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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Qlaira, film-coated tablets
Bayer Schering AG, Germany

estradiol valerate and dienogest

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1230/001/DC
Registration number in the Netherlands: RVG 101491

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Pharmacotherapeutic group:	progestogens and estrogens, sequential preparations
ATC code:	G03AB
Route of administration:	oral use
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	12 November 2008
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Qlaira, film-coated tablets from Bayer Schering Pharma AG. The date of authorisation was on 12 November 2008 in the Netherlands. The product is indicated for oral contraception.

Each wallet for 28 days contains
- 2 tablets containing 3 mg estradiol valerate
- 5 tablets containing 2 mg estradiol valerate and 2 mg dienogest
- 17 tablets containing 2 mg estradiol valerate and 3 mg dienogest
- 2 tablets containing 1 mg estradiol valerate
- 2 tablets do not contain active substances

A comprehensive description of the indications and posology is given in the SPC.

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation, changes in the cervical secretion, and changes in the endometrium.
The estrogen in Qlaira is estradiol valerate, an ester of the natural human 17ß-estradiol (1 mg estradiol valerate corresponds to 0.76 mg 17 ß-estradiol). This estrogen differs from the estrogens ethinylestradiol or its prodrug mestranol used in all other COCs by the lack of an ethinyl group in 17alpha position.
Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third of the same amount of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10% of the relative affinity of progesterone. Despite its low affinity to the progesterone receptor, dienogest has a strong progestogenic effect in vivo. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity in vivo.

This decentralised procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinial and clinical data. Parts of these data were already submitted in the dossiers of the fixed combination of estradiol valerate 2 mg and dienogest 2 mg (Climodien, NL License RVG 24830) and the lower dosed medicinal product of estradiol valerate 1 mg and dienogest 2 mg (Climodien 1/2 , NL License RVG 30401). However, these products are approved for another indication, i.e., hormone replacement therapy in postmenopausal women.

No scientific advice has been given to the MAH with respect to this product.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Active substances
General information
The active substances are estradiol valerate and dienogest. Estradiol valerate is described in the European Pharmacopoeia (Ph.Eur.*), whereas dienogest is a well-known active substance, not described in a Pharmacopoeia.

Estradiol valerate and dienogest are both practically insoluble in water. Both drug substances have a number of chiral centers. Dienogest does not exhibit polymorphism.

Manufacturing process
For estradiol valerate, the MAH makes use of a CEP. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

For dienogest the ASMF-procedure is followed. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.
For dienogest the manufacturing process is described in detail in the restricted part of the DMF. The structure, other characteristics and quality control of dienogest are described in the applicants's part of the DMF which is part of the Module 3, too.

Quality control of drug substance
For estradiol valerate the drug substance specification is in line with the Ph.Eur. with additional requirements for residual solvents and particle size distribution. Furthermore, the CEP specifies a more tight requirement for Ph.Eur. impurity E.
For dienogest the drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Stability of drug substance
Estradiol valerate:
Stability data on the active substance have been provided for six full-scaled batches stored at 25°C/60% RH (5 years), two full-scaled batches stored at 30°/70% RH (5 years) and two full scaled-batches stored at 40°C/75% RH (6 months). The batches were adequately stored.
No changes are seen at all storage conditions for the stability indicating parameters. The claimed re-test period of 5 years is justified, without an additional storage condition.

Dienogest:
Stability data on the active substance have been provided for three full-scaled batches stored at 25°C/60% RH (5 years), 30°/65% RH (5 years) and 40°C/75% RH (6 months). The batches were adequately stored. No changes or trends were observed at all storage conditions. The claimed re-test period of 5 years is justified, when stored in the original package to protect from light.

** Ph.Eur.is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Drug Product
Composition
The film-coated tablets consist of four different formulations with active substances and one formulation does not contain active substances ('placebo' tablets). The different formulations cover a 28-day cycle of one tablet each day.
Each wallet (28 film-coated tablets) contains in the following order:

Estradiol valerate (mg)	Dienogest (mg)	Colour	Number of tablets per blister	Embossed letters
3	-	Dark yellow	2	DD
2	2	Medium red	5	DJ
2	3	Light yellow	17	DH
1	-	Dark red	2	DN
0	0	White	2	DT

The tablets with active substances contain lactose monohydrate, maize starch, pregelatinised maize starch, povidone, magnesium stearate and a coating of hypromellose, macrogol, talc, titanium dioxide and ferric oxide red and/or yellow. The 'placebo' tablets consist of lactose monohydrate, maize starch, povidone, magnesium stearate and a coating, consisting of hypromellose, macrogol 6000, talc, titanium dioxide and ferric oxides. The tablets are packaged in PVC-Alu blisters.
The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The development is based on a standard formulation for hormone products. Holding times of the intermediates have been investigated and the dissolution method is developed.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process comprises a granulation, tabletting and film-coating. First granulation is performed. The magnesium stearate is added to the granules and the mixture is blended. The granules are tabletted by direct compression and coated by spraying an aqueous coating solution on the tablet cores.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches.

Excipients
The excipients comply with the Ph.Eur. and the ferric oxides with the NF (National Formulary) and Directive 95/45/EC. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, dissolution, microbial quality and uniformity of dosage units.
The release and shelf life limits are the same, except for the impurities and lower limit for assay. The different shelf life requirements are acceptable based on the increase in impurities during the stability studies. Other requirements are acceptable in view of the current regulations.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on five production-scaled batches of each formulation, demonstrating compliance with the release specification.

Packaging
The film-coated tablets are packaged in a PVC-Alu blister. The blister is glued into a carton wallet. The number of the day in the cycle is printed on the blister.

Stability of drug product
Stability data on the product have been provided at least three full-scaled batches of each formulation stored at 25°C/60% RH (36, 48 and 60 months), 30°C/70% RH (36, 48 and 60 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a transparent PVC-Alu blister. For three formulations results from long-term stability studies for 60 months are available. For the fourth formulation 48 months of data are currently available.
At accelerated storage conditions only a slight increase in impurities is observed. At long-term storage conditions variability in assay of both active substances is observed. There is a minor increase in total impurities of estradiol valerate. The increase is more pronounced in tablets containing less estradiol valerate. For dienogest a minor increase in total impurities is observed.

At intermediate storage conditions, the same trends are observed as at long-term storage conditions. Furthermore a decrease in the dissolution of estradiol valerate is observed. However, this decrease is observed after 36 months. The NfG on stability testing for existing active substances and related finished products specifies the requirements for stability data for climatic zones I and II (Europe). Therefore in Europe only 12 months data at intermediate conditions are required and no additional storage conditions are necessary. Based on the stability data provided, the claimed shelf-life of 60 months is justified without a special storage condition.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A TSE free declaration for lactose monohydrate has been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

Good Laboratory Practice
Part of the non-clinical studies was carried out in accordance with Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC). Many other older studies were not in accordance with GLP and were incomplete. New studies have been conducted to replace these older ones, in accordance with GLP regulations. The MEB has been assured that sufficient non-clinical studies have been conducted in accordance with acceptable standards of GLP.

Pharmacology
Relative binding of dienogest to the progesterone receptor as compared to progesteron or other synthetic progestogens is 10 to 30 fold less. Binding to the glucocorticoid receptor and to the androgen receptor is low. Binding of dienogest to the mineralocorticoid receptor and the estrogen receptor is negligible. Other studies have showed that dienogest does not bind to the sex hormone binding globulin (SHBG) and the corticoid binding globulin (CBG).
Metabolites showed hardly any binding and activity at the steroid receptors tested with the exception of the aromatic metabolite of dienogest which has some activity for the estradiol receptor. Due to the low plasma levels at which this metabolite is present in humans, a significant estrogenic activity of this metabolite is not anticipated.
Protein binding is comparable among species, but tends to be higher in human. The strong in vivo progestational activity of dienogest in rabbits as compared to other prostagens is probably due to a higher volume of distribution and a longer residence time in rabbits as compared to other species.
Antigonadotropic activity was seen in male rats at low doses. In female rats and monkeys however, the exposures at which antiovulatory effects were seen, were higher than human exposures; at least 20 times in rats, and 2 times in monkeys.
Dienogest as compared to levonorgestrel has stronger antiprogestional properties. Dienogest as compared to Levonorgestrel has stronger estrogenic activity. Dienogest has marginal androgenic effects as compared to 3-keto-desogestrel and has clear antiandrogenic effects. Dienogest has no mineralocorticoid effects, or glucocorticoid properties.
In the safety pharmacological studies after high doses of dienogest no relevant effects on the nervous system, blood pressure, heart rate, respiratory system or on kidney functions were observed.
No pharmacodynamic drug interaction studies have been performed.

Pharmacokinetics

Overall, the pharmacokinetics/toxicokinetics of dienogest are sufficiently investigated.

Absorption
It can be concluded that dienogest was rapidly absorbed after oral administration. T_{max} in mice and rats was about 0.5 hour and in rhesus monkeys 1-2 hour (concluded from repeated dose experiments, because these are the most reliable). In rabbits, dogs and monkeys (baboon, bonnet) T_{max} varied between 2-6 hours (single dose experiments). A high absolute bioavailability (F) was observed (70% in rats, 70% in baboon, and 85% in dogs).

Distribution in normal and pregnant animals used in reproduction studies
Plasma protein binding determined by ultra-filtration was 86-99% in rats, dogs, in baboons and in humans. The volume of distribution among species ranged from 0.6 l/kg in rats and dogs to 3.2 l/kg in rabbits.
Dienogest was rapidly distributed in female rats. At 1 hour after oral administration, the highest concentration of radioactivity in organ tissues were observed in adrenal glands, liver, stomach, ovaries and kidney. Other organs had concentrations similar or lower than blood plasma. After 21 times repeated daily oral administration of 1 mg/kg in female rats concentrations in white fat, skeletal muscle, cerebellum, blood, skin and spleen were 11-14 fold higher as compared to the data after the first administration, while in other organs 3-10 fold higher concentrations were observed.

Metabolism
In monkey and human mainly unchanged dienogest was found in plasma, while in rat plasma besides unchanged DNG some metabolites were found. It was demonstrated that the aromatic metabolite in rat plasma was responsible for the estrogenic effects seen in this species.
Only 6-8% of dienogest was excreted unchanged in urine. A number of metabolites were detected, indicating that hydroxylation plays the major role in metabolism of DNG in all species investigated. Metabolites were excreted as free steroids, glucuronoids and sulphates.
In in vitro studies with liver microsomes of rat, dog, monkey and humans approximately 30% of dienogest was metabolised. CYP3A4 was identified as the predominant isoenzyme. Dienogest does not inhibit CYP1A2, CYP2D6, CYP2E1, CYP3A4, CYP2C9 and CYP2C19.
Because of sufficient toxicity data in rat and monkey, no additional data are requested. All metabolites observed in human were also observed in these species.

Excretion
Excretion was studied in rat, rabbit, dog and monkey (baboon). Dienogest was rapidly eliminated from plasma with $t_{1/2}$ of 5-9 hrs. Radioactivity was mainly excreted via urine in all species. Biliary excretion was studied in rats and rabbits, and 30 to 50% of the radioactivity was excreted via this route. Based on the plasma concentration versus time curve in rats and mice there was evidence for enterohepatic circulation.

Pharmacokinetic drug interactions
On the basis of in vitro interaction studies, no effect on the CYP family of enzymes by dienogest is expected. At high doses, increases in liver enzymes were observed. Also at high doses, drug-drug interactions with respect to pharmacokinetics were observed between dienogest and estradiolvalerate, but clinical relevance is unlikely.

Pharmacokinetics after a single dose/repeated administration
Pharmacokinetic parameters after single dose administration were determined in mice, rats, rabbits, dogs and various strains of monkeys (bonnet, baboon, cynomolgus). In general, these single dose studies are of insufficient quality to conclude. Because of the good quality of the pharmacokinetic parameters in the toxicity studies it would not be necessary to perform additional studies with single administration.
The studies with mice and with monkeys were the only studies describing the effect of multiple dosing. In most of the multiple dose studies a linear relationship between dose and AUC was observed in the tested dose ranges.

Toxicology

Single-dose toxicity
Single-dose toxicity studies with oral administration were performed in mice, rats, rabbits and dogs and revealed a very low acute toxicity of dienogest, in particular when compared to the intended human dose. Non-lethal doses were between 1000 and 4000 mg/kg with the exception of male rabbits were it was below 1000 mg/kg. Signs of toxicity observed at high doses were central depression in mice, none in rats, anorexia, weight loss and convulsions in rabbits and a transient increase in GPT in dogs without histopathological findings.

Repeated dose toxicity

A large number of oral repeated dose toxicity studies with dienogest was provided in rats (4 studies: one 1 year study in females, two 6 month studies in both sexes, with dose in the range of 0.1 - 10 mg/kg/day, one 3 month study in females, dose range 0.3-30 mg/kg/day), Rhesus monkeys (an one year and a 3 months study both with dose range of 0.1-10 mg/kg/day), dogs (1 month, 3 months and 6 months, dose ranges of respectively 0.1-10 mg/kg/day, 0.03-3 mg/kg/day and 0.01-1 mg/kg/day) and mice (3 months, 5-125 mg/kg/day). A sufficient number of studies (e.g. one year rat, one year monkey) was carried out according to GLP guidelines.

In all four species predominantly the expected pharmacological effects on the reproductive system were found. Furthermore, effects were found on liver and on serum parameters (cholesterol, blood clotting factors, alkaline phosphatase) and red blood parameters.

In rats effects consisted of, e.g. decrease of estrous cycle, effects on uterus (decreased weight, thinning of wall, decrease of uterine glands), vagina (epithelial mucification), ovary (e.g. increased relative organ weight, decrease of Graafs follicles, increase of corpora lutea), mammary glands (increase in weight, size or activity, both sexes), pituitary (increase of chromophobe cells, both sexes), testes (atrophy) and spermiogenesis (decreased). In addition signs of effects on the liver were observed (fat deposition in some studies, decreased phospholipid content), no effects on liver function as examined by means of bromsulfalein were found. Some effects on serum cholesterol (decrease) and free fatty acids (increase in one year study) and blood clotting factors indicated effects on liver metabolism. Only in the three months study a decrease of red blood cell parameters was observed. Most effects were reversible, but some effects on the female reproductive organs persisted for one month after termination of treatment.

In monkeys effects consisted of discontinuation of menstruation. The following changes were found on reproductive organs: hyperplasia of the interstitial cells of the uterine intima and thinning of the basal layer, vaginal epithelial atrophy and follicular atresia. The follicular atresia reflected continuing inhibition of ovulation during the one year study. The uterine intima was necrotic (focal hemorrhagic) and the relative uterus weight was increased after high dose administration. Increased serum phospholipids indicated that the drug affected lipid metabolism. Only in the middle dose group effects on blood clotting factors were found, but the blood coagulation and fibrinolysis capacity were not affected. Alkaline phosphatase activity in bone, liver and serum was inhibited in a dose-related manner.

Female dogs showed the following effects: inhibition of heat, decrease of absolute ovary weights and increase of relative uterus weight. Mammary glands as well as the pituitary cells (prolacting-forming) were hyperplastic. The study revealed also muco- and pyometra. Moderate atrophy of the zona reticularis in the adrenals was found. Serum proteins, triglycerides and β-lipoprotein were also increased. Two months after termination of treatment, effects on the reproductive system had not yet completely disappeared.

In mice, periacinar hepatocytic hypertrophy was observed at the highest dose. In addition, only the expected pharmacological effects on the endocrine system were found.

It is noted that effects on ECG were not examined in any of the studies.

The toxicity profile of the combination therapy is very similar to those of the individual components, and is thus not likely to result in any safety concerns.

Reproduction studies

Reproductive toxicity was studied in rats, mice, and rabbits. These studies comprised fertility/early embryonic development to implantation and embryo-fetal development in mentioned animals. There were no remarkable effects except embryotoxicity only at maternally toxic doses.

Mutagenic potential

A full battery of negative *in vitro* mutagenicity tests was obtained with dienogest; the Ames test, the TK locus mutation test, UDS assay and the chromosomal aberration test .*In vivo* the mutagenicity of Dienogest was found to be negative in the UDS assay in rats, the micronucleus test in mice and a liver foci bioassay in rats. On basis of the presented studies, it can be concluded that dienogest has no mutagenic potential.

Oncogenic/carcinogenic potential

Three carcinogenicity studies with dienogest were conducted, one in the mouse and two in the rat. In general, dienogest produced effects which could be expected based on its hormonal action.

In male mice (B401) a non-significant increase of hemopoietic malignant lymphomas and pituitary adenomas was observed. In female mice an increased incidence of benign stromal polyps in the uterus

was observed at doses of 100 mg/kg body weight/day, which is a factor 12 times higher compared to the human therapeutic level based on AUC values.
In the first rat study (B399), in male rats no increase of tumours was observed. In female rats a slight increase of mammary hyperplasia and mammary gland adenomas was observed after exposure to dienogest at levels of approximately 0.12 and 1.24 mg dienogest/kg body weight, which corresponds to a fraction of the human therapeutic dose level based on AUC values. Norgestrel, used as a positive control, did not show any effect on the mammary area. Critical comments on this study were that the highest dose did not exceed the human intake based on AUC levels.
In the second rat study (B398) observed neoplastic changes in male rats were an increase of benign pituitary adenomas, benign adenomas in the kidney and benign fibroepithelial tumours in the mammary area. These changes were observed at 10 mg/kg bw, which is a factor 7 above the human intake based AUC levels. In female rats small non-neoplastic effects on the mammary area and the endometrium were observed but no increase of tumours was found. Critical comment on this study was that the mortality throughout the experiment was high; less than 20% of the male animals survived till the end of the trial.
It is concluded that no unexpected effects of dienogest were observed. The observed tumour types were indicative for the (weak) estrogenic properties of dienogest.
No combination studies with estrogen valerate and dienogest were performed. It was argued that it was not useful to test the combination of estrogen valerate and dienogest because the ratio of these compounds in human does not reflect the physiological condition of the test species and it was shown that dienogest has a strong progestogenic capacity which will inhibit estrogen induced tumour formation. Therefore additional carcinogenicity studies with the combination of estradiol valerate and dienogest are not necessary.
It is concluded that dienogest has no carcinogenic potential in rodents which is relevant to human health.

Special toxicity studies
Dienogest caused no antigenicity in tests for Active Systemic Anaphylactic (ASA) reactions in guinea pigs, and heterogeneous Passive Cutaneous Anaphylaxis (PCA) reactions in rats to sensitized mouse serum
Evidence for immunomodulation was suggested in a published report. In functional assays in mice, dienogest affected neither the graft versus host reactions nor the rejection reaction of skin allografts, but it dose-dependently stimulated humoral antibody formation against sheep erythrocytes. The results from other repeated dose studies gave no indications for immunomodulating effects. No effects of progestins on SRBC assay with mice were reported. The stimulation of humoral antibody formation might be the estrogenic activity of dienogest. Therefore, no immunotoxic potential of dienogest is to be expected.

Ecotoxicity/Environmental risk assessment
Based on the provided information for Qlaira, a risk posed by the drug substance estradiol(-valerate) for surface water is determined. For groundwater and sediment the risk is acceptable; for sewage treatment and soil the risk assessment could not be completed.
Based on the provided information for Qlaira, a risk posed by the drug substance dienogest for surface water is determined. For soil, sewage treatment and groundwater risk is acceptable; for sediment the risk assessment could not be completed.
For both substances post-approval commitments were agreed to complete the environmental risk assessment.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
The MAH declares that all clinical studies performed in the framework of this submission were conducted in accordance with Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed, and that the protocols and protocol amendments were reviewed and approved by Independent Ethics Committees or Institutional Review Boards.

Pharmacokinetics

Absorption

After oral administration of DNG either as immediate-release tablets or as a microcrystalline suspension, the absorption of the drug was rapid as indicated by the short time of 0.67 to 2 h to reach maximum concentrations of DNG in serum. Maximum serum concentrations at steady state are reached at about 1 hour after the oral administration of Qlaira containing 2 mg EV/3 mg DNG. The absolute bioavailability of 2 mg DNG was estimated to be 91% indicating almost complete absorption and a small firstpass effect.
Dose linearity of DNG pharmacokinetics was observed following single dose oral administration of DNG tablets over a dose range of 1 to 8 mg to young Caucasian. Linear pharmacokinetic behavior of DNG was also observed when administered as a single dose in combination with 4 mg EV and in combination with 2 mg EV in postmenopausal women.
Food decreased the rate of absorption of dienogest by nearly 30% but not the extent. Since DNG is a highly soluble and highly permeable drug, the observed food effect is likely caused by the delay in gastric emptying time.
Similarly, food did not affect the extent of absorption for E2 but increased the rate of absorption as C_{max} was increased by 23% under fed conditions. Such an increase appeared to be the result of increased solubility of estradiol with high-fat meals. The biotransformation of E2 to E1 was not affected by the concomitant food intake.
Therefore Qlaira tablets can be taken without regard to meals during all phases of the Qlaira regimen which is supported by the fact that all of the clinical trials with the Qlaira tablets were performed without any restrictions concerning food.

Distribution

After oral administration of Qlaira, post-maximum concentrations declined biphasically with a terminal half-life of about 12 hours. A fraction of 10% of circulating DNG is present in the free form with approximately 90% being bound non-specifically to albumin. DNG does not bind to the specific transporter proteins SHBG and CBG. Thus, DNG pharmacokinetics are not influenced by changes of SHBG or CBG concentrations and displacement of testosterone from SHBG or cortisol from CBG by DNG is unlikely.
The volume of distribution at steady state (Vd,ss) of DNG is 46 l after the intravenous administration of 85 µg ^{3}H-dienogest.

Metabolism and Elimination

DNG is nearly completely metabolized by the known pathways of steroid metabolism (hydroxylation, conjugation), with the formation of mostly inactive metabolites. Within the first 24 h after administration, 59% of circulating radioactivity is attributable to unchanged DNG, there was no major peak besides unchanged DNG; the proportion of water-soluble conjugates or metabolites is relatively low. . Nevertheless, the in vivo biotransformation of DNG is very intensive, only approximately 6 to 8% DNG is excreted unchanged, mainly in conjugated form. Its metabolites are excreted as free steroids, glucuronides, and sulfates in all species investigated.
In vitro CYP3A4 was identified as a predominant enzyme catalyzing the metabolism of DNG, whereas CYP1A2, CYP2C9, CYP2A6, CYP2C19, CYP2D6 and CYP2E1 are not involved in vitro.
At a multiple of the clinically relevant concentration, DNG does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E, and CYP3A4. The inhibition constant Ki, calculated for CYP2C19 and CYP3A4, was more than 100-fold the maximum serum concentration observed after oral administration of the 2 mg EV/3 mg DNG tablet contained in Qlaira. Therefore, it is to be concluded that DNG at clinically relevant doses will not affect the metabolism of other drugs metabolized by cytochrome P450 enzymes.

DNG and its metabolites are predominantly excreted with the urine. In total, 42% of the applied dose was renally eliminated within 24 h, 63% within 6 days, and the total elimination by urine and feces amounted to 86% after 6 days. In urine, approximately 20% of the steroids are unconjugated. The remainder consists of conjugates and other polar substances, with approximately equal proportions of glucuronides and sulfates.

Pharmacokinetics at steady-state

Steady state is reached after daily administration for 3 days of the 2 mg EV/3 mg DNG dose. Trough, maximum and average DNG serum concentrations at steady state are 11.8 ng/ml, 82.9 ng/ml and 33.7

ng/ml, respectively. The mean accumulation ratio for AUC (0-24h) was determined to be 1.24. The pharmacokinetic parameters of DNG at steady state following 2 mg EV/3 mg DNG in fertile women are similar to those observed in postmenopausal women with the same dose.
The pharmacokinetics of DNG are comparable over multiple treatment cycles in healthy, fertile women, indicating that the pharmacokinetics of DNG are cycle-independent and do not change during long-term therapy.

Pharmacokinetic Drug-drug Interactions
As DNG and E2 are substrates for CYP3A4 and an effect of known CYP3A4 inhibitors and inducers on DNG and E2 metabolism is possible, two drug-drug interaction studies were performed with the Qlaira tablets. Coadministration of rifampicin with Qlaira tablets showed a significant decreases in steady state concentrations and systemic exposures of DNG. The systemic exposure of DNG at steady state, measured by AUC(0-24h), was decreased by 83%. Similarly, significant decreases in steady state concentrations and systemic exposures of E2 were observed. The systemic exposure of E2 at steady state was decreased by 44%.
Known CYP3A4 inhibitors like azole antifungals, cimetidine, verapamil, macrolides, diltiazem, antidepressants and grapefruit juice may increase plasma levels of DNG and E2. Co-administration with the strong inhibitor ketoconazole resulted in a 186% increase of AUC(0-24h) at steady state for DNG and a 57% increase of AUC(0-24h) for E2. When co-administered with the moderate inhibitor erythromycin, the AUC (0-24h) of DNG and E2 at steady state were increased by 62% and 33%, respectively.

Combined administration of DNG together with EV has no effect on DNG pharmacokinetics. The same holds true for EV, whereby combined administration of EV together with DNG has no effect on EV pharmacokinetics.

Special populations
No studies in patients with impaired renal function were performed. However, according to the MAH no special risk for these patients is to be expected, since DNG is metabolized before excretion and its metabolites are pharmacologically inactive.
No studies were performed in patients with impaired liver function because severe liver diseases are contraindicated.
No studies were performed in children because Qlaira is not indicated before menarche.

No population pharmacokinetic analysis was carried out by the MAH.

Pharmacodynamics

Effects of DNG
Despite its low affinity to the progesterone receptor, DNG was shown to have strong peripheral progestogenic effect on the endometrium. . Two studies characterized the progestogenic activity of DNG by the determination of the transformation dose in estrogen-deficient women who were treated with EE for 2 weeks and with a combination of EE and DNG for 2 consecutive weeks. However, a complete transformation of the endometrium in 100% of the volunteers could not be documented at any of the doses tested up to 0.55 mg DNG.
Daily administration of 0.2 or 0.4 mg DNG for 21 days showed a progestogenic effect on the cervical secretion in normocyclic women. In estrogen-deficient women treated with 0.05 mg EE, the additional administration of 0.1 to 0.55 mg DNG had a anti-estrogenic effect on the cervical secretion. The anti-estrogenic effect was independent of the dose of DNG, suggesting that the maximum effect was already reached at a dose of 0.1 mg. DNG has a slight anti-estrogenic effect on the proliferation of the vaginal epithelium during the pre-ovulatory phase of normocyclic women
The ovulation inhibition dose of DNG was determined in healthy young women. Basis for judgment was the concentration of progesterone in serum supported by measurements of E2, FSH, and LH. Doses equal to or greater than 1 mg DNG per day inhibited ovulation. However, follicular maturation processes evident by a rise in serum E2 levels were not completely suppressed even with the highest dose of 2 mg DNG.

Effects of EV compared to EE

The MAH investigated whether substitution of EE with EV in Qlaira offers additional benefit due to the supposed lower estrogenicity of EV. The MAH concluded, also from literature, that 20 µg EE compared to 2 mg EV is comparable to or greater at the antigonadotropic level, slightly more active at the endometrial level, comparable at the vaginal level, more active at the hepatic level. The lower activity on the hepatic level has however not been clinically shown with the dose regimen for the current application.

Inhibition of ovulation with Qlaira

In view of the current application, **inhibition of ovulation** is the major pharmacodynamic action of interest. After inadequate ovulation inhibition in earlier studies with lower dose regimens (1-2 mg DNG), a ovulation inhibition study was conducted for this application investigating higher doses, Qlaira (2-3 mg) versus the 'DNG-increased regimen' (3-4 mg). The Hoogland score was found to be only slightly better for the 'DNG increased regimen' (only 2 women with ovulation in cycles 2 and 3) than for the Qlaira tablets with 5 ovulating volunteers in cycle 2 and 3. However, both regimens were comparable with regard to other measurements indicating suppression of ovarian function. The Qlaira (2-3 mg) regimen was therefore selected for further development.

Contraceptive efficacy

Two phase III studies were conducted, of which the large long-term study (A35179) is considered pivotal. The second comparative study primarily focussed on **bleeding control** (A35644) (see also table 1). Furthermore, an US study has been conducted and submitted later in the procedure (A39818).

Table 1: Overview of European and US clinical phase III studies and design of the studies.

Study (protocol no.)	Study design	Total no. of women by treatment group*	Treatment duration	Efficacy parameters
A35179	Multicenter, open, uncontrolled, one-arm	Qlaira: 1377 (18 to 50 years) By age subgroups: 998 (18 to 35 years) 379 (36 to 50 years)	20 cycles	**Primary:** number of pregnancies (unintended pregnancies during study treatment) **Secondary:** bleeding patterns and cycle control The subjective assessment of treatment by women was also evaluated
A35644	Multicenter, double-blind, double-dummy, controlled, randomized	Qlaira: 399 (18 to 50 years) By age subgroups: 199 (18 to 35 years) 200 (36 to 50 years) Miranova**: 399 (18 to 50 years) By age subgroups: 201 (18 to 35 years) 198 (36 to 50 years)	7 cycles	No distinction was made between primary and secondary variables The following efficacy variables were investigated: - bleeding patterns - cycle control - cycle control for cycles 2 to 7 - number of unintended pregnancies - subjective assessment of treatment by the women - mean change in the PGWBI total score and subscale scores from baseline to treatment cycles 4 to 7 - change in the MFSQ subscale scores from baseline to treatment cycles 4 and 7
A39818	Multicenter, open, uncontrolled, one-arm	Qlaira: 490 (18 to 35 years)	13 cycles	**Primary:** number of pregnancies (unintended pregnancies during study treatment) **Secondary:** bleeding patterns and cycle control
*Note: the number of women refers to the full analysis set				

**Microgynon or Miranova are identical names for the same products, 1-21 days 0.03 mg EE + 0.15 mg LNG
MFSQ = Mc Coy Female Sexuality Questionnaire
PGWBI = Psychological General Well-Being Index

The study participants started tablet intake on the first day of withdrawal bleeding at the beginning of the first medication cycle and recorded compliance and bleeding patterns through a diary.

Table 2: Study treatment during each 28-day cycle and handling missed pills

Days	Content of EV/DNG	Actions (if delay > 12 hours)
1 to 2	3.0 mg EV	1. Intake of missed tablet immediately and the following tablet as usual and 2. Use of backup contraception until Day 9
3 to 7	2.0 mg EV + 2.0 mg DNG	1. Intake of missed tablet immediately and the following tablet as usual and 2. Use of backup contraception for the next 7 days
8 to 17	2.0 mg EV + 3.0 mg DNG	
18 to 24	2.0 mg EV + 3.0 mg DNG	1. Intake of missed tablet and continuation of tablet intake as usual (intake of all tablets from the blister in the given sequence) and 2. Use of backup contraception until Day 9 of the following cycle
25 to 26	1.0 mg EV	1. Intake of missed tablet (no further action)
27 to 28	Placebo	

Missed pills were handled according table 2, which is different from the advice given in the SPC.

- **General inclusion/exclusion criteria**

Healthy women between 18 and 50 years, smokers maximum age of 30 at inclusion, Papanicolaou (Pap) smear taken or non-suspicious Pap smear within the last six months prior to start, and at least three cycles had to follow delivery, abortion, or lactation before start of treatment, were included.
Exclusion was mainly focussed on pregnancy, lactation, presence of liver disease, vascular disease, uncontrolled thyroid disorder, uncontrolled hypertension, diabetes mellitus, tumors (known or suspected), other severe diseases that might interfere, substantial overweight, prohibited concomitant medication.

The most important **baseline characteristics** are in line with the inclusion and exclusion criteria in both studies. Almost only Caucasians were included in both studies.

- **Statistical methods**

Contraception

- The unadjusted Pearl Index and the corresponding 95% CI were to be calculated according to the EMEA Note for Guidance on Clinical Investigation on Steroid Contraceptives in Women (EMEA. CPMP/EWP/519/98.) as planned in the Study Protocol. Cycles with back-up contraception were excluded.
- The adjusted Pearl Index for method failure and the corresponding upper confidence limit were calculated with the same methods as were used for the unadjusted Pearl Index. For the calculation of time of correct treatment exposure, treatment cycles that were not considered compliant and cycles with back-up contraception were excluded.
- Additionally, a life-table analysis (survival analysis) was performed. The cumulative failure rate, i.e., the probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of the known pregnancies under treatment (Kaplan EL and Meier P, 1958).

The **bleeding pattern** indices were analyzed using the following descriptive statistics: Number of non-missing observations, arithmetic mean, SD, minimum, 1st quartile, median, 3rd quartile, and maximum. The statistics were calculated for each reference period. Additionally, 95% confidence intervals were calculated for bleeding/ spotting days *per* reference period, age group, and treatment group.

- **Results on contraceptive reliability**

The number of pregnancies observed in the pivotal clinical trials are given in table 3**.**

Table 3: Unadjusted Pearl Index (PI_U) and Adjusted Pearl Index (PI_A)

A39818, A35179, and A35644, Treatment: EV/DNG tablets						
Age group	Total time of exposure [days]	Days with back-up contraception	Relevant exposure time [days]	Number of pregnancies	PI_U	Upper limit of two-sided 95% CI
18-35	684030	30763	653267	18	1.0064	1.5906
18-50	914918	33968	880950	19	0.7878	1.2302

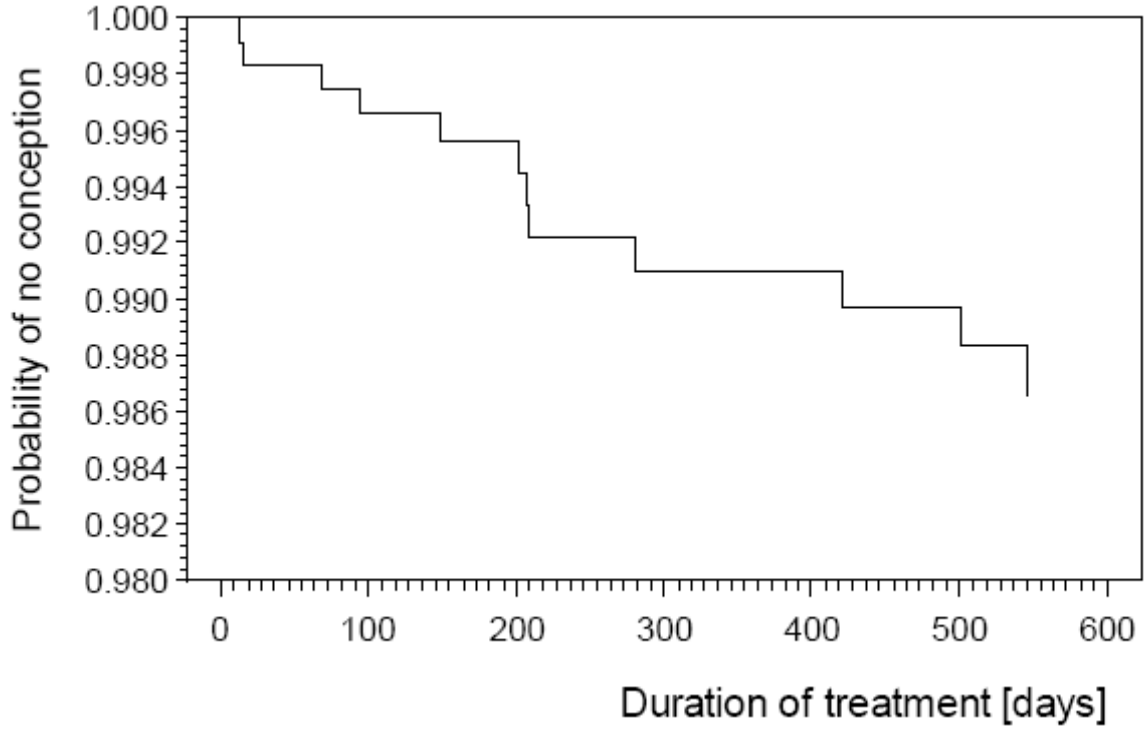
A39818, A35179, and A35644; Treatment: EV/DNG tablets							
Age group	Total time of exposure [days]	Days with back-up contraception	Days non-compliant	Relevant exposure time [days]	Number of pregnancies	PI_A	Upper limit of two-sided 95%- CI
18-35	684030	30763	8939	644328	9	0.5102	0.9685
18-50	914918	33968	9859	871091	10	0.4193	0.7711

The **unadjusted Pearl Index (PI_U)** based on pooled data across studies A35179 and A35644 conducted in the EU for women aged 18-50 years is **0.65** (upper limit 95% CI 1.11), and **0.87** (upper limit 95% CI: 1.52) for women aged 18-35 years, obtained with adequate precision as requested in the CHMP guideline, i.e. the upper limit of the 95% CI is within one from the point estimate.
The **Pearl index for method failure (PI_A)** is **0.30** for women aged 18-50 and **0.37** for women aged 18-35 years, and therefore comparable with that noted for other combined oral contraceptives.
The relative contraceptive efficacy compared to other combined oral contraceptives (based on the Pearl Index for method failure) cannot directly assessed as there is no comparative trial assessing contraceptive reliability. Indirect comparison suggests a lower contraceptive efficacy in comparison to approved standard dosed second and third generation contraceptives e.g. Yasmin. However, it should be taken into consideration that the age groups are different, i.e. respectively 18-35 years of age and 18-50 years. Up to now only overall analyses were calculated based on the age group of 18 to 40 or 45 years.

Taken the **US study A39818** separately, the **unadjusted Pearl Index (PI_U)** for women aged 18-35 years is **1.45** (upper limit 95% CI 3.16) and **1.00** for **method failure (PI_A)** (upper limit 95% CI 2.57). Combined with the European studies the **unadjusted Pearl Index (PI_U)** for women aged 18-35 years is **1.01** (upper limit 95% CI 1.59) and **0.51** for **method failure (PI_A)** (upper limit 95% CI 0.97). For women aged 18-50 years the unadjusted (PI_U) is 0.79 (upper limit 95% CI 1.23) and 0.42 for method failure (PI_A) (upper limit 95% CI 0.77) as given in table 3.

The study size requirements and pregnancy reporting of the NtG on clinical investigation of steroid contraceptives in women regarding efficacy for a new contraceptive method are considered fulfilled:
- The calculation of efficacy was based on the Pearl Index and life table analysis.
- The difference between the point estimate and the upper limit of the 95% confidence interval does not exceed 1.
- At least 400 women have completed one year of treatment
- No relevant differences in demography between the women in the Qlaira and Miranova/Microgynon® groups, respectively.

Figure 1: Survival curve for Kaplan Meier estimate – study A35179 (FAS, women aged 18 to 50 years)



- **Results on cycle control**

A **withdrawal bleeding** episode during treatment was **defined as** the first bleeding episode after the last day of progestogen intake (i.e. after day 24 for Qlaira or after day 21 for Miranova). In case a bleeding episode was ongoing on the last day of Qlaira or Miranova intake and on the following day, this episode was regarded as the withdrawal bleeding episode, provided it started not more than 4 days before withdrawal of Qlaira or Miranova. All other (unexpected) bleeding episodes were considered as **intracyclic bleeding**. If no bleeding occurred until the next withdrawal of the progestogen component, this was assessed as absence of withdrawal bleeding in the previous treatment cycle (provided that pregnancy had been excluded).

Qlaira shows less withdrawal bleedings than the comparator and in general of less intensity than with the comparator Miranova. There were generally more intracyclic bleedings and they tend to be more severe with Qlaira (see table 4). However, the total number of days with bleeding/spotting is less with Qlaira. Based on patient diaries from a comparative clinical trial, the percentage of women per cycle experiencing intracyclic bleeding was 10 – 18 % for women using Qlaira. Amenorrhea occurs in approximately 15% of cycles. Overall, there are not many differences between groups.

Table 4: Numbers and % of volunteers with intracyclic bleeding - PPS

	Age 18 – 50 years		Stratum 18 – 35 years		Stratum 36 – 50 years	
	Treatment	Comparator	Treatment	Comparator	Treatment	Comparator
Cycle 1	68 (18.9)	61 (17.1)	32 (18.5)	30 (16.9)	36 (19.3)	31 (17.2)
Cycle 2	57 (15.8)	43 (12.0)	35 (20.2)	17 (9.6)	22 (11.8)	26 (14.4)
Cycle 3	41 (11.4)	49 (13.7)	22 (12.7)	27 (15.3)	19 (10.2)	22 (12.2)
Cycle 4	55 (15.3)	38 (10.6)	35 (20.2)	17 (9.6)	20 (10.7)	21 (11.7)
Cycle 5	39 (10.8)	37 (10.4)	17 (9.8)	19 (10.7)	22 (11.8)	18 (10.0)
Cycle 6	37 (10.3)	35 (9.8)	23 (13.3)	18 (10.2)	14 (7.5)	17 (9.4)
Cycle 7	46 (12.8)	35 (9.8)	24 (13.9)	16 (9.0)	22 (11.8)	19 (10.6)

In the **US study A39818**, the number of bleeding and spotting days, the length of bleeding or spotting episodes, number of subjects with withdrawal bleeding, were similar as seen with the other 2 pivotal EU studies. The number of intracyclic bleeding tended to be slightly more.

Ongoing studies

Two clinical phase 3 studies are ongoing to investigate Qlaira for the treatment of dysfunctional uterine bleeding (DUB). These studies are not considered relevant to this submission for the indication of oral contraception.

Clinical safety

- **General AE's and discontinuation**

Out of 1776 Qlaira -treated women (pooled data across studies A35179 and A35644 conducted in the EU), a total of 187 **Adverse Events (Aes) leading to premature discontinuation** were recorded for 155 (8.7%). The most frequently reported AEs leading to study discontinuation included metrorrhagia (24 women, 1.4%), acne (15 women, 0.8%), weight increase (13 women, 0.7%), headache (9 women, 0.5%), depression (8 women, 0.5%), hypertension (8 women, 0.5%), cervical dysplasia (6 women, 0.3%), decreased libido (6 women, 0.3%), and breast pain (5 women, 0.3%). Other AEs leading to discontinuation were reported for fewer than 5 women each. In the Miranova group, 20 AEs leading to discontinuation of the study medication were reported for 13 (3.3%) women. The most frequently reported AEs leading to discontinuation were acne (4 women), weight increase (3 women) and migraine (3 women). Other AEs leading to withdrawal were reported for 2 or 1 woman only.
A direct comparison of Qlaira and Miranova in study A35644 revealed that common **drug-related AEs** under Qlaira were breast pain (3.3%), headache (1.8%), and acne (1.3%) and differed in ranking and type from those documented under Miranova (acne [2.3%], headache [1.8%], migraine [1.3%], alopecia [1.0%], breast pain [1.0%]; and weight increase [1.0%]). No age-related differences were observed with regard to the frequency of drug-related AEs.

- **Serious adverse events**

Serious adverse events do not show a safety pattern deviating from that known for other COCs. A total of 65 SAEs were recorded for 48 (2.7%) out of 1776 Qlaira -treated women, of which 5 were classified as drug-related (against 3 drug-related in the Miranova-group).
Gynaecologic examination included breast palpation, TVU (Transvaginal ultrasonography), cervical smear for all subjects, with 18 (1.1%) in the Qlaira group and 3 (0.8%) in the Miranova group found PAP III or worse. Endometrial biopsies for 219 women in study A35179 revealed **endometrial metaplasia** in 2 women (0.9%) specified as "limited". Serious adverse events do not show safety pattern deviating from that known for other COCs. Three women were reported with cervical carcinoma stage 0, which had no impact during follow-up.

Two **deaths** were reported which were not considered related to the study treatment (one in natural disaster, one due to aneurysm).
No venous thromboembolisms (VTE's) were reported.
Except for one case of myocardial infarction in a woman at high risk, no further **arterial thromboembolic events** were reported.

Specific safety studies
An overview of specific safety studies is given in tabel 5

Table 5: Further studies relevant for laboratory evaluations including metabolism and hemostatis parameters

Study (protocol no) Phase	**Main study objective**	**Design**	**Total no. of women by treatment (FAS)**	**Treatment duration**
A33022 (301886) Phase 2	Plasma lipids, hemostatic variables and carbohydrate metabolism	Single-center, open-label, controlled, randomized	EV/DNG 30 Triquilar 28	7 cycles
A38220 (310122) Phase 2	Hemostatic parameters	Single-center, open-label, crossover controlled, randomized	EV/DNG 27 * Microgynon 29*	3 cycles per period
A25364 (307300) Phase 2	Ovulation inhibition	Multicenter, open-label, randomized, comparative	EV/DNG 100 'DNG-increased regimen' 103	3 cycles

- **Laboratory findings**

For **liver enzyme** investigation in the A35644 study, 1 subject (0.3%) in Qlaira and 3 (0.8%) in Miranova had a clinical relevant change of GGT and ALAT 1 subject (0.3%) and 1 (0.3%) had a clinical relevant change in ALAT, and no clinical relevant changes appeared in AP and cholinesterase.
Glucose mean HbA1c levels remained normal for both groups in study A35644.
For the comparative study A35644 versus Miranova, no differences in **lipid metabolism** between treatment groups were observed.
In the cross-over study A38220, following 3 treatment cycles, **mean SHBG** concentrations increased to comparable levels from 48.80 ± 19.335 to 72.61 ± 27.952 nmol/L for Qlaira and from 51.73 ± 21.269 to 72.60 ± 30.123 nmol/L for Miranova.

- **Effects on haemostatic variables/VTE risk**

The haemostatic cross-over study with Miranova (A38220) is considered of more value than the comparative study versus a tri-phasic LNG-containing COC. Tri-phasic LNG COCs are reported to have higher VTE risk than mono-phasic LNG-containing COCs. In study 38220, although there is a suggestion of less effect on variables selected in the EV/DNG group, the differences are very small, i.e. the results on haemostatic parameters were rather comparable for Qlaira compared to Miranova.
The MAH committed that after the launch of Qlaira, a large comparative **post-marketing safety** surveillance study will be conducted to assess the **VTE risk** of Qlaira compared to other COCs in a non-selected target population. The comparator is a second generation COC e.g. Miranova/Microgynon.

- **Safety of US study A39818**

The safety profile was considered similar to the safety profile found in the European phase III studies. Most frequently reported **drug-related AEs** were metrorrhagia (12.4% of women), headache (7.5% of women), and amenorrhea (7.3% of women). A total of 73 (14.9%) women **discontinued** study medication **as a result of an AE**. One woman had an **abnormal cervix biopsy and an adenocarcinoma of the cervix** and recovered after surgery. For 13 women **cervical dysplasia** (i.e. PAP smears with outcome ASCUS, low grade SIL or CIN1) was reported. No AEs relevant to the risk of VTE were reported in the course of this study.

The **drug-related AEs** from the two European studies A35179 and A35644 pooled with the US study A39818 (N=2,266 women) are presented in the SPC.

Pharmacovigilance System and Risk Management System

Pharmacovigilance System

The RMS considers that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management System

- The MAH committed that after the launch of Qlaira, a large comparative **post-marketing safety** surveillance study will be conducted to assess the **VTE risk** of Qlaira compared to other COCs in a non-selected target population.
- The MAH committed that soon after the launch of Qlaira a preferential prescribing monitoring program (observational study) will be conducted.

Further the MAH committed to perform additional safety studies as mentioned under commitments below.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The user test was performed in 2 test phases with 10 subjects each. The test persons were women of childbearing potential age (15 to 50 years), 50% of whom are or have been users of oral contraceptives. Inclusion and exclusion criteria were specified in the protocol. Test persons were able to read and speak English. Educational levels correspond with the inclusion criteria set in the protocol.

The test was performed by face-to-face interviews. Questions were designed to determine whether users can identify key information that is necessary for appropriate use. There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. The test included 14 questions related to the content of the package leaflet. Eight questions were related to critical safety information, 2 questions addressed the readability of the presentation of side effects, and 4 questions were focused on the correct use. Another three questions were related to the structure/appearance of the PL, The results of the test were satisfactory. In round 1 at least 9 of 10 participants were able to locate the requested information and give the correct answer for all 14 questions. All participants appeared to make use of the table of contents. No changes to the booklet were therefore warranted after the first test round. In the second round, information was found for 13 of 14 questions and explained correctly by at least 9 of the participants. The investigators gave recommendations for improvement only with regard to some minor grammatical and typographical errors, as well as medical translation to lay terms.

III BENEFIT RISK ASSESSMENT

The applicant proposes an indication for ‘oral contraception’ for the combination of estradiol valerate (EV) combined with dienogest (DNG). The applicant proposed additionally claims that due to the estradiol valerate component instead of the standard used ethinylestradiol, Qlaira leads to lower hepatic effects when compared to a triphasic EE/LNG-containing COC. Further, the applicant proposed claims that the impact on SHBG levels and hemostasis parameters was shown to be lower.

Benefit

With an uncontrolled open phase III study, a controlled comparative phase 3 study, and a US open-label uncontrolled study, contraceptive efficacy has been sufficiently shown as the overall (ITT) Pearl Index of the combined is within the upper range of Pearl indices noted with approved combined oral contraceptives, while the Pearl index for method failure is comparable with that noted for other combined oral contraceptives. Furthermore, these figures were obtained with adequate precision as requested in the CHMP guideline (EMEA/CPMP/EWP/519/98 Rev 1.), i.e. the upper limit of the 95% CI is within 1.0 from the point estimate. The open phase 3 studies, including sufficient number of women, had a new design by including women of 18-50 years of age and a protocol stratification of young aged women (18-35 years) and older age women (36-50 years), while up to now only overall analyses were calculated based on the age group of 18 to 40 or 45 years. This should be taken into consideration when comparing to standard dosed second and third generation contraceptives e.g. Miranova. This can however not be assessed as there is no comparative trial assessing contraceptive reliability. Indirect comparison suggests a slightly lower contraceptive efficacy for Qlaira.

In the controlled comparative study, Qlaira shows less withdrawal bleedings than the comparator and in general of less intensity than with the comparator Miranova. Based on patient diaries from a comparative clinical trial, the percentage of women per cycle experiencing intracyclic bleeding was 10 – 18 % for women using Qlaira. Amenorrhea occurs in approximately 15% of cycles.

Risk

Clinical safety of Qlaira was adequately documented. Both European phase III studies included a sufficient number of women with sufficient duration of exposure according to the Guideline on clinical investigation of steroid contraceptives in women. No unexpected adverse events appeared with the use of Qlaira. The adverse events reported are known to be associated with the use of oestrogens and progestagens. The pattern of adverse drug reactions (ADRs) observed during treatment with Qlaira is considered typical for a combined oral contraceptive and did not deviate from that observed in the references group treated with Miranova. Also the phase III US study did not deviate from this safety profile.

Evaluation of endometrial effects, in general, showed a pattern known for COCs. The 2 cases of endometrial metaplasia and the 3 cases of cervical cancer (1 invasive, 2 stage 0) had no impact during follow-up.

Serious adverse events do not show safety pattern deviating from that known for other COCs.

Regarding effects on haemostasis, a comparative cross-over phase II study on haemostatic parameters is included, with a comparator with an established VTE risk profile, according to the recommendations in CHMP guideline, showing hardly any differences in effects.

However, registration dossiers are too limited to adequately quantify the risk of rare events such as VTE. Therefore, the MAH committed that after the launch of Qlaira, a large comparative post-marketing safety surveillance study will be conducted to assess the VTE risk of Qlaira compared to other COCs in a non-selected target population. The combined cohort will include 50,000 women recruited in the United States and Europe. Patients should undergo follow-up for at least 3 years.

The MAH has proposed additional claims in pharmacodynamic properties concerning hepatic effects, and lower impact on SHBG levels and hemostasis parameters due to the use of estradiol valerate, a prodrug of the natural human 17ß-estradiol instead of ethinyl estradiol. The estrogenic component used in this COC is therefore different from the estrogens usually used in COCs.

The claims of the MAH were based on a comparison to a triphasic EE/LNG-containing COC Triquilar . In this comparative study effects on SHBG levels and hemostasis parameters were shown to be lower. However, the triphasic COC Triquilar is not considered an adequate comparator for such comparisons, as it contains a higher amount of ethinyl estradiol (2nd week EE dose 40 micrograms) than standard COCs. The comparative study versus the monophasic LNG-containing COC, Miranova) did not show differences in increase in SHBG level between COCs. Furthermore, the clinical relevance of differences in SHBG increase is unknown.

Generally, hemostatic parameters were numerically lower for Qlaira compared to Microgynon 30. However, the clinical relevance of these minor differences in the absence of clinical data is unknown. However, it has to be taken into consideration that none of the haemostatic variables are validated surrogate parameters for the clinical endpoint of venous thrombosis. In conclusion, inclusion of this

statement is considered not acceptable as the clinical relevance is unknown. The planned large comparative post-marketing safety surveillance study that will be conducted to assess the VTE risk of Qlaira compared to other COCs in a non-selected target population is the only way to reliably assess the impact of estradiol valerate instead of ethinyl estradiol on VTE risk.

Effects on lipids

The MAH claims that in combination with dienogest, estradiol valerate displays an increase in HDL, while LDL-cholesterol levels are slightly decreased. Apart from the observation that in the comparative study versus microgynon (LNG-COC) no differences were noted, none of the COCs currently on the market have any statement regarding effects on lipids. In general, the clinical relevance of any effects on lipid metabolism induced by COC-use is unknown. The only relevance is the increase in triglycerides, demonstrated for all COCs, which may be of importance in women with high triglycerides levels or (family) history of pancreatitis, see general statement in SPCs of all COCs including Qlaira "*Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs*". In conclusion, inclusion of this statement is considered not acceptable as the clinical relevance is unknown.

In conclusion, contraceptive reliability of the Qlaira COC was shown to be adequate. Indirect comparison suggests contraceptive efficacy for Qlaira, within the range of that noted for COCs recently approved in the EU. A typical safety profile compared to other COCs is found for Qlaira. The claims on lower hepatic effects and lower impact on SHBG levels and hemostasis parameters cannot be justified due to unknown clinical relevance. The planned large comparative post-marketing safety surveillance study that will be conducted to assess the VTE risk of Qlaira compared to other COCs in a non-selected target population is the only way to reliably assess the impact of estradiol valerate instead of ethinyl estradiol on VTE risk.

IV OVERALL CONCLUSION

The first assessment report of the MEB was discussed in the Board meeting of 14 February 2008. The Board decided to follow the advice of the assessors. Questions on the choice of the dosages of both hormones and on potency differences of estradiol versus ethinylestradiol were added.

During the Decentralised Procedure a number of changes were introduced in the product-information because of the comments raised by the RMS in their assessment, but also because of the comments of the Concerned Member States. The major issues for discussion were the contribution of the endometrial changes to the contraceptive effect of Qlaira, the calculation of the Pearl Index, the bleeding data, the endometrial safety and the environmental risk assessment

At Day 210 agreement was reached between the member states and the MAH on product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling. The Decentralised procedure was finished on 14 October 2008
There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

On the basis of the data submitted, the concerned member states have granted a marketing authorisation. Qlaira film-coated tablets from Bayer Schering Pharma AG was authorised in the Netherlands on 12 November 2008.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The PSUR submission cycle is 6-monthly during the first 2 years. Thereafter once a year for the following two years and thereafter at 3-yearly intervals. The international birth date (IBD) is unknown. The MAH is requested to inform as soon as possible the RMS and CMSs of the date of granting of the first marketing authorisation in the EU to determine the date for the first renewal.

Post-approval commitments
The following post-approval commitments have been made during the procedure.

Quality

- The MAH committed to provide the stability data of all Qlaira formulations covering the whole shelf-life when available.

Risk management plan

- The MAH committed that soon after the launch of Qlaira, a large comparative post-marketing safety surveillance study will be conducted to assess the VTE risk of Qlaira compared to other COCs in a non-selected target population, (INAS-EV) and a preferential prescribing monitoring program (observational study). The MAH will take care that unexpected market uptake or incidence rates will not violate the power of the post-marketing VTE and preferential prescribing studies.

- As outlined in the INAS-EV study protocol, the MAH committed to gather data on pregnancies, including data on return to fertility and pregnancy outcomes. The results of the INAS-EV study with data on return to fertility and pregnancy outcomes will be provided.

- As outlined in the INAS-EV study protocol, the MAH committed, that all women who receive a new prescription for a COC at the participating centers will be asked to participate in the study. Thus,

also women below the age of 18 years taking Qlaira will be included. The results of the INAS-EV study with data in adolescents below 18 years will be provided.

- The MAH committed to report the endometrial and cervical safety results of the two studies (308960 and 308961) conducted in women suffering from dysfunctional uterine bleeding after availability and prior to start of the forthcoming clinical phase IV comparative post-marketing safety surveillance study (INAS-EV) . A decision in what extent endometrial and cervical safety should be investigated in this study will be made on the endometrial and cervical safety results from the two studies (308960 and 308961).

- The MAH committed to report the safety results of the two studies (308960 and 308961) conducted in women suffering from dysfunctional uterine bleeding in the PSURs of Qlaira. The first PSUR is planned to have a data lock point six month after marketing authorization.

- The MAH committed to closely monitor endometrial safety with Qlaira in the postmarketing period. The evaluation of spontaneous reports, as well as reports from literature, clinical and observational trials on endometrial safety will be reported in PSURs.

- The MAH committed to submit a variation type II (new indication) after availability of an agreed pediatric investigational plan (i.e. approximately end of 2009 or later, depending on the progress of the procedure), if the efficacy results of the two studies (308960 and 308961) conducted in women suffering from dysfunctional uterine bleeding are favorable. At this point in time, the MAH will submit the efficacy data as well as the safety data supporting the new indication. When the indication dysfunctional uterine bleeding will be granted, the label will be updated accordingly.

Environmental risk assessment

For the completion of the environmental risk assessment (ERA) the MAH commits to perform the following studies and to update the environmental risk assessment :

Estradiol

Substance; study type	Start experimental phase	End experimental phase	End chemical analysis	Final report
Activated sludge respiration inhibition	September 2008	September 2008	September 2008	October 2008
Bioaccumulation fish	September 2008	October 2008	December 2008	January 2009

- The literature data on a full life cycle test with estradiol on the medaka (Oryzes latipes) published by Seki et al. 2005 will be used to support the environmental risk assessment of estradiol. Accordingly, the no-effect level determined in that study (3 ng/L) will be used to update the ERA of estradiol.

Dienogest

Substance	Start experimental phase	End experimental phase	End analytical chemistry and histopathology	Final report
Dienogest				
Aquatic-sediment test	June 2008	November 2008	March 2009	April 2009
Fish sexual development test (FSDT)	November 2008	January 2009	May 2009	June 2009
Short-term reproduction test	January 2009	March 2009	May 2009	June 2009

- If there are unexpected effects observed in the FSDT or short-term reproduction assay, the necessity to conduct a fish full life-cycle (FFLC) test will be further discussed.

- The ERA for estradiol and dienogest will be updated in the 3rd quarter in 2009 after the completion of the whole study programme.

List of abbreviations

AE	Adverse event
ALAT	Alanine aminotransferase
Alu	Aluminium
AP	Alkaline phosphatase
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CBG	corticoid binding globulin
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
COC	Combined oral contraceptive
CV	Coefficient of Variation
CYP	cytochrome P450
DNG	Dienogest
ECG	electrocardiograph
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
E2	17β-estradiol
EE	Ethinylestradiol
ERA	Environmental Risk Assessment
EU	European Union
EV	Estradiol valerate
FAS	Full analysis set
FFLC	Fish full lyfe-cycle
FSDT	Fish sexual development test
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPT	glutamic pyruvic transaminase
HDL	High-density lipoprotein
ICH	International Conference of Harmonisation
ITT	Intention to Treat
LDL	Low-density lipoprotein
LDPE	Low Density Polyethylene
LNG	Levonorgestrel
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NF	National Formulary
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PI	Pearl Index = (number of unintended pregnancies / number of women years) x 100
PIA	Adjusted Pearl Index
PIU	Unadjusted Pearl Index
PL	Package Leaflet
PPS	Per-protocol set
PSUR	Periodic Safety Update Report
PVC	Poly vinyl chloride
RH	Relative Humidity

SD	Standard Deviation
SHBG	sex hormone binding globulin
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
VTE	venous thromboembolism

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the user instructions (beginning missed pill chart) in the final agreed PL and labelling (wallet) in line wit the text in the final agreed SPC/PL.	NL/H/1230/ 001/P/001	P	3-12-2008	23-12-2008	Approved	N
Update PL with change of tradename in IT.	NL/H/1230/ 001/P/002	P	21-10-2009	10-11-2009	Approved	N
Changes to the address of the marketing authorisation holder in Belgium.	NL/H/1230/ 001/IA/001	IA	5-8-2009	19-8-2009	Approved	N
Changes to the address of the marketing authorisation holder in France.	NL/H/1230/ 001/IA/002	IA	5-8-2009	19-8-2009	Approved	N
Two suppliers for the starting material for the synthesis of the active substance diegonest, have been added. The route of synthesis is different to the current approved supplier.	NL/H/1230/ 001/II/003	II	14-9-2009	13-11-2009	Approved	N
Update of Detailed Description of Pharmacovigilance System (Version 9.7 June 18, 2009).	NL/H/1230/ 001/II/004	II	19-10-2009	17-12-2009	Approved	N
Update of the environmental risk assessment (ERA) for estradiol and dienogest.	NL/H/1230/ 001/II/005	II	4-1-2010	21-4-2010	Approval	N
Addition of a new therapeutic indication	NL/H/1230/ 001/II/006	II	15-2-2010	8-10-2010	Approval	Y, Annex I
Changes to an existing pharmacovigilance system as described in the DDPS. Other change(s) to the DDPS that do(es) not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes, update of acronyms, naming changes of functions/procedures).	NL/H/1230/ 001/IA/ 008/G	IA/G	19-7-2010	18-8-2010	Approval	N
Changes to an existing pharmacovigilance system as described in the DDPS. Change of the back-up procedure of the QPPV Other change(s) to the DDPS that do(es) not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes, update of acronyms, naming changes of functions/procedures).	NL/H/1230/ 001/IA/ 009/G	IA/G	22-12-2010	21-1-2011	Approved	N
Change in the name of the MAH in Finland.	NL/H/1230/ 001/IA/ 010	IA	25-1-2011	24-2-2011	Approval	N
Change in the name and/or address of the marketing authorisation holder in the Slovac Republic.	NL/H/1230/ 001/IA/ 011	IA	2-3-2011	1-4-2011	Approval	N

Annex I - Addition of a new therapeutic indication - variation NL/H/1230/001/II/006

I Recommendation

Based on the review of the data on safety and efficacy, the RMS considers that the variation application NL/H/1230/001/II/006 for Qlaira for the following additional indication "Treatment of heavy menstrual bleeding in women without organic pathology who desire oral contraception" is approvable.

Major objections have been resolved and the SPC has been amended accordingly.

II Executive Summary

II.1 Scope of the variation

The type II variation NL/H/1230/001/II/006 concerns an application for an additional indication "***Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception***".

As a result, changes in the SPC were proposed in sections 4.1, 4.8, and 5.1 to include the information and study results related to this new indication.

Regulatory advice regarding this new indication of dysfunctional uterine bleeding (DUB):
After a first scientific advice meeting with the FDA on the development plan for EV/DNG for this new indication in January 2005 a national scientific advice meeting with the Dutch MEB took place in July 2005.
The recommendations by the MEB and by the FDA (July 2005) were incorporated in the two final clinical study protocols (September/October 2005).
On request by the FDA, the two final clinical study protocols were amended in 2006.

The DUB part of the NDA was discussed in a Pre-NDA meeting with the FDA in February 2009 and this EU Variation Type II was discussed in a Pre-submission meeting with the MEB (2009).

Clinical documentation in support of the indication of DUB
The clinical documentation in support of this application for the indication of "Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception" consists of 2 phase III, double-blind, placebo-controlled clinical studies (A29849 and A42568) of similar design conducted to demonstrate the efficacy and safety of EV/DNG for treating symptoms of DUB. Study A29849 was conducted in the USA and Canada, Study A42568 was conducted in multiple countries in Europe and Australia.

GCP
The planning and conduct of the clinical studies were subject to FDA and MEB discussion, national laws and in accordance with the International Conference on Harmonization – Good Clinical Practice (International Conference on Harmonization (ICH)-Good Clinical Practice (GCP) of 17 Jan 1997) and the ethical principles of the Declaration of Helsinki.

II.2 Supplementary paragraph

Dysfunctional uterine bleeding
The usual duration of menstrual flow is about 4-6 days, but ranges between 2 to 7 days. The average volume of menstrual blood loss is 30 ml; greater than 80 ml is considered abnormal.
Abnormal uterine bleeding is further defined as a change in menstrual loss, or the degree of loss or vaginal bleeding pattern differs from that experienced by the age-matched general female population.

Dysfunctional uterine bleeding (DUB) presents a spectrum of abnormal menstrual bleeding patterns that includes irregular, heavy or prolonged menstrual bleeding or an altered bleeding pattern. These menstrual cycles may be ovulatory or anovulatory.
Terms in use are menorrhagia (abnormally heavy and prolonged menstrual period at regular intervals), metrorrhagia (uterine bleeding at irregular intervals, particularly between the expected menstrual periods), and metromenorrhagia (combination of both).
DUB is one of the most frequent gynaecologic disorders observed by general practitioners and gynaecologists. DUB is an exclusion diagnosis; an organic cause should always be ruled out. Organic causes of DUB include benign uterine neoplasia, especially cervical and endometrial polyps and myoma's, adenomyosis, and malignancies of the cervix and endometrium.
Further, infection, unnoticed complicated pregnancy, medicinal treatment, and coagulation disorders like von Willebrand disease should be considered.

Approved medicinal treatment options for DUB:

Mirena (first choice in DUB according to NICE[1])

Levonorgestrel-containing IUD
Indication examples:

- Treatment of heavy menstrual blood loss or menorrhagia (NL);
- Idiopathic menorrhagia. Mirena may be particularly useful in women with idiopathic menorrhagia requiring (reversible) contraception (UK).

Tranexamic acid (Cyklokapron):

Antifibrinolytic agent.
Indication examples:

- Menorrhagia (NL, UK).
- Heavy menstrual bleeding (USA)

Etamsylate:

Etamsylate is thought to act by increasing capillary vascular wall resistance and platelet adhesiveness; in the presence of a vascular lesion, it inhibits the biosynthesis and action of those prostaglandins which cause platelet disaggregation, vasodilation and increased capillary permeability.
Indication:

- Indicated for menorrhagia; for the short term treatment of blood loss in primary and IUD-induced menorrhagia.

Synthetic progestagens:

Medroxyprogesterone; norethisterone; dydrogesterone, lynestrenol (treatment in luteal phase of cycle)
(5 - 10 mg daily for 5 - 10 days commencing on the assumed or calculated 16th - 21st day of the cycle. Treatment should be given for two consecutive cycles.
Indication example:

- Dysfunctional (anovulatory) uterine bleeding
- Menorrhagia, irregular cycles
- Polymenorrhoe, menorrhagia and metrorrhagia

Oral combined contraceptives 2-4 tablets per day (UK-only):

There is currently no COC available with an approved indication in the standard dose.

- Ovranette®, a COC containing 30 µg EE and 150 µg LNG, **2-4 tablets have to be taken per day** in a 21/7 day regimen, in UK indicated for treatment of spasmodic dysmenorrhoea and premenstrual tension; treatment of functional uterine bleeding (menorrhagia, metrorrhagia, metropathia haemorrhatica); emergency treatment of acute uterine bleeding.

Non-contraceptive combinations of estradiol + progestagen for use in premenopausal women:

- Cyclo Progynova® (EV and LNG in a sequential regimen) and indicated for control of irregular menstrual cycles and primary and secondary amenorrhea

[1] Women and Children's Health: National Institute for Health and Clinical Excellence (NICE) Clinical guideline Heavy menstrual bleeding. 2007:CG44:1-192

- Climene® (EV and cyproterone acetate in a sequential regimen), indicated for control of irregular menstrual cycles and primary and secondary amenorrhea.

NSAID Mefanamic acid:
Indication:
- Menorrhagia due to dysfunctional causes and presence of an IUD when other pelvic pathology has been ruled out.

Off-label medicinal treatments:
- Other combined oral contraceptives
- GnRH-agonists
- Danazol

Chirurgical treatments:
- Ablation
- Hysterectomy

Comparison of efficacy of medicinal treatments
Though DUB is a very common problem, the amount of adequate active comparative trials is limited and placebo-controlled trials are sparse. Further, the methods used to evaluate effects on DUB are not uniform; a number of different approaches are used. Although approved for treatment of menstrual bleeding disorders, the efficacy of several older therapeutic agents (e.g. progestagens) is not consistently proven in public literature.
The levonorgestrel IUD is reported to reduce menstrual blood loss from 71%[2] to 90%[3] from baseline.
Progestagen therapy during the luteal phase is reported to be significantly less effective at reducing menstrual blood loss when compared with tranexamic acid, danazol and the progesterone-releasing intrauterine system (IUS).[4]
As to the use of COCs in the treatment of DUB, according to the recently published Cochrane review[5] there is only one clinical study available that fulfilled the Cochrane requirements, the study by Fraser and McCarron in 1991.[6] In that study, 12 women were treated with a COC and were reported to have a reduction of 43% in menstrual blood loss by using the alkaline hematin method.

An overview is given in Drug safety[7], but the number of studies per treatment referred to is limited and methods of blood loss evaluation differed, see table below.

[2] Barrington et al. Comparison between the levonorgestrel intrauterine system (LNG-IUS) and thermal balloon ablation in the treatment of menorrhagia. Eur J Obstet Gynecol Reprod Biol 2003;108(1):72-74.
[3] Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Lethaby A et al. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD002126. DOI: 10.1002/14651858.CD002126.pub2.
[4] Lethaby et al. Cyclic progestagens for heavy menstrual bleeding. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD001016.
[5] Iyer V, Farquhar C, Jepson RG. Oral contraceptive pills for heavy menstrual bleeding (Review) In: Cochrane Database of Systematic Reviews, Issue 2, 2009. CD000154
[6] Fraser IS, McCarron G. Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. Aust N Z J Obstet Gynaecol 1991;31(1):66-70.
[7] Roy et al. Benefits and Risks of Pharmacological Agents Used for the Treatment of Menorrhagia. Drug Safety 2004; 27 (2): 75-90

Table II. Efficacy and tolerability of individual pharmacological treatments for the treatment of menorrhagia

Outcome	Reduction of menstrual blood loss	Adverse effects	Additional beneficial effects
Mefenamic acid	20–50%[20]	Gastric intolerance, nausea, vomiting bronchospasm	Use during menstruation. Improves dysmenorrhoea and menstrual migraine
Tranexamic acid	47–54%[25]	Nausea, vomiting, diarrhoea, occasional disturbances in colour vision	Use during menstruation
Oral progestogen for 21 days	32–50%[26]	Bloating, fluid retention, breast tenderness, weight gain, nausea, dizziness, headache, depression, acne, rash, hirsutism, alopecia	Cycle regularisation, endometrial protection in anovular bleeding
LNG-IUS	74–97%[27,28]	Intermenstrual bleeding in first three cycles. Other adverse effects similar to progestogens	Contraceptive agent, endometrial protection
Long-acting progestogen	50–66%[29] of patients experience amenorrhoea between 1–2 years of use	Menstrual irregularity, weight gain, vaginal dryness, reduced libido, mood changes	Contraceptive agent
Combined oral contraceptive	43%[30]	Nausea, vomiting, headache, breast tenderness, break-through bleeding, weight gain	Contraceptive agent, cycle regulation, improves dysmenorrhoea, and premenstrual syndrome. Reduces the risk of pelvic inflammatory disease, ovarian and endometrial cancer and benign breast disease
Danazol	49.7%[16]	Muscle cramps, fatigue, weight gain, fluid retention, breast atrophy, acne, oily skin, hirsutism, atrophic vaginitis	Improves dysmenorrhoea
GnRH analogues	>90%[31]	Hot flushes, night sweats, vaginal dryness, dyspareunia and loss of libido, bone loss	Improves dysmenorrhoea and severe premenstrual symptoms

GnRH = gonadotropin-releasing hormone; **LNG-IUS** = levonorgestrel-releasing intrauterine system.

Consensus treatment options

Though there is no generally recognized treatment approach, most gynaecological associations recommend treatment options as presented in the algorithm like NICE:

Pharmaceutical treatments for DUB/heavy menstrual blood loss:

If history and investigations indicate that pharmaceutical treatment is appropriate and either hormonal or non-hormonal treatments are acceptable, treatments should be considered in the following order:

1. Levonorgestrel-releasing intrauterine system (LNG-IUS) provided long-term (at least 12 months) use is anticipated
2. Tranexamic acid [A] or nonsteroidal anti-inflammatory drugs (NSAIDs) or combined oral contraceptives (COCs)
3. Oral progestagens like norethisterone (15 mg) daily from days 5 to 26 of the menstrual cycle, or injected long-acting progestagens.

III Scientific discussion

III.1 Quality aspects

N/A

III.2 Non clinical aspects

An Environmental Risk Assessment was previously submitted at the time of registration of Qlaira. Subsequently, an updated ERA was submitted as part of a FUM (NL/H/1230/001/II/005). In this procedure it was concluded that additional studies were necessary (BCF study for β-estradiol (OECD 305) and sediment toxicity study according to OECD 218 with Hyalella sp., Lumbriculus sp. or Chironomus sp. for

dienogest). The same ERA has now been submitted for the current variation procedure and still the same conclusions applies. These studies will be submitted in 2011.

III.3 Clinical aspects

III.3.1 Clinical pharmacology

No new data have been submitted.

III.3.2 Clinical efficacy

Main studies (2)

Two identical multicenter, double-blind, randomised, placebo-controlled studies were performed in support of this new indication.

Aim of the studies

Evaluation of the efficacy and safety of EV/DNG in the indication of dysfunctional uterine bleeding.
The methods of assessment, the study design and the efficacy variables were similar in both clinical studies performed in support of this indication, see Table 1.

Text Table 1 Overview of clinical Phase 3 studies evaluating the efficacy of EV/DNG in DUB

Study (protocol no.)	Main study objective	Design	Treatment and total no. of women by treatment group (intent to treat set)	Treatment duration
A29849 (308960)	efficacy and safety in subjects with DUB, defined as prolonged, frequent, or excessive uterine bleeding	multicenter, double-blind, randomized, parallel-group, placebo-controlled	EV/DNG: 120 Placebo: 70	screening (up to 28 days), a 90-day run-in phase, 196 days of study drug administration, and a 30-day follow-up
A42568 (308961)	efficacy and safety in subjects with DUB, defined as prolonged, frequent, or excessive uterine bleeding	multicenter, double-blind, randomized, parallel-group, placebo-controlled	EV/DNG: 149 Placebo: 82	screening (up to 28 days), a 90-day run-in phase, 196 days of study drug administration, and a 30-day follow-up

Study A29849 was performed in the United States and Canada, while study A42568 was performed in Australia, and European countries (Czech Republic, Finland, Germany, Hungary, The Netherlands, Poland, Sweden, United Kingdom, and Ukraine).

Comment RMS:
Although there are several treatment options approved for DUB, the clinical efficacy of these methods versus placebo is not adequately established. Further, the methods applied to evaluate efficacy in DUB are far from uniform. Therefore the RMS considers it justified to select a placebo-controlled design.

Methods

In both studies, the same inclusion and exclusion criteria were utilized, see details below:

Inclusion criteria

Women, 18 years of age or older, in generally good health, not pregnant or nursing, with a diagnosis of prolonged, frequent or excessive uterine bleeding without organic cause who desire oral contraception were included.

- *Prolonged bleeding: 2 or more bleeding episodes, each lasting 8 or more days*
- *Frequent bleeding: greater than 5 bleeding episodes, with a minimum of 20 bleeding days overall*

- *Excessive bleeding: 2 or more bleeding episodes each with blood loss volume of 80 mL or more, as assessed by the alkaline hematin method*

Comment RMS:
Though there is no consensus within the area of DUB in medical literature, the inclusion criteria applied for the study population are considered reasonable in view of the indication requested.

Exclusion criteria
General exclusion was mainly focussed on pregnancy, lactation, presence of liver disease, vascular disease, uncontrolled thyroid disorder, uncontrolled hypertension, diabetes mellitus, tumors (known or suspected), other severe diseases that might interfere, substantial overweight (BMI >32), prohibited concomitant medication.
Specific:
- Current diagnosis of organic uterine bleeding such as von Willebrand disease, chronic endometritis, adenomyosis, endometriosis, endometrial polyps, endometrial carcinomas, mixed mullerian mesenchymal tumors, leiomyomas, leiosarcomas, or endometrial stromal tumors
- Not willing to discontinue the use of NSAIDs during menses throughout the study
- Use of medication intended for treatment of DUB symptoms (eg, tranexamic acid), hormonal contraception, use of steroidal OC agents during the study

Methodology
Subjects entered a 90-day run-in to document menstrual bleeding criteria (prolonged bleeding, frequent bleeding, and excessive bleeding).
The documentation of ***prolonged*** and ***frequent*** menstrual bleeding was done through the use of electronic-diaries.
The documentation of ***excessive*** bleeding was done through the collection of used sanitary protection (pads and tampons) to quantify blood loss according to the alkaline hematin method. The run-in was also used to eliminate an organic cause for the disorder.

Efficacy assessment

Primary efficacy variable (2 parts):
1. **Overall success rate** defined by the number of subjects with the absence of any DUB symptom and who have met all the relevant criteria for success during the 90-day efficacy assessment phase1 (see below), as compared to the number of subjects having at least one qualifying DUB symptom during the run-in phase.

With respect to the primary efficacy variable, each subject was allocated to one of the following categories:
- **Responder**: Subject with the absence of any DUB symptom and who has met all the relevant criteria for success during the 90-day efficacy assessment phase.
- **Non responder**, ***symptomatic***: Subject with at least one remaining DUB symptom or who has not met all relevant criteria for success during the 90-day efficacy assessment phase
- **Non responder**, ***missing values***: Subject whose number of missing values was too high to be replaced by applying the data imputation rules. All early dropouts (i.e. subjects who did not complete a minimum of 90 days of treatment) but also patients with longer treatment duration but too many missing diary entries were allocated to this category.

2. For an "**overall success**" **of the study**, two criteria were to be fulfilled:

   - The proportion of responders in the EV/DNG arm must be statistically significantly greater than the proportion of responders in the placebo arm.
     This criterion was tested by the analysis of the primary efficacy variable ("***overall success rate***") using the ITT population.

But also

- The proportion of responders in EV/DNG arm must be at least 50%.
  This criterion was tested by calculating point estimates for the proportion of responders for (1) the ITT population and (2) the ITT population excluding "non-responders, missing values".

Note:
The protocols of both studies, as agreed with the FDA and the MEB, allow for some flexibility and state that, in case of a response in the EV/DNG group of below 50%, the clinical significance has to be established with the help of secondary efficacy outcomes.

Comment RMS:
As has been extensively discussed in scientific advisory settings, the selection and justification of the primary end points selected is considered adequate. The additional request that responder rates should be at least 50% was requested by the FDA. Nevertheless the expected effect size of 50% success rate was considered rather optimistic.

Individual components of the primary efficacy variable
Absence of DUB symptoms was defined as having:

- No bleeding episodes lasting more than 7 days
- And no more than 4 bleeding episodes
- And no bleeding episodes with blood loss volume of 80 mL or more.

In addition,

- No more than 1 bleeding episode increase from baseline

and

- Total number of bleeding days not to exceed 24 days
- No increase from baseline in an individual patient's total number of bleeding days

In addition, for patients enrolled with specific symptoms, the following criteria had to be met:

- If patients enrolled with prolonged bleeding, the decrease between the maximum duration during run-in phase and the maximum duration during the efficacy phase was at least 2 days
- If patients enrolled with excessive bleeding:
  (1) the blood loss volume associated with each episode was < 80 mL and
  (2) the blood loss volume associated with each bleeding episode represented a decrease of at least 50% from the average of the qualifying bleeding episodes, where the qualifying bleeding episodes were those with a blood loss volume of ≥ 80 mL (per episode) that occurred during the run-in phase

Secondary efficacy variables

- Proportion of patients cured or significant decrease from each individual symptom
- Change in blood loss volume for all patients and for patients with excessive bleeding
- Change in number of bleeding days and bleeding episodes
- Change in number of sanitary protection used
- Proportion of patients with improvement in the investigator's global assessment scale at days 84 and 196
- Proportion of patients with improvement in the patient's overall assessment scale at days 84 and 196
- Change from baseline in QoL scores at days 84 and 196
- Resource use assessment at baseline, days 84 and 196
- Change from baseline in hemoglobin and serum ferritin concentrations at days 84 and 196

Efficacy measurements
Efficacy was determined by:

- DUB symptoms as recorded in the e-diary
- Measurements of menstrual blood loss by the alkaline hematin method
- Investigator's global assessment scale
- Patient's overall assessment scale
- QoL and resource use assessment scores by questionnaires

Analysis sets
The analysis of the primary efficacy variable was based on the intent-to-treat (ITT) population, and on the per protocol (PP) set. The analysis of all secondary efficacy variables was performed on the ITT population.
The data sets are defined below.

- ITT population: All randomized patients
- PP set: All randomized patients who met all inclusion/exclusion criteria, did not take any prohibited medication, had at least 75% overall study drug compliance, had no major protocol violations, and completed 7 treatment cycles. The sponsor determined whether or not a patient met these criteria prior to unblinding the data for analysis.
- SAF set: All randomized patients who took at least one pill of study medication.

Statistical methods
Analysis of primary efficacy variable
The analysis of the primary efficacy variable was based on the ITT population.

The primary efficacy variable, ***overall success rate***, was analyzed by the difference in the EV/DNG and placebo arm in proportion of subjects with absence of DUB and the corresponding two-sided 95% confidence intervals.

In addition, the point estimate for the proportion of successful responders between EV/DNG and placebo (the additional requirement for the definition of ***overall success*** of study) was compared with a logistic regression model.
For the sake of the primary analysis, any randomized subject who did not complete at least 90 days of treatment or did not have sufficient data to evaluate the absence or presence of DUB symptoms was considered a treatment failure (worst case scenario).

Comment RMS:
The statistical methods applied were considered acceptable.

Sample size determination
A sample sizes ratio of 2:1 (EV/DNG: placebo) was planned for the study. Assuming a dropout rate of 30% and overall success rates in the EV/DNG group and the placebo group of 50% and 20%, respectively, 120 patients in the EV/DNG group and 60 patients in the placebo group (180 total) provided a power of 90% to test the null hypothesis that the proportions of success in the 2 treatment groups were equal, at a 5% significance level. A total of 190 patients were randomized in the study (120 patients in the EV/DNG group and 70 patients in the placebo group).

Rationale of the sample size selected
As this study was the first of its kind and no clinical development guidelines existed at the time the study was being planned. Hence, some additional justification for the clinical efficacy hypothesis was provided in the protocol.

- **Rationale MAH for 50% complete response effect in the EV/DNG group**

When compared with other symptomatic treatments, a 50% complete clinical response was clinically relevant.
Due to the nature of DUB, a disorder without organic cause, and due to the fact that physicians weigh their treatment decision between a medical treatment or a surgical intervention (eg, hysterectomy) the selection of a 50% complete response seemed relevant to be accepted.
The selection of a 50% threshold was also supported by a review of the literature, suggesting that a cyclic treatment incorporating a sufficient duration of a potent progestin could cure the various symptoms of DUB in at least 50% of patients.

- **20% complete response on placebo**

The literature suggested that with variable DUB definitions up to 20% of patients on placebo could experience a complete remission of their symptoms.

Compared with previously published studies, this study incorporated new design features that should have controlled for the variability of symptoms and decrease the placebo response. These features included:
1) strict and measurable criteria to define each individual symptom;
2) inclusion of bleeding only days rather than bleeding and spotting;
3) inclusion of a 3-month screening phase to establish eligibility;
4) inclusion of a similar 3-month phase to establish efficacy by comparison to the screening phase;
5) a 6-month treatment duration.
Hence, the 20% response on placebo hypothesized in this study was a realistic assumption.

Comment RMS:
The considerations of the MAH with regard to selection of 50% response in the EV/DNG group and a 20% response in the placebo group are considered an educated guess, as there is limited adequate literature to support these assumptions. Nevertheless, at least these assumptions are in accordance with the requirements of the FDA, i.e. 50% response rate.

Results
Individual and pooled results were presented in the dossier. As no relevant differences could be observed between the individual study results and the pooled analysis, the results of the pooled analysis are presented and discussed below.

Disposition
Overall, a total of 421 women were assigned to the ITT of the pooled efficacy assessment, i.e. 269 women in the EV/DNG group and 152 women in the placebo group. In the EV/DNG group, 202 women (75.1%) and in the placebo group 116 women (76.3%) completed the study, see details in table below.

Text Table 20 Frequency of women who completed or prematurely discontinued the study course and reason for discontinuation, by treatment, individual study and pooled data – ITT (studies A29849 and A42568)

No. (%) of women	Pooled data				Study A29849				Study A42568			
	EV/DNG		Placebo		EV/DNG		Placebo		EV/DNG		Placebo	
Total	269	(100.0%)	152	(100.0%)	120	(100.0%)	70	(100.0%)	149	(100.0%)	82	(100.0%)
Completed	202	(75.1%)	116	(76.3%)	85	(70.8%)	51	(72.9%)	117	(78.5%)	65	(79.3%)
Discontinued study course	67	(24.9%)	36	(23.7%)	35	(29.2%)	19	(27.1%)	32	(21.5%)	17	(20.7%)
Reason for premature discontinuation of the study course												
Adverse event	24	(8.9%)	7	(4.6%)	12	(10.0%)	3	(4.3%)	12	(8.1%)	4	(4.9%)
Withdrawal of consent	20	(7.4%)	8	(5.3%)	11	(9.2%)	4	(5.7%)	9	(6.0%)	4	(4.9%)
Other reason	12	(4.5%)	10	(6.6%)	6	(5.0%)	4	(5.7%)	6	(4.0%)	6	(7.3%)
Missing	5	(1.9%)	5	(3.3%)	3	(2.5%)	5	(7.1%)	2	(1.3%)	0	(0.0%)
Protocol deviations	5	(1.9%)	2	(1.3%)	2	(1.7%)	0	(0.0%)	3	(2.0%)	2	(2.4%)
Lost to follow-up	1	(0.4%)	2	(1.3%)	1	(0.8%)	2	(2.9%)	0	(0.0%)	0	(0.0%)
Pregnancy	0	(0.0%)	2	(1.3%)	0	(0.0%)	1	(1.4%)	0	(0.0%)	1	(1.2%)

Source: Module 5.3.5.3 Efficacy Summary DUB, Table 2

- **Duration of treatment**

The overall mean treatment duration for EV/DNG-treated women was 168.1 days (SD 54.7 and 166.4 days for placebo-treated women (SD 58.1). In study A29849, the mean treatment duration was 162.7 (SD 60.3) in the EV/DNG group and 164.0 (SD 63.2) in the placebo group. In study A42568, the mean treatment duration of the ITT in the EV/DNG group was 172.4 (SD 49.4), in the placebo group 168.3 (SD 53.8).

- **Demographics**

Except for ethnicity, demographics were comparable between studies. Based on the pooled ITT data, the mean age of EV/DNG-treated women was 38.3 years. For placebo-treated women, the mean age was 37.8 years. Mean body weight was 71.0 kg, and mean BMI 25.5 kg/m2 in the EV/DNG group, which values were 71.0 kg and BMI of 25.9 kg/m2 in the placebo group.
Regarding ethnicity, the percentage of Caucasian women was 96% in study A42568. In study A29849, 59% were Caucasian women, followed by 31.7% of Black women, 6.7% of Hispanic women, 0.8% of Asian women and 1.7% of other ethnicity in the EV/DNG group. In the placebo group, there were 65.7% Caucasian women, followed by 20.0% Black women, 8.6% Hispanic women, 2.9% Asian women and 2.9% of other ethnicity.

- **DUB symptoms at baseline**

The baseline findings are summarized in table 13.

Text Table 13 DUB symptoms at baseline by treatment by individual study and pooled data – ITT (studies A29849 and A42568)

No. (%) of women with bleeding	Pooled data				Study A29849				Study A42568			
	EV/DNG		Placebo		EV/DNG		Placebo		EV/DNG		Placebo	
Total	269	(100.0%)	152	(100.0%)	120	(100.0%)	70	(100.0%)	149	(100.0%)	82	(100.0%)
Prolonged	46	(17.1%)	22	(14.5%)	26	(21.7%)	12	(17.1%)	20	(13.4%)	10	(12.2%)
Frequent	4	(1.5%)	2	(1.3%)	4	(3.3%)	2	(2.9%)	0	(0.0%)	0	(0.0%)
Excessive	227	(84.4%)	136	(89.5%)	91	(75.8%)	60	(85.7%)	136	(91.3%)	76	(92.7%)
Prolonged and frequent	3	(1.1%)	2	(1.3%)	3	(2.5%)	2	(2.9%)	0	(0.0%)	0	(0.0%)
Prolonged and excessive	24	(8.9%)	18	(11.8%)	9	(7.5%)	9	(12.9%)	15	(10.1%)	9	(11.0%)
Frequent and excessive	1	(0.4%)	0	(0.0%)	1	(0.8%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Prolonged, frequent and excessive	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)

Source: Module 5.3.5.3 Efficacy Summary DUB, Table 10

- **Gynecological and menstrual history**

Generally, age at menarche, number of pregnancies and births, and number of abortions were similar in both studies and treatment groups.

- **Compliance with study drug**

At least 75% study drug compliant were 249 (92.6%) of the EV/DNG subjects and 141 (92.8%) of the placebo group subjects.

Efficacy results

Primary Efficacy Variable – Overall success rate – Pooled Results

- **Responder analysis**

For the pooled dataset (ITT), in the EV/DNG treatment group, there were 79 (29.37%) responders. In the placebo group there were 3 (1.97%). Amongst the non-responders, distinguish between 2 groups was made:

- *non-responders due to missing values:*
  Patients with missing data, this includes patients who never received study medication, who did not complete the minimum 90 days of treatment (early drop-outs) or who had too many missing bleeding data to define a valid 90-day efficacy phase
- *non-responders symptomatic:*
  Patients who failed to satisfy all of the relevant DUB criteria during the 90-day efficacy phase).

Pooled data for the ITT population were presented in table 2. A total of 81 (30.11%) subjects were classified as non-responders due to missing values and 109 (40.52%) because not all success criteria were met. Out of 152 subjects in the placebo group, 3 (1.97%) subjects were responders and 149 (98.03) non-responders, 42 (27.63%) subjects were classified as non-responders due to missing values and 107 (70.39%) because not all success criteria were met.

For the ITT population, the difference in the proportion of responders between treatment groups was statistically significant (P < .0001) as shown in Table 2.

Text Table 2 Responder Analysis for Overall DUB Symptoms by Treatment (ITT)

	QLAIRA (N = 269)	Placebo (N = 152)	
Responder a	79 (29.37%)	3 (1.97%)	
Non-reponderb	190 (70.63%)	149 (98.3%)	
Non-responder, symptomatic	109 (40.52%)	107 (70.39%)	
Non-responder, missing values	81 (30.11%)	42 (27.63%)	
Proportion of responders	0.2937	0.0197	
Difference (QLAIRA-placebo)			0.2739
P-value c			<.0001
95% confidence limits d			0.2123,0.3347

Reference: Module 5.3.5.3 Efficacy Summary DUB, Table 22.

[a] A responder is defined as having no DUB symptoms in the 90-day efficacy phase.

[b] A non-responder is defined as 1. non-responders due to missing values: patients with missing data (this included patients who never received study medication, who did not complete the minimum 90 days of treatment (early drop-outs) or who had too many missing bleeding data to define a valid 90-day efficacy phase; or 2. non-responders symptomatic: patients who failed to satisfy all of the relevant DUB criteria during the 90-day efficacy phase

[c] Two-sided exact P-value was obtained from Statistical software for data analysis (StatXact) using binomial procedure.

[d] 95% two-sided exact confidence interval was obtained by converting 2 separate one-sided test of half the nominal significance level each.

In subjects with evaluable response, i.e. ***ITT excluding non-responders due to missing data***, the point estimate for the proportion of successful responders was 42.02% (CI 34.88% - 49.42%) in the EV/DNG group compared to 2.73% (CI 0.57% - 7.76%) in the placebo group (Table 24).

Text Table 24 Responder Analysis for Responders/Nonresponders (Symptomatic) for Overall DUB Symptoms by Treatment (ITT excluding non-responders due to missing data)

	EV/DNG (N = 188)	Placebo (N = 110)
Responder [a]	79 (42.02%)	3 (2.73%)
Nonresponder, symptomatic	109 (57.98%)	107 (97.27%)
95% confidence limits	0.3488, 0.4942	0.0057, 0.0776

Reference: Module 5.3.5.3 Efficacy Summary DUB, Table 24

[a] A responder is defined as having no DUB symptoms in the 90-day efficacy phase.

Comment RMS:
The placebo response is surprisingly low. There are only few placebo-controlled studies in public literature on DUB. Of these, very low placebo responses in DUB were noted. As already indicated, in the absence of adequate evidence in public literature, the assumed response rate of 20% in placebo group is considered an educated guess. It should also be taken into account that the chosen primacy efficacy

analyses applied in the company studies are very different from that in published studies, i.e. much more stringent efficacy end points were selected. Nevertheless, the difference between active and placebo treatment is in line with that assumed in the sample size calculations.

- **Overall study success**

Table 26 displays the logistic regression analysis for the ITT set and shows a statistically significantly (P<.0001) greater proportion of responders vs non-responders in the EV/DNG group than in the placebo group. The proportion of responders vs non responders is 20.66 fold higher in the EV/DNG group compared to placebo.

Text Table 26 Logistic Regression Analysis for Overall DUB Symptoms Response Rate (ITT)

	EV/DNG (N = 269)	Placebo (N = 152)	
Responder [a]	79 (29.37%)	3 (1.97%)	
Nonresponder	190 (70.63%)	149 (98.03%)	
Proportion of responders	0.2937	0.0197	
Odds ratio (EV/DNG:placebo)			20.659
95% confidence limits			(7.5260,85.392)
P-value			<.0001

Reference: Module 5.3.5.3 Efficacy Summary DUB, Table 26

[a] A responder is defined as having no DUB symptoms in the 90-day efficacy phase. The odds ratio, 95% confidence limits, and p-value were obtained from Cochran Mantel-Haenszel statistic stratified by center, logistic regression model did not converge/the maximum likelihood estimates did not exist.

The point estimate in the EV/DNG arm was below 50% which was the pre-defined threshold for an overall study success. However, according to the MAH, the difference to placebo met the expectations, was substantial and clinically relevant.

Comment RMS:
Though the strict pre-defined threshold of 50% was not reached, the proportion of responders vs non responders is 20.66 fold higher in the EV/DNG group compared to placebo. It is therefore agreed that difference can be considered clinically relevant.

- **Summary of primary and secondary end point results, separate study results**

Note:
All secondary variables were analyzed based on the ITT population, i.e. patients classified as non-responders due to missing data are included. This has to be considered when interpreting the point estimates of the proportion of subjects relieved from each individual symptom.
In the table below, separate results of the primary and all secondary efficacy results are included.

Text Table 2 Efficacy parameters by study and treatment – ITT (studies A29849 and A42568)

	A29849		A42568	
	EV/DNG N = 120	**Placebo N = 70**	**EV/DNG N = 149**	**Placebo N = 82**
Primary variable: (overall success rate)**				
Responders*	29.17%	2.86%	29.53%	1.22%
Non-responders, symptomatic	37.50%	65.71%	42.95%	74.39%
Non-responders, missing value	33.33%	31.43%	27.52%	24.39%
	p<0.0001		p<0.0001	
Proportion of responders versus (vs) symptomatic non-responders, 95% two-sided exact confidence intervals**	43.75%	4.71%	40.74%	1.61.%
	32.68% - 55.30%	0.51% -14.25%	31.38% - 50.62%	0.04% - 8.66%
Secondary variables: Cure rates from individual symptoms				
Excessive	38.46%	5.00%	44.12%	1.32%
	p<0.0001		P<0.0001	
Prolonged	15.38%	8.33%	35.00%	10.06%
	p=0.8228		p=0.1766	
Change in MBLV per 90 day period	-353.1mL	-130.4mL	-458.4mL	-93.2mL
	p<0.0001		p<0.0001	
Change in bleeding days per 90 day period	-5.2 days	-2.0 days	-5.13 days	-3.08 days
	p=0.0240		p=0.0186	
Change in bleeding episodes per 90 day period	-0.52	-0.30	-0.38	-0.35
	p=0.0804		p=0.5095	
Change in sanitary protection used per 90 day period	-43.6	-21.2	-38.4	-16.5
	p<0.0001		p<0.0001	
Patient's global assessment scale improvement (Day 196)	81.2%	38.3%	77.9%	45.1%
	p<0.0001		p<0.0001	
Investigator's global assessment scale improvement (Day 196)	80.7%	41.9%	84.7%	39.5%
	p<0.0001		p<0.0001	
QoL questionnaires	Overall, very small changes from baseline. Differences between groups not considered clinically relevant and not statistically significant.		Overall, very small changes from baseline. Differences between groups not considered clinically relevant but statistically signif icant at the 5% level in favor of placebo in some domains.	
Iron metabolism	Moderate increases in hematocrit, hemoglobin and ferritin in the EV/DNG group. Differences from placebo were statistically significant.		Moderate increases in hematocrit, hemoglobin and ferritin in the EV/DNG group. Differences from placebo were statistically significant.	

***Responder**: Subject with absence of any DUB symptom who has met all the relevant criteria for success during the 90-day efficacy assessment phase. ** The definition of an **overall success** of the study required that the proportion of successful responders in the active treatment arm EV/DNG be statistically significantly greater than that in the placebo arm and the point estimate for the proportion of successful responders in the active treatment arm EV/DNG be at least 50%. Source: Module 5.3.5.1 Clinical Study Reports (CSRs) A29849 and A42568. N = Number (entire population under study)

Change in blood loss volume for all subjects (2nd secondary end point) per cycle:

Text Table 31 Descriptive Statistics for Blood Loss Volume (mL) by Treatment and Cycle (ITT)

Treatment		Run-in Phase [a]	Treatment Cycle						
			1	2	3	4	5	6	7
EV/DNG									
	n	268	261	253	240	230	219	209	197
	Mean	585.61	158.07	69.29	64.69	61.78	54.10	50.54	43.17
	SD	462.91	169.684	98.898	103.239	98.115	79.609	67.863	64.043
	Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Median	455.59	121.75	40.64	34.36	31.10	30.51	26.56	16.81
	Max	3472	1376	878.2	1005	826.8	688.8	360.6	350.7
Placebo									
	n	145	147	141	131	123	120	116	112
	Mean	632.74	173.00	172.52	170.51	151.13	156.13	148.76	143.59
	SD	408.93	156.803	142.832	137.808	115.782	104.560	108.522	101.432
	Min	86.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Median	493.60	130.90	140.45	144.13	129.80	129.93	131.87	116.92
	Max	2030	1002	764.2	790.5	677.3	450.6	537.2	540.4

Reference: Module 5.3.5.3 Efficacy Summary DUB, Table 34

[a] Run-in phase is the first 90 days.

After 6 months of treatment the median menstrual blood loss (MBL) was decreased by 88% from 142 mL to 17 mL in the Qlaira group compared to 24% from 154 mL to 117 mL in the placebo group.

Table / 1: Menstrual blood loss (MBL) - the percent change from baseline MBL - descriptive statistics by cycle and treatment group (intent to treat)

		Value at Visit							Change from Baseline (%)						
Treatment	Cycle	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
EV/DNG (N=269)	98	268	182.19	144.02	0.0	99.50	141.75	218.45	1080.0								
	Cycle 1	261	158.07	169.69	0.0	45.40	121.80	213.60	1376.0	258	-10.73	66.81	-100.0	-57.87	-18.89	27.41	245.9
	Cycle 2	253	69.29	98.90	0.0	12.70	40.60	89.70	878.2	250	-56.09	71.88	-100.0	-91.40	-73.02	-47.80	686.5
	Cycle 3	240	64.70	103.26	0.0	12.40	34.35	73.60	1005.0	237	-62.75	52.07	-100.0	-92.10	-77.37	-50.02	476.6
	Cycle 4	230	61.78	98.12	0.0	11.80	31.10	75.40	826.8	227	-61.04	74.92	-100.0	-91.29	-78.82	-57.97	850.8
	Cycle 5	219	54.10	79.61	0.0	9.60	30.50	64.60	688.8	216	-61.89	89.32	-100.0	-94.23	-77.22	-55.43	1122.2
	Cycle 6	209	50.55	67.87	0.0	9.50	26.60	65.80	360.6	206	-60.70	99.56	-100.0	-93.73	-82.74	-56.93	1231.0
	Cycle 7	197	43.17	64.05	0.0	3.40	16.80	54.90	350.7	195	-72.81	49.66	-100.0	-97.75	-88.02	-66.11	432.5
Placebo (N=152)	98	145	196.85	127.22	26.9	113.60	153.60	234.70	631.6								
	Cycle 1	147	173.00	156.81	0.0	64.90	130.90	227.90	1002.0	141	-3.39	68.62	-100.0	-45.25	-11.01	36.61	228.6
	Cycle 2	141	172.52	142.83	0.0	60.80	140.50	228.70	764.2	135	-2.72	71.87	-100.0	-40.92	-9.55	22.10	364.4
	Cycle 3	131	170.52	137.81	0.0	65.10	144.10	232.10	790.5	125	1.93	92.41	-100.0	-41.03	-10.44	21.40	685.8
	Cycle 4	123	151.13	115.79	0.0	62.90	129.80	207.60	677.3	117	-9.85	68.53	-100.0	-49.75	-19.45	14.18	330.5
	Cycle 5	120	156.13	104.56	0.0	82.65	129.95	196.75	450.6	115	-7.49	57.24	-100.0	-42.78	-23.01	10.90	196.7
	Cycle 6	116	148.76	108.52	0.0	74.35	131.85	185.80	537.2	111	-13.91	54.73	-100.0	-39.11	-22.04	7.33	230.2
	Cycle 7	112	143.59	101.43	0.0	75.30	116.95	200.65	540.4	107	-13.84	60.52	-100.0	-49.67	-24.08	15.17	308.9

For baseline the MBL of the 90 day run-in phase divided by 90/28

Comment RMS:
Though the secondary endpoints were not powered for statistical significance, clinically relevantly greater improvement versus placebo-treatment was noted for secondary end points evaluated. Especially the large difference in percentage of women cured from excessive bleeding, the change in menstrual blood loss volume (MBLV) and sanitary protection is considered substantially contributing to a clinically relevant effect.

In conclusion, the efficacy of Qlaira in the treatment of DUB is considered adequately proven. The wording proposed for this indication, is acceptable, though the addition 'prolonged' needs to be deleted as the number of women with prolonged bleeding is considered too small (see DUB symptoms at baseline).

- *Comparison of efficacy of other treatments licensed for DUB (Mirena, progestagen, tranexamic acid) see also table in introduction of this PAR*
  The noted improvements are difficult to compare to the efficacy noted in public literature, as the number of active- and placebo-controlled studies is limited and the methods used to evaluate efficacy in DUB are far from uniform.
  Indirect comparison to the standard of care, i.e. levonorgestrel-IUD (***Mirena***® MAH BSP) is based on the results obtained in the pivotal clinical study 309849 submitted at the FDA in support of the application for the indication heavy menstrual blood loss. This study compared Mirena versus medroxyprogesterone (***MPA***) 10 mg/day on the 16th day of menstrual cycle, for 10 consecutive days for during 6 cycles in patients with DUB. Mirena was shown to reduce absolute MBL (median blood loss) from baseline to End-of-study with -128.8 mL LNG IUS versus -17.7 mL MPA. The percentage women in whom MBL had decreased 50% or more was 85% versus 27% for MPA.
  The additionally submitted Mirena-like post-hoc analysis of bleeding data obtained with ENG/EV indicated absolute reduction in MBL to be in the same range as noted for Mirena (from 167 mL baseline to 59.6 mL end study; difference -113.1mL and from 182.3 mL to 31.8 mL at end study; difference -132.7 mL) in study 308961. The proportion of women with 50% or more decrease in MBL from baseline somewhat lower; 56.8% and 78.8% in both studies, respectively.
  Indirect comparison of these results suggests that efficacy of Qlaira with regard to reduction MBL is in the range of that noted for Mirena though the proportion of women with 50% or more reduction in MBL was somewhat lower but far better than noted for MPA.
  Tranexamic acid is reported to reduce MBL with 47-53%.

- *Comparison to efficacy in DUB noted with COCs*
  As to the off-label use of COCs in DUB, these are frequently used and recommended in the treatment of DUB. However, but this is based on expert opinion only, as their assumed efficacy is not evidence-based.
  According to the recently published Cochrane review[8] there is only one clinical study available that fulfilled the Cochrane requirements, the study by Fraser and McCarron in 1991. This means that although COCs are used of-label in the treatment of DUB, there is no adequate clinical efficacy data available in the public domain.

III.3.3 Clinical safety - DUB

A total of 411 women were included in the safety evaluation from the 2 studies performed for the DUB indication (264 received EV/DNG and 147 received placebo).
The safety of EV/DNG tablets has been demonstrated previously in the clinical development program for the indication of oral contraception. Subsequently, Qlaira was approved in all European member states (except Liechtenstein) and Australia for the indication 'oral contraception' and has been marketed since May 2009. So far, post-marketing data are available for Qlaira for a total of 29981 woman years of exposure. Data obtained since approval in Europe and Australia have been reported in the first and second PSUR (data lock of 08 Mar 2009 and 08 Sep 2009). During the postmarketing period no new safety information has been obtained that changes the overall positive benefit risk assessment of EV/DNG.

Patient exposure
Of the 411 subjects in the SAF, 264 subjects were exposed to EV/DNG tablets and 147 subjects were exposed to placebo. Study drug administration comprised 196 days (7 cycles of 28 days each). Text Table 3 presents the number of subjects exposed by treatment and by the number of cycles reached.

[8] Iyer V, Farquhar C, Jepson RG. Oral contraceptive pills for heavy menstrual bleeding (Review) In: Cochrane Database of Systematic Reviews, Issue 2, 2009. CD000154

Text Table 3: Number (%) of Subjects Exposure by Reached Cycle and Treatment – Two Final Regimen DUB Studies

Cycles	EV/DNG Tablets	Placebo	Total
Number of subjects	264 (100%)	147 (100%)	411 (100%)
≤ 1	11 (4.2%)	6 (4.1%)	17 (4.1%)
> 1 – 3	24 (9.1%)	19 (12.9%)	43 (10.5%)
> 3 – 7	164 (62.1%)	78 (53.1%)	242 (58.9%)
>7	64 (24.2%)	44 (29.9%)	108 (26.3%)
Missing	1 (0.4%)	0 (0.0%)	1 (0.2%)

Reference: 5.3.5.3 Safety Summary DUB, Table 2

As expected the mean age in the studies performed for the new indication was higher than that recorded in the studies for the OC indication, namely 38.1 years, 38.3 years for EV/DNG and 37.8 years for placebo, with a range of 18 to 54 years. Approximately two-thirds of subjects exposed to EV/DNG were 36 years of age or older.
Besides mean age, which was distinctly higher in subjects participating in the DUB studies than in women who participated in the pivotal studies for the OC indication, no unexpected clinically relevant differences were found between the treatment groups in the selected baseline characteristics of subjects who participated in the clinical studies.

Adverse events (Overall)
Of the 411 subjects, 259 (63.0%) subjects reported at least one AE; 174 (65.9%) subjects were in the EV/DNG tablets group and 85 (57.8%) subjects were in the placebo group. The rates of AEs were similar in the 2 studies.

Adverse drug reactions
The proportion of subjects who had at least 1 AE that was considered by the investigators to be related to study drug was more than twice as high in the EV/DNG tablet group than in the placebo group (37.1% versus 17.0%, respectively).

Text Table 7: Number (%) of Subjects With Common (Occurring in ≥ 1.00% of Subjects in the EV/DNG Tablets Group) Related AEs by Preferred Term and Treatment – Two Final Regimen DUB Studies

Preferred Term (MedDRA)	EV/DNG Tablets N=264 n (%)	Placebo N=147 n (%)	Total N=411 n (%)
Abdominal distension	3 (1.1)	2 (1.4)	5 (1.2)
Acne	9 (3.4)	3 (2.0)	12 (2.9)
Aspartate aminotransferase increased	3 (1.1)	1 (0.7)	4 (1.0)
Breast discomfort	3 (1.1)	0	3 (0.7)
Breast pain	13 (4.9)	0	13 (3.2)
Breast tenderness	8 (3.0)	2 (1.4)	10 (2.4)
Dysmenorrhea	7 (2.7)	0	7 (1.7)
Fatigue	4 (1.5)	1 (0.7)	5 (1.2)
Genital hemorrhage	4 (1.5)	0	4 (1.0)
Headache	17 (6.4)	10 (6.8)	27 (6.6)
Insomnia	3 (1.1)	1 (0.7)	4 (1.0)
Libido decreased	4 (1.5)	1 (0.7)	5 (1.2)
Menorrhagia	3 (1.1)	0	3 (0.7)
Metrorrhagia	11 (4.2)	1 (0.7)	12 (2.9)
Migraine	4 (1.5)	2 (1.4)	6 (1.5)
Mood swings	3 (1.1)	0	3 (0.7)
Nausea	9 (3.4)	2 (1.4)	11 (2.7)
Tension headache	4 (1.5)	0	4 (1.0)
Vaginal discharge	3 (1.1)	0	3 (0.7)
Weight increased	8 (3.0)	1 (0.7)	9 (2.2)

Reference: 5.3.5.3 Safety Summary DUB, Table 84
n = Number (sample of polulation under study)

RMS comment:
The pattern of adverse drug reactions (ADRs) observed during treatment with Qlaira is considered typical for a combined oral contraceptive and did not deviate from that observed with OCs.

Deaths

No deaths were reported in the course of the clinical studies to investigate the efficacy and safety of Qlaira in the treatment of DUB.

Other serious adverse events

Three (1.1%) subjects in the EV/DNG tablets group each experienced one nonfatal, serious adverse event (SAE), all of which were severe in intensity. Four (2.7%) subjects in the placebo group experienced 6 SAEs; 2 of these SAEs were considered severe in intensity. One subject (131003 in the EV/DNG tablets group; Report 5.3.5.1 A29849) had study drug discontinued due to her SAE (myocardial infarction). All SAEs resolved and all subjects recovered from these events. Text Table 9 shows the subjects with SAEs.

Text Table 9: Subjects with SAEs – Two Final Regimen DUB Studies

Subject No./ Report	MedDRA term (reported term)	Study drug relationship	Intensity	Study drug action	Outcome
Placebo					
104026 A42568	Vertigo (vertigo)	unlikely	moderate	Dose not changed	Recovered /resolved
	Panic attack (panic attack)	unlikely	moderate	Dose not changed	Recovered /resolved
132002 A29849	Chest pain (chest pain)	unlikely	severe	Dose not changed	Recovered /resolved
201005 A42568	Complication of pregnancy (suspicion of abnormal pregnancy)	no	mild	Not applicable (drug already withdrawn due to pregnancy)	Recovered /resolved
	Abortion spontaneous (miscarriage)	no	mild	Not applicable	Recovered /resolved
208011 A29849	Suicide attempt (hospitalization following a suicide attempt)	no	severe	Dose not changed	Recovered /resolved
EV/DNG Tablets					
131003 A29849	Myocardial infarction (myocardial infarction)	possible	severe	Drug withdrawn [a]	Recovered /resolved
702019 A42568	Breast cancer in situ (sin. lateral ductal carcinoma in situ [DCIS])	possible	severe	Not applicable [b]	Recovered /resolved
852034 A42568	Cholecystitis chronic (chronic acalculous cholecystitis)	possible	severe	Dose not changed	Recovered /resolved

[a] Drug withdrawn is stated in the case report form (CRF), but the last dose of study medication was taken on 20 Dec 2007 (Day 194 of treatment), 2 days prior to the SAE onset. On Dec 21 and 22, 2007, the subject forgot to take her study medication. These last 2 doses (inactive pills) would have concluded the 196 day study medication course for the subject.

[b] According to Council for International Organizations of Medical Sciences (CIOMS) last intake prior to SAE was 30 Jan 2008 but SAE was dated 25 Jan 2008.

Reference: 5.3.5.3 Safety Summary DUB, Table 87, Report 5.3.5.1 A42568 and Report 5.3.5.1 A29849

Adverse events leading to discontinuation

In the EV/DNG tablets group, 27 (10.2%) subjects experienced 37 AEs that led to their discontinuation of study medication. In the placebo group, 9 (6.1%) subjects experienced 25 AEs that led to their discontinuation of study medication. The rates between the 2 studies for premature discontinuation of study medication due to AEs were similar. The most frequent events that led to discontinuation of study medication were nervous system disorders (headache, migraine) and psychiatric disorders (altered mood, libido decreased, emotional disorder). Six (2.3%) subjects in the EV/DNG tablets group and 4 (2.7%) subjects in the placebo group had one or more events in each of these System Class Orders (SOCs).

Rare events: and venous thromboembolism, cardiovascular events, neoplasms

In the Summary of Clinical Safety (section 2.7.4) special attention was drawn to cardiovascular events, cases of venous thromboembolism (VTE) and cancer, regardless of whether they were considered treatment-related or serious (see section 2.7.4.2.1.5).

- Neoplasms benign, malignant and unspecified (including cysts and polyps)

Five (1.9%) subjects reported an AE of the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps): breast cancer in situ (ductal carcinoma in situ), uterine leiomyoma (2 women), skin papilloma, and thyroid nodule in euthyreosis. The breast cancer was considered severe in intensity and possibly related to the study drug. A further treatment-related case was one of the uterine leiomyoma cases, the remaining 3 cases were assessed as not related to study drug. Apart from the breast cancer case, all other cases were considered moderate (both cases of uterine leiomyoma) or mild in intensity.

- Venous thromboembolism (VTE)

There were no venous thromboembolic events reported.

- Cardiovascular events

A total of two (0.8%) subjects treated with EV/DNG reported an AE of the SOC Cardiac disorders. One woman experienced a myocardial infarction in a woman with history of hyperlipidaemia and positive family history, severe in intensity that was considered serious and possibly related to study drug. The second subject experienced palpitations, considered mild in intensity and possibly related to study drug.
Additionally, hypertension (5 cases), hot flush (2 cases), phlebitis superficial and vein pain were reported. The following AEs were rated as ADRs: hot flush, hypertension, phlebitis superficial, and vein pain (1 woman each).

Conclusion MAH on rare events:
The exposure of EV/DNG-treated women in clinical studies is too limited to adequately quantify the risk of rare events such as VTE, other cardiovascular events, or cancer. It must be emphasized that clinical studies for marketing approval are not a reliable source for evaluating incidence rates of rare clinical events such as VTEs because they generally include too few women. As no epidemiological studies on the effects of E2 or EV-containing COCs exist, the warnings and precautions included in the draft labeling are derived from clinical and epidemiological data of EE-containing COCs. Whether these warning and precautions apply to EV/DNG is unknown. Nevertheless, the findings obtained for EV/DNG did not give rise to any new ADRs other than those already known for COCs.

Clinical laboratory evaluations
Safety laboratory variables included hematology, serum chemistry, special serum chemistry parameters (hormones and SHBG (SHBG only at screening and final visit), and urine (glucose, total protein and negative log of hydrogen ion concentration (pH)) compared treatment or in case of premature discontinuation).
Efficacy laboratory variables: hematocrit, hemoglobin, and ferritin.

- *Hematology*

The mean values for all hematology parameters were similar between treatment groups at each time point, except for hematocrit and hemoglobin, which were analyzed as efficacy variables.
The mean values were similar between treatment groups at baseline, but slightly higher in the EV/DNG tablets group at Visit 11, suggesting an improvement under treatment with EV/DNG tablets regarding these parameters.

- *Serum chemistry:*

The mean and median values were within the normal ranges for all chemistry parameters at all time points with the exception of ferritin and SHBG.
Ferritin was analyzed as an efficacy variable in the DUB studies. Descriptive statistics for ferritin show an improvement under treatment with EV/DNG tablets.

The mean baseline levels of SHBG were within the reference range and comparable for both treatments. Following 7 treatment cycles, the mean and median SHBG concentrations increased for EV/DNG whereas they remained nearly unchanged for placebo. As expected, because COC use is associated with an increase in SHBG, the levels of SHBG increased during EV/DNG treatment other than placebo.

Vital signs
Vital signs included measurements of heart rate, systolic and diastolic blood pressure. No relevant changes were observed for any of the treatment groups with respect to vital signs.

Gynaecological examinations

- Cervical smears and endometrial biopsy were evaluated in the Qlaira PAC (Post-approval commitment) which is discussed in PSUR 1, see also postmarketing experience.

Endometrial safety
As a post approval commitment (PAC) for Qlaira in the EU, reports of the endometrial and cervical safety results of the two clinical phase 3 studies, A29849) and A42568 performed with Qlaira that support the proposed new indication “Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception” have already been submitted in March 2009. It was

concluded in June 2009 that the PAC has been fulfilled. “The results of these two studies do not reveal any new safety issue at the level of cervical and endometrial safety. The currently available data on endometrial and cervical safety during treatment with Qlaira are sufficiently large to conclude that the effects of Qlaira did not raise a safety concern on this point different from that known from approved COCs.

Post marketing experience
The first launch of Qlaira® was in the EU on 07 May 2009 in the Czech Republic and in Slovakia. Until 08 September 2009 Qlaira has been marketed in 13 countries.
PSURs
The first Qlaira PSUR with a reporting period 14 Oct 2008 – 08 Mar 2009 was submitted in May 2009. As committed, the two PACs discussed above were covered by this PSUR. The review of the PSUR safety data did not reveal new safety issues that warrant an update of the SPC of Qlaira. The benefit-risk remains favorable.

Further PACs for Qlaira in the EU were made to the Risk Management plan

1. Soon after the launch of EV/DNG15, a large comparative post-marketing safety surveillance study will be conducted to assess the VTE risk of EV/DNG compared to other COCs in a non-selected target population, (INAS-EV) and a preferential prescribing monitoring program (observational study). The applicant will take care that unexpected market uptake or incidence rates will not violate the power of the post-marketing VTE and preferential prescribing studies,
2. As outlined in the INAS-EV study protocol, data on pregnancies, including data on return to fertility and pregnancy outcomes will be gathered. The results of the INAS-EV study with data on return to fertility and pregnancy outcomes will be provided.
3. As outlined in the INAS-EV study protocol, all women who receive a new prescription for a COC at the participating centres will be asked to participate in the study. Thus, also women below the age of 18 years taking Qlaira will be included. The results of the INAS-EV study with data in adolescents below 18 years will be provided.

INAS-SCOREstudy
As committed, the International Active Surveillance Study of Women taking EV/DNG (INAS- SCORE study previously named INAS-EV study) has started in September 2009 in the EU. The primary objective of the study is to assess the risks of short and long-term use of estradiol valerate/dienogest (EV/DNG) and of established oral contraceptives (OCs) in a study population that is representative for the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes.The secondary objectives are:

1) To analyze the drug utilization pattern of EV/DNG and established OCs in a study population that is representative for typical use of the individual preparations under routine medical conditions;
2) To investigate pregnancy related data on discontinuation of EV/DNG and established OCs. i.e. return to fertility and pregnancy outcomes;
3) To investigate risks of short and long-term use of EV/DNG in adolescents below the age of 18 years. The INAS-EV study start was acknowledged end of October 2009.

The 2nd Qlaira PSUR with a reporting period 09 Mar 2009 – 08 Sep 2009 has been submitted in November 2009. As committed, a PAC was covered by this PSUR. In addition to the PAC to closely monitor endometrial safety with Qlaira in the postmarketing period and to evaluate spontaneous reports, as well as reports from literature, clinical and observational trials on endometrial safety, as a conclusion of the first PSUR, cardiovascular events, including myocardial infarction were closely monitored. The evaluation is ongoing.

Ongoing studies
Four Phase 3b studies for further profiling of EV/DNG tablets are currently ongoing. There are currently no plans to seek a labeling change based on the results of any of these studies.

Study 1
The primary objective of this study is to show superiority of EV/DNG tablets to Ortho Tri-Cyclen Lo with regard to the change in frequency and intensity of the hormone withdrawal-associated symptoms of pelvic

pain or headache, during cycle days 22 to 28 from Baseline to Cycle 6. 272 subjects were randomized and 28 of these prematurely discontinued. One woman experienced an unlisted, serious adverse event, assessed as not associated by the investigator or the sponsor, as the 27 year old woman was not yet randomized. The subject died due to a congenital malformation of the brain (Arnold-Chiari malformation). So far, two pregnancies have been reported before start of treatment (SOT). Three pregnancies were reported.

Study 2
The second study is nearly identical to study 13108. The comparator used is Microgynon. 138 women have been randomized, 4 of them prematurely discontinued. So far no SAEs or pregnancies have been reported.

Study 3:
The primary objective of the third study is to show non-inferiority of EV/DNG tablets to Microgynon on libido in women with acquired female sexual dysfunction (FSD) associated with OC-use. 119 women have been randomized of which 6 prematurely discontinued. 2 SAEs (1 DVT in a 23 year old woman, about 2.5 months after SOT; 1 acute appendicitis before SOT), but no pregnancies have been reported.

Study 4:
The fourth study (91781) is to show superiority of EV/DNG over EE 20/LNG 100 on primary dysmenorrhea after 3 cycles of treatment (approximately 3 months).
Women aged between 14-50 years suffering from primary dysmenorrhea with a need for oral contraception will be treated for 3 cycles either with EV/DNG tablets or with EE 20/LNG 100.
36 women randomized were randomised and no drop-outs. So far no SAEs but one pregnancy before SOT have been reported.

Comment RMS:
The safety profile observed in both DUB studies does not indicate any additional safety issue than seen in the contraception studies performed with Qlaira.

III.4 Pharmacovigilance System

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance.

III.5 Risk Management Plan

Performed and planned/ongoing risk minimization activities are described in Section 3 and 5 of the EU Risk Management Plan.

Summary of the EU Risk Management Plan:

Safety concern	**Pharmacovigilance activities (routine and additional)**	**Risk minimisation Activities (routine and additional)**
Preferential prescription of EV / DNG tablets to high-risk population	Routine pharmacovigilance	Preferential prescribing monitoring program (observational study)
Risk of VTEs and ATEs Performance of a Postmarketing	Safety Surveillance Study	None

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Benefit

The indication requested has been changed to 'Treatment of heavy menstrual bleeding in women without organic pathology, as the number of women with prolonged menstrual bleeding was considered too small.' The evidence in support of this revised indication is sufficiently robust and considered clinically relevant, which conclusion is based on the following considerations:

The efficacy results of both randomised double-blind placebo-controlled studies (US study + EU-Australia study) have adequately documented a clinically relevant treatment effect of Qlaira over placebo in the treatment of DUB. This conclusion is based on the following considerations:

- Adequate inclusion criteria were applied, providing that only those women were included who were objectively diagnosed as definitely having DUB.

- The primary efficacy variables applied were very stringent and consisted of the following:

  - Part 1 of the primary efficacy variable selected, i.e**. the overall success rate**, is considered the most stringent responder analysis, as it accepts only a 100% response:
    The overall success rate is defined as the number of subjects with the absence of any DUB symptom and who have met **all** the relevant criteria for success during the 90-day efficacy assessment phase, as compared to the number of subjects having at least one qualifying DUB symptom during the run-in phase. For subjects who were randomized with ***excessive bleeding***, e.g., the menstrual blood loss decrease had to be at least 50%, and for subjects randomized with ***prolonged bleeding***, e.g., the decrease in the bleeding episode of maximum (max) length had to be at least 2 days.

    In the ITT population, the proportion of responders in the EV/DNG group was ***29%, 29%, and 30%*** for the pooled analysis, Study A29849, and Study A42568, respectively, compared to ***2%, 2%, and 1%*** in the placebo group.

  - Part 2 of the primary efficacy variable selected was the "**overall success**" **of the study**, for which two criteria were to be fulfilled:
    - The proportion of responders in the EV/DNG arm must be statistically significantly greater than the proportion of responders in the placebo arm. This criterion was tested by the analysis of the primary efficacy variable ("***overall success rate***") using the ITT population, see part 1.

    But also:
    - The proportion of responders in EV/DNG arm must be at least 50%.
      This criterion was tested by calculating point estimates for the proportion of responders for (1) the ITT population and (2) the ITT population excluding "non-responders, missing values".
      However, the protocols of both studies, as agreed with the FDA and the MEB, allow for some flexibility and state that, in case of a response in the EV/DNG group of below 50%, the clinical significance has to be established with the help of secondary efficacy outcomes.

      In the ITT population excluding non-responders due to missing data, the proportion of responders in the EV/DNG group was ***42%, 44%, and 41%*** for the pooled analysis, Study A29849, and Study A42568, respectively, compared to ***3%, 4%, and 2%*** in the placebo group.

    However, it is noted that for the sample size determination defined in the protocols, it was assumed that 50% of subjects in the EV/DNG group and 20% of subjects in the placebo group would qualify as responders with respect to the primary efficacy variable.
    The placebo response was very low. There are however only few placebo-controlled studies in public literature on DUB. Of these, very low placebo responses in DUB were noted. Further, there is only one adequate but small study (1991) in which efficacy of a COC in DUB was evaluated. As already indicated, in the absence of adequate evidence in public literature, the assumed response

rate of 20% in placebo group versus a 50% response with DNG/EV was therefore considered an educated guess.

It need further be taken into account that the chosen primacy efficacy analyses applied in both studies are very different from that in published studies, i.e. the primary efficacy variable selected is the most stringent responder analysis, as it accepts only a 100% response. Nevertheless, the difference between active and placebo treatment is in line with that assumed in the sample size calculations, i.e. the size of the treatment effect for the pooled EV/DNG group (ITT population excluding non-responders due to missing data) is 39% (i.e., 42% - 3%), is greater than the assumed 30% treatment effect (by 30%) that was originally anticipated in the sample size calculations (i.e. success rate 50% for the EV/DNG group compared to 20% for the placebo group).

- As a 2nd criterion for overall success of each study, the point estimate for the proportion of responders in the treatment arm EV/DNG should be at least 50%. This criterion was not met.
  In the ITT population excluding non-responders due to missing data, the proportion of responders in the EV/DNG group was 42%, 44%, and 41% for the pooled analysis, Study A29849, and Study A42568, respectively, compared to 3%, 4%, and 2% in the placebo group. These were 29%, 29%, and 30%, in the EV/DNG group and 2%, 3%, and 1%, in the placebo group when also the non-responders due to missing data were taken into account.

  However, it is noted that for the sample size determination defined in the protocols, it was assumed that 50% of subjects in the EV/DNG group and 20% of subjects in the placebo group would qualify as responders with respect to the primary efficacy variable.
  The response in the placebo group however, was minimal (2 responders in Study A29849 and one in Study A42568) and far below the assumed 20%. When taking this into consideration, when interpreting the observed response rates in EV/DNG subjects in relation to the pre-defined threshold of 50%, it can be concluded that the observed difference versus placebo is nevertheless in the same range, i.e. 30% greater proportion of successful responders.

- *Contribution of Secondary efficacy endpoints*
  Though the secondary endpoints were not powered for statistical significance, clinically relevantly larger improvement versus placebo-treatment was noted for secondary endpoints evaluated. Especially the large difference in percentage of women 'cured' from excessive bleeding, the considerable drop in menstrual blood loss volume (MBLV) and sanitary protection is considered substantially contributing to a clinically relevant effect.

- *Comparison of efficacy of other treatments licensed for DUB (Mirena, progestagen, tranexamic acid) see also table in introduction of this Annex*
  The noted improvements are difficult to compare to the efficacy noted in public literature, as the number of active- and placebo-controlled studies is limited and the methods used to evaluate efficacy in DUB are far from uniform.
  Indirect comparison to the standard of care, i.e. levonorgestrel-IUD (***Mirena***® MAH BSP) is based on the results obtained in the pivotal clinical study 309849 submitted at the FDA in support of the application for the indication heavy menstrual blood loss. This study compared Mirena versus medroxyprogesterone (***MPA***) 10 mg/day on the 16th day of menstrual cycle, for 10 consecutive days for during 6 cycles in patients with DUB. Mirena was shown to reduce absolute MBL (median blood loss) from baseline to End-of-study with -128.8 mL LNG IUS versus -17.7 mL MPA. The percentage women in whom MBL had decreased 50% or more was 85% versus 27% for MPA.
  The additionally submitted Mirena-like analysis of bleeding data obtained with ENG/EV indicated absolute reduction in MBL to be in the same range as noted for Mirena (from 167 mL baseline to 59.6 mL end study; difference -113.1mL and from 182.3 mL to 31.8 mL at end study; difference -132.7 mL) in study 308961. The proportion of women with 50% or more decrease in MBL from baseline somewhat lower; 56.8% and 78.8% in both studies, respectively.
  Indirect comparison of these results suggests that efficacy of Qlaira with regard to reduction MBL is in the range of that noted for Mirena though the proportion of women with 50% or more reduction in MBL was somewhat lower but far better than noted for MPA.
  Tranexamic acid is reported to reduce MBL with 47-53%.

- *Comparison to efficacy in DUB noted with COCs*
  As to the off-label use of COCs in DUB, these are frequently used and recommended in the treatment of DUB. However, this is based on expert opinion only, as their assumed efficacy is not evidence-based.
  According to the recently published Cochrane review[9] there is only one clinical study available that fulfilled the Cochrane requirements, the study by Fraser and McCarron in 1991. This means that although COCs are used of-label in the treatment of DUB, there is no adequate clinical efficacy data available in the public domain.

Risk
Despite the higher mean age of women treated in this indication, i.e. 38 years, the safety profile observed in both DUB studies is comparable with that shown in the contraception studies performed with Qlaira.

Benefit/risk
The benefit/risk ratio of Qlaira in the indication of treatment of DUB is considered acceptable.

Overall conclusion
Agreement between member states was reached. The type II variation was finished on 8 October 2010.

V Product information

Summary of Product Characteristics (SmPC)

The following changes in the SmPC have been agreed:

4.1 Therapeutic indications

Treatment of heavy menstrual bleeding in women without organic pathology who desire oral contraception".

5.1 Pharmacodynamic properties

Qlaira is dosed using an estrogen step-down and a progestin step-up regimen that can be used to treat heavy menstrual bleeding in the absence of an organic pathology, symptoms sometimes referred to as dysfunctional uterine bleeding (DUB).

Two multicenter, double blind randomised studies of similar design were performed to evaluate the efficacy and safety of Qlaira in women with symptoms of DUB who desired oral contraception. In total, 269 women were randomised on Qlaira and 152 patients on placebo. After 6 months of treatment the median menstrual blood loss (MBL) was decreased by 88% from 142 mL to 17 mL in the Qlaira group compared to 24% from 154 mL to 117 mL in the placebo group.

After 6 months of treatment, the proportion of women who were completely cured from any DUB symptom was 29% in the Qlaira group compared to 2% in the placebo group.

In addition section 4.8 has been updated.

Package Leaflet (PL)

The new indication has been added to the PL as follows:

[9] Iyer V, Farquhar C, Jepson RG. Oral contraceptive pills for heavy menstrual bleeding (Review) In: Cochrane Database of Systematic Reviews, Issue 2, 2009. CD000154

Qlaira is used for the treatment of heavy menstrual bleeding (not caused by any disease of the womb) in women who wish to use oral contraception.

In addition chapter 4 (Possible Side effects) has been updated.

It was agreed with the MAH that a new user test is not required for these changes in the PL. Bridging to the results of user testing submitted during the initial registration procedure of Qlaira is adequate.

List of abbreviations

ADR	Adverse Drug Reactions
COC	Combined Oral Contraceptive
DNG	Dienogest
DUB	Dysfunctional Uterine Bleeding
EV	Estradiol Valerate
FDA	Food and Drug Administration (US)
ITT	Intention to Treat
IUS	Intrauterine System
MBLV	Menstrual Blood Loss Volume
MPA	Medroxyprogesterone
NDA	New Drug Application
NICE	National Institute for Health and Clinical Excellence
NSAID	NonSteroidal Anti-Inflammatory Drugs
PAC	Post Approval Commitment
SAE	Serious Adverse Events
SOC	System Class Orders
VTE	Venous Thromboembolism