single 91 day cycle of a formulation identical with that submitted for marketing in Australia except that a 30 µg rather than 10 µg dose of ethinyloestradiol was used in place of the HFI, a difference which does not affect the conclusions of the study. The relevant finding was that steady state was reached for both ethinyloestradiol and levonorgestrel by day 21, with no evidence of accumulation thereafter.

4.3. Evaluator's overall conclusions on pharmacokinetics

The sponsor has provided sufficient data to extend existing knowledge on the PK of the product's constituent substances to cover the particular characteristics of the applicant product Seasonique and describes these adequately in the draft PI.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Summaries of the pharmacodynamic studies are presented. Table 2 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 2. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on inhibition of ovarian function	DR-PSE-310
		DR-PSE-312
	Effect on suppression of ovulation	DR-105-101
Secondary Pharmacology	Effect on blood coagulation	PSE-HSP-203

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

The mechanism of action of combined OCPs, including those containing ethinyloestradiol and levonorgestrel, is well-established. The primary mechanism is to inhibit ovulation by negative feedback on gonadotrophin secretion so as to suppress circulating levels of LH and FSH. There are also effects on cervical mucus function which impair sperm transport, and endometrial effects.

The issue for this evaluation is the PD effect of the additional, small, 10 µg ethinyloestradiol dosage which occupies the 7 days of the traditional hormone free interval in cyclical OCPs. The PD studies described below illustrate the effect of this additional steroid dosage on the pituitary-ovarian relationship during the suppressive action of the extended cycle OCP.

5.2.2. Pharmacodynamic effects

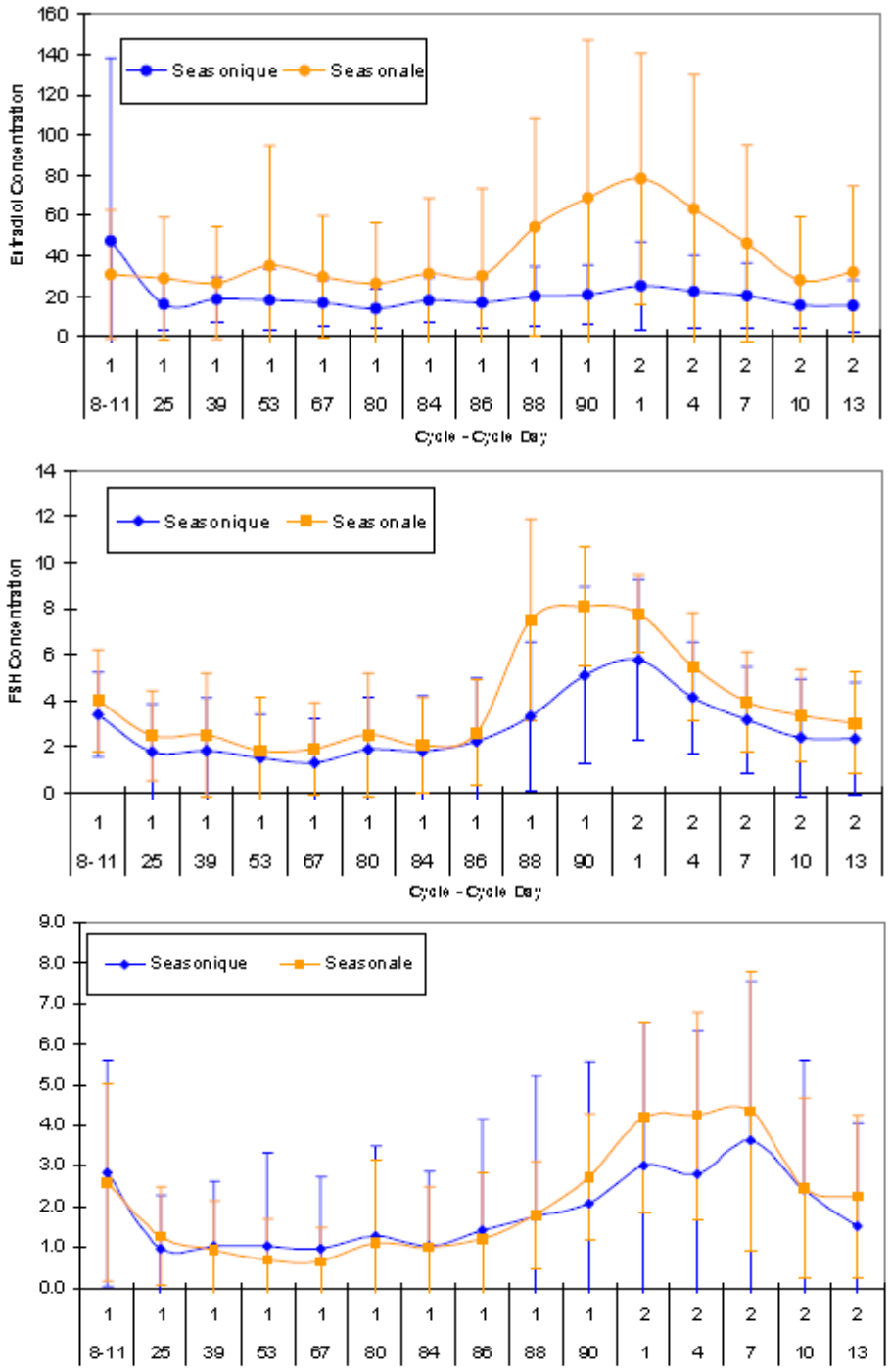
5.2.2.1. Primary pharmacodynamic effects

Inhibition of ovarian function

Pituitary (LH and FSH) and ovarian (oestradiol) hormones were measured throughout a single cycle of extended OCP and into the beginning of a following cycle. Ovarian follicular activity was also measured by ultrasound. Although three treatment arms were employed, the important

comparison for the purpose of this evaluation is between the Seasonique and Seasonale arms, the latter being identical to the applicant Seasonique product except that it has a conventional HFI rather than 7 days of 10 µg ethinyloestradiol. The third treatment arm consisted of three cycles of Portia, a conventional 28 day cycle OCP not marketed in Australia but containing the same doses of the active substances ethinyloestradiol and levonorgestrel. The sample size employed was too small to allow assessment of significant difference between the Seasonique and Seasonale groups, but nevertheless the time course of the hormonal changes in particular shows a clear difference between them, as illustrated in Figure 1.

Figure 1: Time pattern of changes in serum oestradiol (upper panel), FSH (middle panel) and LH (lower panel) in the Seasonique and Seasonale treatment groups.



All three hormones begin to rise between days 3-5 of the HFI of the extended cycle regimen, but this rise is blunted, and in the case of oestradiol almost abolished, in the Seasonique group. The LH and FSH values take 7-10 days to return to suppressed values in the following cycle employing Portia which, although of only 21 days duration, contains the same doses of ethinyloestradiol and levonorgestrel.

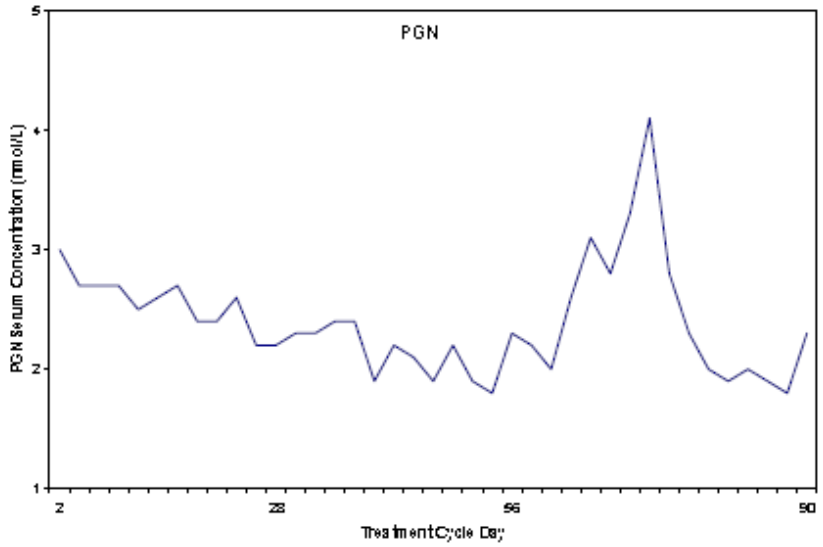
Consistent with these findings, there was supportive evidence that the group treated with Seasonique exhibited less ovarian follicular activity in the early part of the follow-up Portia cycle.

Study DR-PSE-312 used a similar protocol to examine the effect of adding 7 days of 10 µg daily ethinyloestradiol to the HFI of a standard 28 day (21 active tablets) 30 µg ethinyloestradiol/150 µg levonorgestrel OCP. A similar pattern of hormonal suppression occurred as seen in study 310 as described above. Although this was again a small study and employed a standard 28 day OCP regimen as opposed to an extended cycle regimen, it yields two important findings: firstly, the difference between the active and placebo groups for oestradiol and inhibin-B achieved statistical significance; and secondly, the study shows that suppression of ovarian activity by 10 µg ethinyloestradiol during the HFI may occur with a conventional OCP and is not confined to the use of this approach with an extended cycle formulation.

Suppression of ovulation

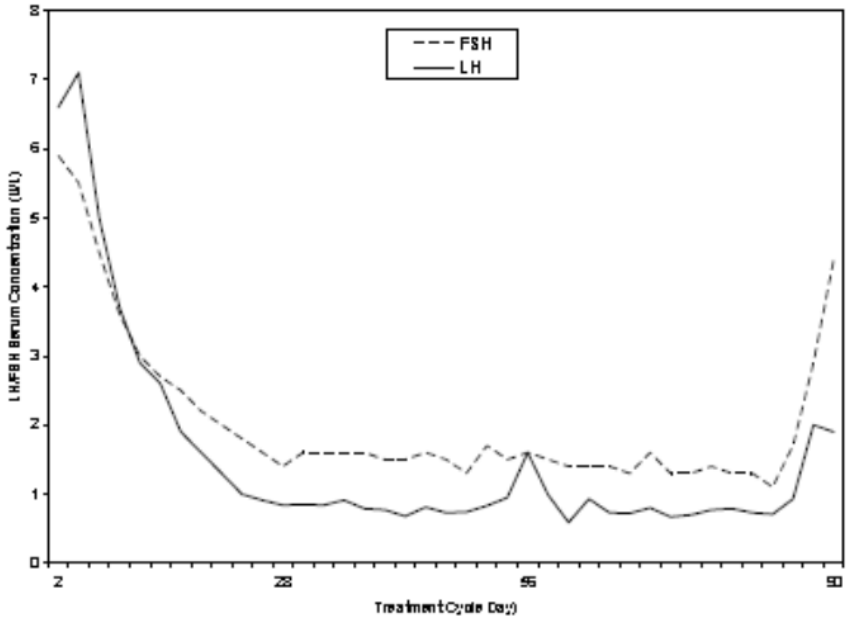
Study DR-105-101 was a formal ovulation inhibition study employing the Seasonique formulation in a single cohort, uncontrolled protocol. The methods employed and results are summarised. Ovarian activity based principally on ultrasound assessment according to the method of Hoogland and Skouby was followed through a 91 day cycle which for the purpose of these assessments was divided into three sections of 28, 28 and 35 days respectively. As can be seen from the results tabulated in the study summary, activity scores were generally low throughout except that two subjects yielded ovulatory scores late in the cycle. Nevertheless, only 3/105 cycle sections assessed demonstrated grade 4 or 5 ovarian activity, corresponding to luteinised unruptured follicle (LUF) or ovulation. These findings are mirrored by serum progesterone levels monitored throughout the 91 day cycle, as shown below in Figure 2.

Figure 2: Serum progesterone levels monitored throughout the 91 day cycle.



Apart from the ovulatory spike on approximately days 69-72, progesterone levels fell progressively, the group average ranging from 1.8 to 3.1 nmol/L by comparison with 29.7 nmol/L during the pretreatment control cycle. Further evidence of suppression of the pituitary-ovarian axis occurring progressively during the extended cycle is seen in the pattern of change of FSH and LH, as illustrated below in Figure 3.

Figure 3: Pattern of change of FSH and LH.



Comment: two things are noted from this data. Firstly, It seems reasonable to presume that the pattern of gonadotrophin suppression from days 1-22 is what would be seen in a 28 day cycle COC of this composition of which there are several, as noted above, so that even though this is an uncontrolled study the greater level of suppression seen between days 28-84 is probably a genuine feature of the extended cycle. Secondly, there is clearly some escape from gonadotrophin suppression from days 85-91 despite the 10 µg ethinyloestradiol dose during that period of the cycle.

5.2.2.2. Secondary pharmacodynamic effects

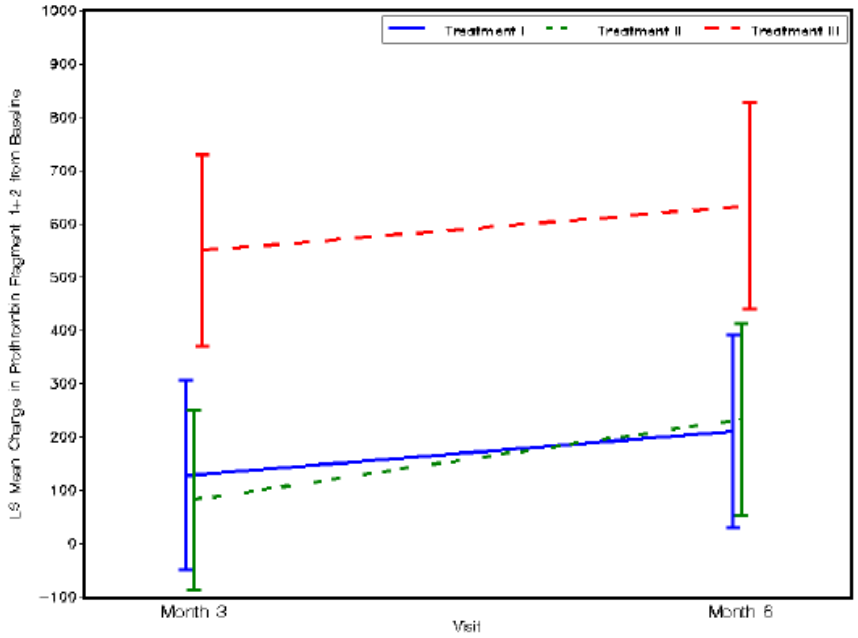
Effects on blood coagulation

As noted above and as is well documented in the clinical overview, COCs are associated with an increased risk of venous thromboembolism. The mechanism of this is known to consist of effects in increasing procoagulatory factors and decreasing fibrinolytic factors, as can be reflected by measurement, as surrogate endpoints, of plasma levels of various substances involved in the process of haemostasis. The clinical overview indicates that the CHMP Guideline on Clinical Investigation of Steroid Contraceptives in Women requires that development programs for new COCs should include a study examining their effect on these parameters. This requirement is the basis for Study PSE-HSP-203 in which the effects of Seasonique on haemostatic parameters as compared with those of existing COC products Minidril (containing levonorgestrel 150 µg/ethinyloestradiol 30 µg, as for Seasonique) and Marvelon (containing desogestrol 150 µg/ethinyloestradiol 30 µg). These combinations are recommended as comparators in the above referenced CHMP guideline.

Comment: Marvelon is registered for use in Australia; Minidril is not although as noted above, a number of identically constituted COCs are so registered.

Study PSE-HSP-203 is summarised. The primary efficacy parameter chosen was the procoagulatory marker prothrombin fragments 1+2. A typical COC user population was treated for six months and the effect measured at three months and six months. The results are illustrated graphically in Figure 4.

Figure 4: Effect on prothrombin fragments, change from baseline at 3 months and 6 months, with Seasonique by comparison with the two COC comparators Minidril and Marvelon.



The effect of the levonorgestrel containing active comparator Minidril (treatment II) is similar to that of Seasonique (treatment I) whereas the effect of the drospirenone containing comparator Marvelon (treatment III) is more exaggerated.

Other procoagulatory variables, including fibrinogen, factor II, factor VII and factor VIII increased over the 6-month treatment period with Seasonique, Minidril and Marvelon. Factor II values slightly increased in all three groups with overall mean change from baseline similar for all treatment groups. Factor VII increased in all 3 treatment groups, significantly more in Minidril compared to Seasonique. Factor VIII slightly decreased with Seasonique, showed almost no change with Minidril and a slight increase with Marvelon.

The anticoagulatory variables, such as protein C activity and free and total protein S slightly decreased or remained constant (although antithrombin slightly increased in Seasonique). Protein C activity slightly decreased at month 3 for all treatment groups and thereafter increased slightly at month 6. Protein C antigen increased for all treatment groups. Free protein S increased with both Seasonique and Minidril and decreased with Marvelon (significantly in comparison to Seasonique). Total protein S decreased in all treatment groups. Antithrombin increased slightly with Seasonique, and showed minimal change with Minidril and Marvelon.

> *Comment: with regard to effects on coagulation mechanisms, this study suggests that use of the extended cycle regimen, by comparison with the conventional 28 day cycle regimen, constitutes no additional thromboembolic risk.*

5.3. Evaluator's overall conclusions on pharmacodynamics

The submitted studies provide evidence that suppression of ovarian function and inhibition of ovulation is maintained throughout the extended cycle form of administration of this OCP formulation, and that replacement of the hormone free interval with 7 days of 10 µg ethinyloestradiol improves these PD actions in a way which would be consistent with improved contraceptive efficacy.

6. Dosage selection for the pivotal studies

The entire development program for Seasonique described by the sponsor employs the dosage combination of ethinyloestradiol 30 µg and levonorgestrel 150 µg for continuous daily administration over the 84 days of active combined oestrogen/progestogen administration, this being a dosage of well-established efficacy in the various 21 or 22 day cycle COC formulations in existing use as described above. The dosage of 10 µg ethinyloestradiol for the 7 day period of administration occupying days 84-91 of the Seasonique cycle finds support in the PD studies described. In pivotal study PSE-301, this 10 µg dose over days 84-91 of the cycle is compared with a 30 µg dose.

7. Clinical efficacy

7.1. Pivotal efficacy study

7.1.1. Study PSE-301

7.1.1.1. Study design, objectives, locations and dates

This was a two arm, randomised, multicentre open-label study conducted at 36 US sites between April 2002 and April 2004. The primary objective was to demonstrate efficacy and safety of two 91 day cycle extended regimen COC formulations: DP3-84/10 (Seasonique), and a similar product DP3-84/30 as described above, in which the HFI was replaced with a 30 µg rather than 10 µg ethinyloestradiol dose. In each arm, subjects were to take the assigned treatment for one year (four 91 day cycles). Secondary objectives were to observe the incidence or severity of "hormonal-related symptoms" during the treatment period and to observe the number of reported days of scheduled (withdrawal) and unscheduled (breakthrough) menstrual bleeding and/or spotting.

7.1.1.2. Inclusion and exclusion criteria

The principal criterion for inclusion was to recruit sexually active adult women aged 18-40 at risk for pregnancy who either had a history of OC use prior to enrolment (continuous users), no prior history of OC use (fresh starts), or a history of OC use but not within the six months prior to enrolment (prior users). Subjects were also required to have a negative urine pregnancy test and to agree to the conditions of the study.

Exclusion criteria comprised a standard list of contraindications to COC use or study participation, routine concomitant use of other contraceptive methods, and undiagnosed abnormal bleeding.

7.1.1.3. Study treatments

Subjects were randomised to one or other of the extended cycle regimens described above. There was no control group.

7.1.1.4. Efficacy variables and outcomes

The single efficacy variable was the on-treatment pregnancy rate, defined as below:

Efficacy was evaluated from the overall pregnancy rate, calculated by the Pearl Index using all “On-treatment” pregnancies, defined as those pregnancies for which the conception date was on or after the date of first dose of study medication, but no more than 14 days after the date of last dose of combination medication.

- Pregnancy was defined as a positive pregnancy test.
- Conception date was based on the ultrasound information.

- If the date of conception clearly occurred before the date of first dose of study medication, then the pregnancy was not considered to be an “on-treatment” pregnancy.
- If the date of conception clearly occurred more than 14 days after the date of last dose of combination medication, then the pregnancy was not considered to be an “on-treatment” pregnancy.
- If no ultrasound-based estimate of conception date was available, or the pregnancy status of a woman was unknown (e.g., delivery date was unknown because the patient was lost-to-follow-up), then the pregnancy was counted as an “on-treatment” pregnancy. Otherwise, the pregnancy was further valuated to determine if it was an on-treatment or off-treatment pregnancy.

As is standard practice in studies of contraceptive efficacy, the Pearl Index is calculated as the number of pregnancies/100 years of woman-use. Contraceptive efficacy was also measured by life-table analysis using the Kaplan Meier estimator as described below. With "correct use" (full compliance), Pearl Index values of <1 are expected in users of combined oral contraceptives (COC), whereas with "typical use", values may be in the range 1-3.

The primary efficacy outcome was the Pearl Index, calculated first on the ITT cohort, consisting of all subjects randomised to treatment and completing at least one cycle of study medication.

This calculation was also made on a number of other cohorts, defined as follows:

- The pregnancy intent-to-treat (PITT) cohort. This cohort includes subjects who became pregnant during the first cycle which they therefore did not complete and on this basis are excluded from the ITT cohort. For this cohort, the cycle in which the subject became pregnant is regarded as a complete cycle. This cohort is also limited to the age group 18-35 by comparison with the study inclusion criterion of 18-40 which applies to the ITT cohort; the reason for this is not clearly spelt out but appears to relate to a protocol amendment of the upper limit of age for the study which occurred at some stage.
- A subset of the PITT cohort excluding those who used other birth control methods (BCMs).
- A subset of the PITT cohort who were regarded as "Compliant-Use".
- A subset with body weight <90 kg.

Overall treatment compliance was calculated from a combination of the patient’s diary and the drug accountability clinical record form. The results of this, derived from the percentage of total days with documented evidence of compliance, are shown for the ITT cohort in Table 3.

Table 3: Overall treatment compliance.

	DP3-84/30 (N=1013)		DP3-84/10 (N=1006)		Total (N=2019)	
Overall Treatment Compliance *	**N**	**%**	**N**	**%**	**N**	**%**
≥80% Compliance	988	97.5	983	97.7	1971	97.6
<80% Compliance	25	2.5	23	2.3	48	2.4

Comment: note that this does not mean that there was 97.6% compliance, or that only 2.4% of tablets were missed; just that 97.6% of subjects had >80% compliance.

A secondary efficacy outcome was calculation of pregnancy rate using life-table analysis. The investigators’ description of this method and its limitations reads as follows: Cumulative pregnancy rates at week 52 and at each 13-week (91-day) interval were estimated using the life table method. Individual treatment group estimates of pregnancy rates were made by evaluating the 95% confidence interval about each treatment group’.s lifetable estimate of cumulative pregnancy rate in relation to the Pearl Index derived estimate. Due to the fact that

individual cycles could not be excluded from this analysis, the typical use cohort included all complete cycles for patients in the PITT cohort and the “Compliant-Use” analysis excluded patients at a patient level instead of a cycle level for compliance.

"Hormone related" symptoms were also evaluated using a scoring system, on an exploratory basis.

Note that the secondary objective of the study in relation to assessment of bleeding patterns is described in the study report as a safety outcome and is discussed below.

7.1.1.5. Randomisation and blinding methods

Subjects were randomised 1:1 to either DP3-84/10 or DP3-84/30 using an IVRS system. As this was an open label study, there was no blinding except that both subjects and investigators remained blinded to the treatment group until the subject had signed the consent form.

7.1.1.6. Analysis populations

As noted above, Pearl Index calculations were carried out on a number of subsets of the ITT cohort. The numbers of subjects in each of these cohorts are shown, along with the Pearl Index values and a comment about the numbers of subjects regarded as "Compliant Use".

7.1.1.7. Sample size

The planned number of randomized patients was 2040 (1020 per treatment arm); a total of 2049 patients were randomized and 2019 were treated with at least one dose of study medication, as follows:

- DP3-84/30: N = 1025 (randomized); 1013 (treated)
- DP3-84/10: N = 1024 (randomized); 1006 (treated)

The study report states that determination of method failure is "generally based" on exposure of approximately 10,000 women-months (28 day cycles), hence the selection of approximately 1000 subjects per treatment group.

7.1.1.8. Statistical methods

As this study involved no form of comparative analysis, the statistical presentation is descriptive. A statistical analysis plan is included and is stated to have been reviewed and revised by the FDA.

7.1.1.9. Participant flow

Of the 2049 subjects randomised, 30 withdrew prior to taking any treatment, most commonly because of pregnancy (n=11). 77.6% of the treated subjects completed at least one 91 day cycle, i.e. 22.4% withdrew. There was a high rate of discontinuations throughout the study which was completed by only 979 subjects (48.5% of those treated). The reasons for withdrawal are shown in Table 4.

Table 4: Participant flow.

	DP3-84/30 (N=1013)		DP3-84/10 (N=1006)		Total (N=2019)	
	N	%	N	%	N	%
Safety Cohort	1013	100.0	1006	100.0	2019	100.0
Discontinued Study	534	52.7	506	50.3	1040	51.5
Primary Reason for Discontinuation						
Adverse Event	200	19.7	164	16.3	364	18.0
Patient Decision	113	11.2	130	12.9	243	12.0
Non-Compliance with Study Protocol	36	3.6	38	3.8	74	3.7
Lost-to-Follow-Up	149	14.7	149	14.8	298	14.8
Pregnancy	18	1.8	5	0.5	23	1.1
Investigator's Discretion	1	0.1	2	0.2	3	0.1
Other/Unknown	17	1.7	18	1.8	35	1.7

Comment: note that in 23 cases pregnancy is stated as the primary reason for discontinuation. In fact, a total of 68 of the randomised subjects became pregnant during the study. Details of these are given in the study report. Only 20 (13 DP3-84/30 and 7 DP3-84/10) were considered as "on treatment" at the time of conception, and these are the pregnancies included in the Pearl Index calculation shown. Of those 20, 11 (8 DP3-84/30 and 3 DP3-84/10) subjects were considered to be "compliant users".

It is presumed from the above that the remaining 48 pregnancies occurred in patients whose primary reason for discontinuation was in another category, such as the large number (243) given as "personal decision". Perusal of the individual narratives of pregnancies occurring during the study (study report) is consistent with this, showing that many of the subjects found on follow-up - sometimes requiring repeated telephone calls - had discontinued treatment some time previously.

Note also the large proportion (n = 364, 18.0%) who discontinued because of adverse events. Of these, 147 (40%) withdrew because of bleeding and/or spotting episodes, in roughly equal proportions between the two treatment groups. 40 (16%) of those discontinuing because of "personal decision" also cited bleeding and/or spotting as at least part of the reason for the decision (study report).

7.1.1.10. Major protocol violations/deviations

Protocol deviations are difficult to evaluate as they are not summarised in the study report except by way of a reference which consists of a listing of several hundred events, mostly failure to return telephone calls, missed appointments, etc. The study report does comment as follows:

The only protocol deviation resulting in a decision by the sponsor to administratively discontinue a patient from the study was if a patient was over the age of 35 years, and was also a smoker, had entered the study under either Version 1 or 2 of the protocol. Under Version 3 of the protocol such a patient would have violated the exclusion criteria.

This implies that the protocol amended the original inclusion criteria to an upper age limit of 35 years. The statement is ambiguous with regard to the significance of smoking status.

7.1.1.11. Baseline data

For all treated patients (n=2019), average age was 27.4 years (18/40.9) and BMI 26.0 (15.2, 57.1). The majority (79.8%) were Caucasian. 62.7% of subjects were continuous users of OCPs, 26.5% prior users, and 10.8% fresh starts. 23.5% were smokers.

No other baseline data is relevant as this was defined as a healthy population.

Comment: the demographic data underlines the high incidence of obesity in the study population, the average BMI of which (26.0) was in the overweight range. The heaviest patient in the DP3-84/30 group weighed 154 kg (BMI 57.1) and in the DP3-84/10, 164 kg (BMI 56.5), both well into the morbidly obese range. No upper weight limit was specified in the inclusion or exclusion criteria for the study.

7.1.1.12. Results for the primary efficacy outcome

The results of Pearl Index calculations for both study treatments in the various cohorts mentioned above are shown in Table 5.

Table 5: Results for primary efficacy outcome

	DP3-84/30		DP3-84/10	
	N	Pearl Index	N	Pearl Index
PITT (Excluding Other BCMs)	581	2.74	621	1.27
PITT (all Complete Cycles)	668	1.95	708	0.92
PITT (Compliant-Use)	560	2.26	607	0.78
ITT (all Complete Cycles)	771	1.66	799	0.80

Comments: 1. As commented above, the pregnancies upon which the above calculations are based number in total 20 (13 DP3-84/30 and 7 DP3-84/10), of which 11 (8 DP3-84/30 and 3 DP3-84/10) occurred in subjects deemed by the investigator to have been "Compliant-Use" at the time of conception. For the remaining 48 pregnancies occurring in the study, conception occurred either when they were no longer taking the study drug or at a time when the responsible investigator deemed the subject to have been non-compliant.

2. The study report postulates that the values for Pearl Index in the category PITT (excluding other BCMs) may be an overestimate as the excluded cycles include those in which subjects have recorded using a condom for prevention of sexually transmitted disease rather than as a BCM. This argument is plausible but it is also possible that the higher estimate in this cohort is a real finding indicative of the product's "typical use" efficacy, at least in this population.

3. The apparent difference between the two treatment groups is not explained, would not have been predicted on the basis of pharmacodynamic data, and is most likely a chance finding reflecting the relatively small numbers of pregnancies involved.

7.1.1.13. Results for other efficacy outcomes

The Pearl Index calculations were repeated on a number of other subsets of the cohorts shown, without any differences being apparent. Of particular interest in view of the potential influence of obesity on OCP efficacy as discussed below, are the results in PITT Compliant-Use subjects with body weight <90 kg, as shown below.

Table 6: Results for other efficacy outcomes.

Treatment Group	Number of Cycles	Number of 28-Day Patient Months	Number of "On-Drug" Pregnancies	Pearl Index
DP3-84/30	1229	3994.25	8	2.60
DP3-84/10	1331	4325.75	3	0.90

Comment: the finding that results for this subcategory are no different from those of the entire study population may reflect no more than the fact that they represent the vast majority of the subjects. From the provided demographic data, it can be calculated that the average height of the subjects was 165 cm. A 90 kg subject of this height has a BMI of

33, well into the obese range. Assessment of subjects <80 kg (BMI 29.4) may have been more appropriate. Comparison with subjects whose body weight was >90 kg would also have been of interest but there were almost certainly insufficient numbers of these to achieve significance.

Life-table analysis of treatment failure rate (i.e. pregnancy rate) was undertaken for all of the various cohorts listed above, and show results comparable with the Pearl Index calculations. Illustrated below are the results of this parameter for the PITT cohort.

Table 7: Results for other efficacy outcomes

DP3-84/30			DP3-84/10		
Cycle	Pregnancy Rate	95% C.I.	Cycle	Pregnancy Rate	95% C.I.
1	0.0046	0.0015-0.0142	1	0.0000	-
2	0.0081	0.0034-0.0194	2	0.0016	0.0002-0.0116
3	0.0123	0.0058-0.0258	3	0.0036	0.0009-0.0145
4	0.0201	0.0107-0.0375	4	0.0061	0.0019-0.0190

The results after cycle 4, i.e. after one year of treatment, indicate failure rates of 2.01% and 0.61% respectively for the two treatment groups, comparable with the Pearl Index values of 1.95% and 0.92% shown for the same cohort above.

Data on "hormone-related symptoms" were stated to have been collected, as noted above, but no results are reported in the efficacy analysis section of the study report.

7.2. Other efficacy studies

7.2.1. Study PSE-302

This four-arm, randomised, multicentre, open label study was conducted at 7 US sites over the same timeframe (April 2002-2004) as the pivotal efficacy study PSE 301. With a much smaller planned study population (400, 100 per arm) its objectives were to provide supportive efficacy data well as additional safety data in the form of endometrial biopsies to be performed before and at the end of the study; the safety data also included analysis of the bleeding profiles and this is detailed below.

The study protocol and the inclusion/exclusion criteria were similar to those of study PSE-301. In addition to treatment arms of DP3-84/30 (95 subjects treated) and DP3-84/10 (Seasonique, 95 treated), two further treatment arms were included:

- DP3-25/30: a 28 day cycle regimen in which ethinyloestradiol 30 µg/levonorgestrel 150 µg is given to 25 days, followed by three days of ethinyloestradiol 30 µg alone, 89 treated; and
- Nordette: a commercially available 28 day cycle preparation of ethinyloestradiol 30 µg levonorgestrel/150 µg given for 21 days followed by seven days placebo, 93 treated.

The 12 month study was completed by 40 (42.1%) of DP3-84/30 subjects and by 46 (48.4%), 44 (49.4%), and 47 (50.5%) of DP3-84/10, DP3-25/30 and Nordette subjects respectively.

The treatment failure rates for the "compliant use" subset of the PITT population, as defined above, were as follows.

Table 8: Study PSE-302

Treatment Group	Number of Cycles	Number of 28-Day Patient Months	Number of "On-Drug" Pregnancies	Pearl Index
DP3-84/30	150	487.50	1	2.67
DP3-84/10	160	520.00	1	2.50
DP3-25/30	586	586.00	0	0.00
Nordette	582	582.00	1	2.23

Comment: the numbers of on treatment pregnancies are insufficient for these data to be of any significance in themselves, but they are consistent with the contraceptive efficacy data of the pivotal efficacy study PSE-301.

No consistent changes were reported for any of the hormone related symptoms. The study report refers to "slight trends" towards reduction in acne and breast tenderness in the DP3-84/10 treatment group but the graphical displays of these data only show comparison with the DP3-84/30 and the changes are unremarkable.

7.3. Analyses performed across trials (pooled & meta analyses)

None provided.

7.4. Evaluator's conclusions on clinical efficacy

All contraceptive methods, including COCs, have a failure rate, the measurement of which is the incidence of on-treatment pregnancy (Pearl index). The measurement of efficacy of any novel COC is therefore how its failure rate compares with that of other established COC products. For this particular submission, the question is whether the extended cycle regimen differs either positively or negatively in efficacy by comparison with a standard 28 day cycle formulation containing the same constituent substances. In this respect the pivotal efficacy study 301 has a high dropout rate, and poor compliance in some subjects. There are multiple confounding factors which contribute to the failure rate of oral contraceptive regimens. The most important of these are compliance and the demography of the study population including cultural (e.g. level of sexual activity) and biological (e.g. incidence of obesity) factors. As is discussed at length in the clinical overview, it is well documented that there is a substantial difference in failure rate between US and European populations. A published comparison of US and European studies using the same methodology showed an approximately four-fold higher failure rate in the US.

The pivotal trial is of low quality (50% drop-outs) but was the same pivotal trial used to register the product in Canada, US and various EU countries.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal efficacy study

In the pivotal efficacy study PSE-301, safety was evaluated by assessment of adverse events (AEs), tabulation of concomitant medications, recording of vital signs and physical examination when appropriate, and the performance of routine laboratory tests as specified in the protocol. These included plasma lipids in view of the known effects of OCPs on these parameters.

AEs were reported during scheduled study visits and also during regular monthly telephone contacts, their severity graded and likely relationship to study medication recorded by the site investigator. In this and in all of the other studies reported below, the subjects' menstrual bleeding pattern was regarded as an AE of particular interest and recorded as days of either spotting or bleeding, the distinction being made on the basis of whether sanitary protection was required.

8.1.2. Non-pivotal efficacy study

One non-pivotal efficacy study provided safety data, as follows:

- Study PSE-302 provided data on 372 subjects randomised to 4 treatment groups as described above. In addition to safety data collected using the same protocol as the pivotal study, endometrial histology was assessed by biopsies obtained before and at the end of the study and is reported as a safety issue of special interest below.

8.1.3. Other studies evaluable for safety only

8.1.3.1. Study DR-PSE-304

This was a long-term extension study which enrolled subjects completing studies PSE-301 and PSE-302. Although designed to document up to 5 years of use, the maximum duration documented in the report is three years, achieved by 116 of the 320 subjects treated. Approximately midway through the study, in June 2005, and following completion of the pivotal study PSE-301, all subjects were switched to the DP3-84/10 (Seasonique) formulation as this, rather than the DP3-84/30 formulation, had been selected for marketing application in the USA.

8.1.3.2. Studies DR-PSE-305 and DR-PSE-306

These two studies were performed to evaluate efficacy of Seasonique for the treatment of cyclical pelvic pain in adult and adolescent females respectively. Safety data were collected using the same protocol as used in the pivotal study. In study 305, subjects were randomised to receive either Seasonique (n=91) or Portia (n=82), a 28 day cycle formulation using the same constituent substances and doses as Seasonique. In study 306, 47 subjects were randomised to Seasonique and 48 to placebo.

8.1.3.3. Study DR-105-202

This study was performed to assess the effect on bone mineral density (BMD) of Seasonique administered to adolescent females (age 12-18 years inclusive) over a period of 12 months. 421 subjects were randomised to Seasonique, and 412 to Lessina, a 28 day cycle OCP formulation containing ethinyloestradiol 20 µg/levonorgestrel 100 µg. In addition there was a control group of 437 subjects who received no treatment. Although strictly not fitting this description, the BMD data are presented as an AE of special interest below.

8.1.4. Clinical pharmacology studies

Safety data collected during the PK/PD studies summarised are included in the overall safety data pool but contribute a relatively small component.

8.2. Pivotal studies that assessed safety as a primary outcome

No studies of this nature are included in the submission.

8.3. Patient exposure

In the clinical development program, the majority of exposure to DP3-84/10 (Seasonique) and comparator products, was of up to 12 months duration and occurred in pivotal study 301 and supporting study 302. Cumulative exposure of all subjects treated in these studies is shown in the following table.

Table 9: Patient exposure

	DP3-84/30 (N=1108)		DP3-84/10 (N=1101)		DP3-25/30 (N=89)		Nordette (N=93)	
28-Day Month on Study	N	%	N	%	N	%	N	%
> 0	1108	100.0	1101	100.0	89	100.0	93	100.0
≥ 1	1025	92.5	1026	93.2	84	94.4	85	91.4
≥ 2	914	82.5	946	85.9	80	89.9	79	84.9
≥ 3	841	75.9	879	79.8	76	85.4	77	82.8
≥ 4	760	68.6	798	72.5	70	78.7	73	78.5
≥ 5	717	64.7	756	68.7	63	70.8	71	76.3
≥ 6	679	61.3	710	64.5	60	67.4	67	72.0
≥ 7	627	56.6	657	59.7	54	60.7	64	68.8
≥ 8	603	54.4	638	57.9	50	56.2	61	65.6
≥ 9	588	53.1	613	55.7	48	53.9	58	62.4
≥ 10	559	50.5	580	52.7	46	51.7	54	58.1
≥ 11	548	49.5	568	51.6	45	50.6	52	55.9
≥ 12	531	47.9	557	50.6	45	50.6	50	53.8
Completed the Study	519	46.8	546	49.6	44	49.4	47	50.5

Comment: the exact number of completed cycles is not given in the study report. However, from the above table it is estimated that total exposure of all treatment groups is approximately 1600 woman-years, or 20,800 completed 28 day cycles (evaluator calculation). Of this, approximately 50% represents exposure to Seasonique itself and the remainder exposure to similar 30 µg ethinyloestradiol/150 µg levonorgestrel products, the majority to DP3-84/30 which also has an 84 day cycle.

Longer term exposure to both 84 cycle day preparations occurred in study DR-PSE-304, as shown below.

Table 10: Patient exposure

	DP3-84/30 (N=147)		DP3-84/10 (N=173)		Total (N=320)	
Years on Study	N	%	N	%	N	%
> 0	147	100.0	173	100.0	320	100.0
≥ 1	113	76.9	131	75.7	244	76.3
≥ 2	79	53.7	94	54.3	173	54.1
≥ 3	43	29.3	42	24.3	85	26.6
≥ 4	0	0.0	0	0.0	0	0.0
Completed the Study	57	100.0	59	100.0	116	100.0

A total of 244 subjects completed one year of treatment, 173 completed two years, and 116 three years. Total exposure was equivalent to 8,292 28 day cycles, 4411 of which were for the Seasonique product, equivalent to 638 woman-years (339 for Seasonique).

In the supportive safety studies, exposure to Seasonique is estimated as follows:

- DR-105-202: 296 woman-years
- PSE-305: 32 woman-years
- PSE-306: 16 woman-years

In summary, overall exposure to the applicant product Seasonique in the submitted studies is approximately 1160 woman-years, equivalent to 15,080 28 day cycles (evaluator calculation) accompanied by a similar amount of exposure to comparator products containing the same constituents and mostly also with the 84 day cycle of continuous exposure.

8.4. Adverse events

Note that in addition to general safety issues, the pattern of scheduled and unscheduled menstrual bleeding is an issue of particular interest for this evaluation and is addressed below. Other issues of particular interest are endometrial safety and effect on bone mineral density.

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

As stated in the report of pivotal study PSE-301 and in the summary of clinical safety, there was no formal analysis of adverse events in any of the Seasonique studies and all reporting of AEs is in the context of treatment-emergent adverse events with an incidence rate of 5% or greater; accordingly, these are commented upon below. For the majority of the safety population, comparison was only between Seasonique (DP3-84/10) and the essentially similar product DP3-84/30; in only one of the supporting studies, DR-105-202, there is data comparing AE incidence with an OCP product of different oestrogen/progestogen dosage, as well as a placebo group, and this is commented below.

8.4.1.2. Other studies

Comment in previous section applies.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal study

In pivotal study PSE-301, which contains the majority of the safety data in the application, the treatment-emergent AE with the highest incidence was intermenstrual bleeding which is discussed below as an AE of special interest. Otherwise, there was a range of AE commonly experienced with COC preparations including nausea, headache, breast tenderness, weight gain and mood swings. The incidence of such events occurring in 2% or more of all treated patients in this study is shown below.

Table 11: Treatment-related adverse events (adverse drug reactions)

MedDRA System Organ Class and Preferred Term	DP3-84/30 (N=1013) N	%	DP3-84/10 (N=1006) N	%	Total (N=2019) N	%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
Intermenstrual bleeding	120	11.85	114	11.33	234	11.59
Menorrhagia	74	7.31	56	5.57	130	6.44
Breast tenderness	21	2.07	28	2.78	49	2.43
Dysmenorrhoea	33	3.26	28	2.78	61	3.02
INVESTIGATIONS						
Weight increased	33	3.26	44	4.37	77	3.81
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Acne NOS	35	3.46	44	4.37	79	3.91
GASTROINTESTINAL DISORDERS						
Nausea	30	2.96	31	3.08	61	3.02
Abdominal distension	18	1.78	22	2.19	40	1.98
PSYCHIATRIC DISORDERS						
Mood swings	27	2.67	30	2.98	57	2.82
NERVOUS SYSTEM DISORDERS						
Headache NOS	28	2.76	27	2.68	55	2.72

8.4.2.2. Other studies

The pattern of general adverse events in the remaining supportive studies (excluding events of specific interest as discussed in following sections) was similar to that in the pivotal study. An integrated safety analysis prepared by the sponsor for the risk management plan (module 1.8.2) includes all subjects in the clinical trial population who received Seasonique (n=1,456) and is presented. The pattern of such treatment-emergent AEs in Study DR-105-202 is of particular interest as there was both an active comparator and placebo group.

Table 12: Treatment-related adverse events (adverse drug reactions)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of subjects[a] SEASONIQUE (N=421)	LESSINA (N=412)	Control (N=437)
Number of subjects with at least 1 treatment-related adverse event	**100 (24)**	**95 (23)**	**7 (2)**
Gastrointestinal disorders			
Nausea	14 (3)	11 (3)	0
Investigations			
Weight increased	7 (2)	5 (1)	0
Nervous system disorders			
Headache	23 (5)	32 (8)	2 (<1)
Reproductive system and breast disorders			
Metrorrhagia	27 (6)	14 (3)	0
Dysmenorrhea	10 (2)	12 (3)	1 (<1)
Skin and subcutaneous tissue disorders			
Acne	10 (2)	7 (2)	2 (<1)

Although influenced by the fact that this was an open label study, these last data do suggest that the reported AEs were genuinely treatment related and possibly of lesser incidence in the lower dose (Lessina) group.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal study

No deaths were reported in the pivotal or any of the supportive studies in the application. In the pivotal study, 55 subjects (evenly distributed between the treatment groups) reported SAEs. Of those events considered related to study medication, none are unusual such as to suggest a previously unrecognised safety signal for this COC product.

8.4.3.2. Other studies

Similar comment applies as in the previous section. The occurrence of an episode of pulmonary embolism in a teenage subject on Seasonique in study DR-105-202 is a salutary reminder of the risks associated with even low-dose COC preparations.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal study

In the pivotal study, 5.8% of Seasonique and 7.1% of DP3-84/30 subjects withdrew because of either intermenstrual bleeding or menorrhagia. These bleeding disorders accounted for the majority of discontinuations, which totalled 6.7% for Seasonique and 8.5% for DP3-84/30. The remainder comprised a variety of symptoms known to be associated with OCP use including headache, breast tenderness and acne.

8.4.4.2. Other studies

Findings were similar to those in the pivotal study.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal study

No clinically significant abnormalities or shifts in values were reported.

8.5.1.2. Other studies

Similar comment applies as for pivotal study.

> *Comment: of particular note in this context, and for laboratory test results generally in the safety population, are the findings of study DR-105-202 in which laboratory tests including those of liver and renal function were performed at baseline and study endpoint in groups each of more than 400 subjects using Seasonique, the COC comparator Lessina, and in one receiving no treatment. There were no differences of significance between baseline and end of study or between either of the active treatment groups and the control group.*

8.5.2. Kidney function

8.5.2.1. Pivotal study

No abnormalities were noted.

8.5.2.2. Other studies

No abnormalities noted.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal study

No abnormalities noted.

8.5.3.2. Other studies

No abnormalities noted.

8.5.4. Haematology

8.5.4.1. Pivotal studies

In the safety cohort comprising studies PSE-301, 302 and 304 there were median increases in platelet count of 14.0 x 1000/µL in the Seasonique group and 19.0 x 1000/µL in the DP3-84/30

group. This median change is approximately 5% of the baseline value, had wide variance in both directions, and it is not clear whether the change a statistically significant.

8.5.4.2. Other studies

See comment above. There were no other haematological changes of note.

8.5.5. Scheduled and unscheduled menstrual bleeding

The pattern of menstrual bleeding is a significant aspect of the suitability of any OCP preparation for clinical use. In one sense it is in efficacy issue (for example, when the user is expecting more regular and predictable periods, or is taking the preparation partly or completely because of irregular menses); and in another, a safety issue (for example, excessive or irregular bleeding could be an adverse effect particularly in the user who has a bleeding diathesis). Some users or prescribers might alternatively regard the ability of an OCP preparation to provide a predictable and regular menstrual bleeding pattern as neither related to efficacy nor safety, but simply convenience. In this case, it would be relevant to assess the observed pattern of bleeding against the expectations of the user or group of users.

Scheduled bleeding, in the context of a cyclical OCP preparation (extended cycle or otherwise), might be better referred to as expected bleeding and is that which occurs during or shortly after the HFI in conventional cyclical preparations, or during or shortly after the period of low-dose ethinyloestradiol supplementation at the end of each cycle in the DP3-84/10 (Seasonique) and DP3-84/30 formulations used in the studies submitted with this application. It occurs in response to withdrawal of the progestogenic component of the COC. It is also that bleeding which is expected at the end of conventional 28 day cycles of preparations such as DP3-25/30 or Nordette, used in study PSE-302.

Unscheduled bleeding is that which is unexpected and occurs during the period of combined oestrogen/progestogen administration and is generally referred to as breakthrough bleeding in routine use of a conventional COC.

While, as already discussed above, one of the aims of continuous or extended cycle COCs might be to reduce all bleeding to a minimum, it can be assumed that in relation to convenience and acceptability for consumers/patients there would be considerable preference for scheduled as opposed to unscheduled bleeding.

8.5.5.1. Pivotal study

For subjects in study PSE-301 (ITT population), the total number of days per 91 day cycle on which some form of bleeding and/or spotting occurred is displayed in the following table.

Table 13: Scheduled and unscheduled menstrual bleeding

Treatment Group	Cycle	N	Mean (SD)	Min	Q1	Median	Q3	Max	Median Per Patient-Month
DP3-84/30	1	739	18.5 (15.63)	0	6	14	28	77	4.3
	2	609	15.3 (14.49)	0	5	10	23	89	3.1
	3	513	12.6 (12.26)	0	4	9	18	66	2.8
	4	421	11.9 (12.39)	0	3	7	16	75	2.2
DP3-84/10	1	758	17.7 (14.50)	0	6	14	26	80	4.3
	2	625	12.6 (11.47)	0	4	9	18	70	2.8
	3	533	10.0 (10.10)	0	3	7	14	57	2.2
	4	446	10.3 (10.37)	0	3	6.5	14	65	2.0

Comment: note that the frequency of bleeding is highest in the first cycle and diminishes by cycle 3 and 4. Note also that although the median number of days affected by bleeding

and/or spotting comes down to about 2 per month during the latter half of the 12 month treatment period (right-hand column), the mean values are 4-5 times higher with a high SD indicating a substantial proportion of subjects with very much higher rates of bleeding. This pattern is evident throughout the complex analysis of bleeding patterns in the study report. For subjects receiving DP3-84/10 (Seasonique), the mean (SD) number of days of unscheduled bleeding and/or spotting per 91 day cycle diminished to 7.6 (9.37) by cycle 4, and for days when there was bleeding only, as opposed to spotting, this value was 3.2 (5.44). Again, while the median value per patient-month was only 0.3, many of the subjects would have experience unscheduled bleeding on 4 or more days per month.

8.5.5.2. Other studies

Data from study 302 contributes significantly to this evaluation in providing a parallel-group comparison of the bleeding profile experienced with DP3-84/10 (Seasonique) with that of an established conventional 28 day cycle preparation using the same ethinyloestradiol 30 µg/levonorgestrel 150 µg combination. The profiles of DP3-84/30 and the 28 day cycle preparation DP3-25/30 are also compared. Summary statistics for the total number of days of scheduled and unscheduled bleeding per cycle for the four preparations over the 12 month study period are shown.

To provide a comparison which removes the factor of the different cycle lengths of the preparations, the following have been calculated from the provided data. Bleeding, as opposed to spotting, days have been employed for this compilation as they are defined as those requiring sanitary protection and would therefore be of more significance to the user/patient:

- Mean total unscheduled bleeding days for the entire study period:
  - DP3-84/10 = 20.1
  - DP3-84/30 = 15.4
  - DP3-25/30 = 34.6
  - Nordette = 11.3
- Mean scheduled bleeding days per cycle over the entire study period:
  - DP3-84/10 = 2.33
  - DP3-84/30 = 1.96
  - DP3-25/30 = 0.34
  - Nordette = 2.07

  Comment: in summary, what this shows is that a user of DP3-84/10 (Seasonique) may expect withdrawal bleeds four times over the first year of use of approximately the same duration (2.33 versus 2.07 days) as those for Nordette which will occur 13 times. However over this year of use approximately twice as many (20.1 versus 11.3) days of unscheduled bleeding will occur. The total number of bleeding days (combined scheduled and unscheduled) in this 12 month study were 29.4 for Seasonique and 38.24 for Nordette. The data for DP3-84/30 are similar to those for Seasonique, and the other comparator DP3-25/30 showed very little withdrawal (scheduled) bleeding but a larger amount of unscheduled bleeding.

  The study report concludes that DP3-84/10 (Seasonique) has "the most favourable bleeding/spotting profile". This is true in terms of the total number of bleeding days over the study period, but arguable in the sense that of these bleeding days, 68% were unscheduled, i.e. unexpected, by comparison with 30% for the conventional comparator product Nordette.

  It is emphasised that the above conclusions are based on the first year of use of the product, and that the data does suggest an improvement over the course of this first year particularly for unscheduled bleeding which was markedly worse during the first cycle.

Information on the effect of more prolonged use on the bleeding pattern is found in study 304 in which subjects used the product for up to 4 years. The progression of unscheduled bleeding pattern for subjects using DP3-84/10 (Seasonique) for up to 12 cycles (three years) is seen in the following table.

Table 14: Scheduled and unscheduled menstrual bleeding

Treatment Group	Cycle	N	Mean (SD)	Min	Q1	Median	Q3	Max	Median Per Patient-Month
DP3-84/10	1	155	4.1 (5.84)	0	0	2	6	28	0.5
	2	145	3.4 (6.25)	0	0	1	4	34	0.3
	3	136	3.0 (5.85)	0	0	1	4	55	0.3
	4	116	3.5 (7.19)	0	0	1	4	54	0.3
	5	111	2.0 (3.88)	0	0	1	2	29	0.3
	6	100	3.1 (6.41)	0	0	0	3	37	0.0
	7	94	2.8 (5.98)	0	0	1	2	33	0.3
	8	86	2.3 (5.26)	0	0	0	2	39	0.0
	9	80	2.8 (4.92)	0	0	1	3	23	0.3
	10	72	2.2 (4.04)	0	0	0.5	2.5	19	0.1
	11	69	2.6 (4.66)	0	0	0	3	23	0.0
	12	43	2.1 (5.00)	0	0	0	2	27	0.0

Comment: a progressive reduction in unscheduled bleeding is suggested, although a confounding factor is that the higher mean and median values in earlier cycles may be contributed to by subjects who dropped out because of unacceptable bleeding.

8.5.6. Endometrial histology

In study PSE-302, endometrial biopsies were obtained in all 372 randomised subjects prior to initiation of treatment and in most subjects (66.3% for the Seasonique group) during the last cycle of the 12 month study period. The results were classified by blinded reviewers and the distribution of the histological classifications is shown in the following two tables for the baseline and end of treatment results, respectively.

Table 15: Distribution of endometrial biopsy results at baseline

N under each treatment group refers to the number of biopsy reviews	DP3-84/30 (N=161)		DP3-84/10 (N=181)		DP3-25/30 (N=141)		Nordette (N=169)		Total (N=651)	
	N	%	N	%	N	%	N	%	N	%
No endometrium	8	5.0	18	9.9	17	12.1	10	5.9	53	8.1
Insufficient endometrial tissue	3	1.9	7	3.9	3	2.1	9	5.3	22	3.4
Inactive	36	22.4	38	21.0	26	18.4	24	14.2	124	19.1
Atrophic	8	5.0	3	1.7	3	2.1	5	3.0	19	2.9
Menstrual	10	6.2	3	1.7	2	1.4	8	4.7	23	3.5
Proliferative	24	14.9	56	30.9	36	25.5	48	28.4	164	25.2
Secretory	71	44.1	56	30.9	53	37.6	63	37.3	242	37.2
Hyperplasia	1	0.6	0	0.0	1	0.7	2	1.2	4	0.6

Table 16: Distribution of end of treatment biopsy results.

N under each treatment group refers to the number of biopsy reviews	DP3-84/30 (N=161)		DP3-84/10 (N=181)		DP3-25/30 (N=141)		Nordette (N=169)		Total (N=651)	
	N	%	N	%	N	%	N	%	N	%
No endometrium	9	5.6	24	13.3	30	21.3	4	2.4	67	10.3
Insufficient endometrial tissue	8	5.0	8	4.4	18	12.8	11	6.5	45	6.9
Inactive	69	42.9	76	42.0	47	33.3	81	47.9	273	41.9
Atrophic	14	8.7	14	7.7	9	6.4	7	4.1	44	6.8
Menstrual	16	9.9	14	7.7	10	7.1	9	5.3	49	7.5
Proliferative	18	11.2	29	16.0	17	12.1	21	12.4	84	12.9
Secretory	27	16.8	16	8.8	10	7.1	36	21.3	89	13.7
Hyperplasia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

The baseline biopsies were not performed with reference to any specific part of the subject's physiological cycle; the majority show a proliferative or secretory pattern with some 20% being inactive. The majority of the on-treatment biopsies show an inactive pattern consistent with suppression of ovarian function. Importantly, there was no evidence of hyperplasia or other abnormal unexpected findings. In a smaller group of subjects not listed in the above tables, who had the biopsies done after the last day of treatment, the results suggested a return towards normal endometrial function.

8.5.7. Bone mineral density

Potential effects of OCPs on bone metabolism are important particularly during adolescence when peak bone mass is being achieved, a process contributed to by sex steroids including oestrogen, progesterone, and testosterone. Suppression of these endogenous hormones by OCPs could potentially have a negative effect on bone mass although administration of synthetic oestrogens and progestogens is known to have a positive effect.

8.5.7.1. Study DR-105 - 202

The protocol for this study is outlined above. The primary efficacy variable was the percent change from baseline to month 12 in lumbar spine BMD as analyzed using the ANCOVA model. All 3 treatment groups showed an increase in lumbar spine BMD over 12 months of treatment. The least squares mean (SE) percent change from baseline to month 12 was 2.26% (0.168) for Seasonique, 1.45% (0.171) for Lessina, and 2.50% (0.139) for the control group. The treatment difference between the Seasonique and control groups was -0.23% (95% CI -0.67%, 0.20%) and treatment difference between Lessina and control groups was -1.05% (95% CI -1.49%, -0.61%). Noninferiority of Seasonique to control was demonstrated since the lower bound of the 2-sided 95% CI (-0.67%) was greater than the predefined noninferiority bound of -3%.

Noninferiority of Lessina to control was also demonstrated since the lower bound of the 2-sided 95% CI (-1.49%) was greater than the predefined noninferiority bound of -3%.

8.6. Post-marketing experience

A summary of post marketing data is provided in the clinical overview. In the period up to December 2013 (7.5 years following market release in the US) 1.55 million prescriptions were written for Seasonique. Exposure was estimated at 385,101 woman-years. During this period 466 AEs were reported, most commonly some form of vaginal bleeding. Based on the sales data the sponsor estimates the rate of such reported bleeding as being 0.06%. A tabulation of adverse events by system organ class notified to the FDA in the period up until June 2010 is provided. This lists 363 reported events covering a wide clinical spectrum. None seem unexpected in the context of long-term COC use.

8.7. Evaluator's overall conclusions on clinical safety

The overall safety of Seasonique is well demonstrated by the included studies, on an adequate number of subjects. The pattern of adverse events demonstrated in the included studies matches that associated with existing approved COC preparations of the same formulation as Seasonique.

Use of Seasonique is associated with a menstrual bleeding profile which differs from that associated with conventional 28 day cycle COCs; the extended cycle regimen means that there are less frequent scheduled withdrawal bleeds, but there is an increased frequency of intermenstrual, unscheduled bleeding which is most prominent during the first year of use and has in the included studies been associated with a significant discontinuation rate. This is not a safety issue but may affect the acceptability of the product for women who use it. The bleeding is not associated with any adverse effects on the endometrium.

The inclusion in the application of safety data on adolescent post-menarchal subjects is appropriate as the proposed indication "use as an oral contraceptive" may include its use in that population.

VTE/ATE are too uncommon/rare to make any sort of estimate from the pre-market clinical trial.

There was one case of venous thrombotic event was reported with Seasonique in a patient having a mutation in factor V Leiden. One case of arterial thrombotic event was reported with DP3-84/30 in a patient with predisposing thrombotic risk factors. No conclusion could be drawn from single cases.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Seasonique in the proposed usage are:

- Contraception with a level of reliability commensurate with that of most currently available oral contraceptive formulations.
- Reduction in the frequency of menstruation from once per month to four times per year.
- For those users who have troublesome menstruation related symptoms, a reduction in frequency of those symptoms also (note that this is not a benefit claimed by the sponsor, but is a likely one).

9.2. First round assessment of risks

The risks of Seasonique in the proposed usage are:

- The established, well documented risks of oral contraceptive formulations containing oestrogen/progestogen doses at the level used in Seasonique (for example, an increased risk of venous thromboembolic disorders).
- Unpredictable intermenstrual bleeding, with the possibility of being in the small proportion of users in whom this occurs to an unacceptable degree.
- VTE/ATE are too rare to be characterised in the pre-market data. It is unknown whether VTE/ATE is more or less common with Seasonique than with other combined hormonal contraceptive (CHC) with shorter cycles.

9.3. First round assessment of benefit-risk balance

At this point in time, pending the sponsor's response and further TGA evaluation, the benefit-risk balance of Seasonique, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

At this point in time, and pending the sponsor's response and further TGA evaluation, no objection is seen to approval of the application.

11. Clinical questions

1. Is there any information about whether the risk of the uncommon adverse reactions of VTE and ATE is greater or lesser with Seasonique compared to 30 day cycle CHC?
2. Are any post marketing studies of the comparative risk of VTE or ATE planned?

12. Second round evaluation

The two questions are reproduced below, together with my comments on the sponsor's responses.

- Question 1: there any information about whether the risk of the uncommon adverse reactions of VTE and ATE is greater or lesser with Seasonique compared to 30 day cycle CHC?

The sponsor's response does not directly answer this question with any actual risk data (comparative incidence of adverse events with extended versus 30 day cycle preparations). It refers to the study by Nappi et al which is the published version of the study referred to in the CER in which levels of coagulation factors were measured in subjects using Seasonique by comparison with a 30 day cycle preparation containing identical doses of constituent substances and also with a preparation in which the progestogen was desogestrol. Changes in the measured factors were markedly less with Seasonique and the other levonorgestrel containing product, which is an important finding, but relevant to the present question was the finding that the change in levels with Seasonique was the same as that with the equivalent 30 day preparation. This surrogate evidence is supportive of a "no difference" answer to the question. The sponsor also provides references to evidence of a very low incidence of VTE in the 91 day levonorgestrel/ethinyloestradiol regimen used in Seasonique. Overall, the evaluator sees no reason to alter the conclusion in the original report that available evidence would support a provisional conclusion that there is no difference in thrombotic risk attributable to the extended cycle regimen. Nevertheless there is still some absolute risk, as illustrated by the occurrence of an episode of pulmonary embolism in one young subject on Seasonique.

- Question 2: Are any post marketing studies of the comparative risk of VTE or ATE planned?

The sponsor has provided a satisfactory answer to this question with the description of a protocol for a post marketing study which will compare incidence of VTE and, as a secondary objective, VTE, in women exposed to Seasonique by comparison with a similarly constituted 28 day cycle preparation. A satisfactory conclusion of this study would relieve the uncertainty expressed in the above comments regarding Question 1.

In overall summary, the evaluator believes that the sponsor has provided satisfactory responses to the questions posed regarding the clinical data.

13. References

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