25 March 2021
EMA/212533/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Drovelis

International non-proprietary name: drospirenone / estetrol

Procedure No. EMEA/H/C/005336/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
ALT	alanine aminotransferase
APC	activated protein C
APTT	activated partial thromboplastin time
ASMF	Active substance master file
ATC	anatomic therapeutic class
ATR	Attenuated total reflectance
AUC	area under the curve
BCRP	breast cancer resistance protein
BMI	body mass index
CEP	Certificate of Suitability
CHC	combined hormonal contraceptive
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum plasma concentration
COC	combined oral contraceptive
COSY	Correlated Spectroscopy
CQA	Critical quality attribute
CRP	C-reactive protein
CV	coefficient of variation
CWB	continued withdrawal bleeding
CYP	cytochrome P450
DHT	dihydrotestosterone
DNG	dienogest
DRSP	drospirenone
DSC	Differential scanning calorimetry
DSG	desogestrel
E1	estrone
E2	estradiol
E2V	estradiol valerate
E3	estriol
E4	estetrol (monohydrate)
EE	ethinylestradiol
EMA	European Medicines Agency
ER	estrogen receptor
EWB	early withdrawal bleeding
F1+2	prothrombin fragments 1+2

FCT	film coated tablet
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FT-IR	Fourier-transform infrared spectroscopy
GCP	Good Clinical Practice
HCV	hepatitis C virus
HDL	high-density lipoprotein
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High performance liquid chromatography
HR-MS	High Resolution Mass Spectrometry
ICH	International Council for Harmonization
IR	Infrared spectroscopy
ITT	intention-to-treat
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LH	luteinizing hormone
LNG	levonorgestrel
PAI-1	plasminogen activator inhibitor-1
Ph. Eur.	European Pharmacopoeia
NMR	Nuclear magnetic resonance
p-gp	p-glycoprotein
PK	pharmacokinetics
PP	per protocol
ppm	Parts per million
QTc	QT interval corrected for heart rate
QTPP	quality target product profile
RA	Risk assessment
R_{AC}	accumulation ratio for the area under the plasma concentration-time curve
ROESY	Rotating frame Overhauser Spectroscopy
SHBG	sex hormone binding globulin
SOC	system organ class
SULT	sulfotransferase
TEAE	treatment-emergent adverse event
TFPI	free tissue factor pathway inhibitor
TGA	Thermogravimetric analysis
T_{max}	time to reach maximum concentration
t-PA	tissue plasminogen activator
UDU	Uniformity of dosage units
UGT	uridine diphosphate -glucuronyltransferase
US	United States
USP	United States Pharmacopeia

UV	Ultraviolet
VAL	valproic acid
V_{max}	maximum velocity
VTE	venous thromboembolism
WY	woman-years
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gedeon Richter Plc. submitted on 24 January 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Drovelis, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 March 2019.

The applicant applied for the following indication: oral contraception.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0478/2020 on the agreement of a paediatric investigation plan (PIP) and granting of a partial waiver for subsets of the population.

At the time of submission of the application, the PIP P/0359/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance estetrol monohydrate contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
18 October 2012	EMEA/H/SA/2407/1/2012/SME/III	Dr Caroline Auriche, Prof. Brigitte Blöchl-Daum
19 November 2015	EMEA/H/SA/2407/1/FU/1/2015/SME/II	Dr Peter Mol, Dr Marleen Laloup
17 December 2015	EMEA/H/SA/2407/2/2015/SME/II	Dr Ira Palminger Hallen, Dr Peter Mol
20 September 2017	EMEA/H/SA/2407/1/FU/2/2017/SME/III	Prof. Minne Casteels, Dr Kolbeinn Gudmundsson
25 January 2018	EMEA/H/SA/2407/1/FU/3/2017/SME/III	Dr Carin Bergquist, Dr Walter Janssens, Dr Jeanette McCallion

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Change in manufacturing process of starting material: appropriateness of comparability analysis
- Need to include polymorphism as part of the drug substance specifications
- Impurity specifications
- ADME characterisation
- Repeat-dose toxicity studies
- Genotoxicity studies
- Carcinogenicity studies
- *In-vivo* and *in-vitro* characterisation of drug metabolism and drug-drug-interactions
- Environmental risk assessment plans
- Overall non-clinical strategy
- Phase 1 and 2 studies to support dose regimen
- Characterisation of clinical pharmacokinetics
- Investigation of effects on coagulation, lipid metabolism, carbohydrate metabolism and endocrine functions
- Confirmatory efficacy/safety study plans: contraceptive efficacy, time to return to fertility, need to analyse effects on cervical mucus
- Need for clinical drug-drug-interaction studies
- Need for thorough QT study
- Plans for a post-authorisation study to investigate effects on bone
- Characterisation of effects on ovarian function

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Paula Boudewina van Hennik

The application was received by the EMA on	24 January 2020
The procedure started on	27 February 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	19 May 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 May 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 May 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 June 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 September 2020
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at the sponsor site located in Belgium and CRO site located in the USA, between 8-18 September 2020. The outcome of the inspection carried out was issued on	03 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	20 October 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 October 2020
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	06 November 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	12 November 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 January 2021

The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	21 January 2021
The CHMP agreed on 2nd List of outstanding issues in writing and to be sent to the applicant on	28 January 2021
The applicant submitted the responses to 2nd CHMP List of Outstanding Issues on	23 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to 2nd List of Outstanding Issues to all CHMP members on	10 March 2021
The Rapporteurs circulated Updated Joint Assessment Report on the responses to 2nd List of Outstanding Issues to all CHMP members on	19 March 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Drovelis on	25 March 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

This is a complete (Article 8.3 of Directive 2001/83/EC, as amended) application for a new combined oral contraceptive product, Drovelis. The proposed therapeutic indication reads:

Oral contraception.

The decision to prescribe Drovelis should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Drovelis compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

2.1.2. Epidemiology

Drovelis is a contraceptive product. Hence, it is not intended to treat a disease and information about epidemiology, pathogenesis and diagnosis are not applicable.

2.1.3. Management

Several contraceptive methods for use by females are already available, both hormonal and non-hormonal. However, since women have different needs and experiences (e.g. side effects, and poor bleeding patterns) with some methods, there can still be a place for a new combined hormonal contraceptive even if there is no large

unmet medical need.

The high EE-dosed early contraceptives were associated with a variety of side-effects, including some rare but serious venous thrombotic effects. To improve the clinical profile, the EE dose was stepwise reduced and more selective progestins were developed. The activity of the newer progestins also allowed further EE dose reduction. However, reductions of EE dose are associated with less acceptable bleeding profiles.

More recently, use of more natural hormones has been attempted with the goal of further improving the safety profile of CHCs, with a potentially less impact on haemostasis, lipid and carbohydrate metabolism compared to their synthetic analogues.

Estetrol (E4) is produced by the human foetal liver. E4 was first described by Diczfalusy and co. in 1965 (Haagen et al., 1965). It is produced only during human pregnancy and reaches the maternal circulation through the placenta. E4 binds very specifically to estrogen receptors (ER) α and β, with a 4- to 5-fold preference for ERα and displays a variety of estrogenic activities (Visser et al., 2008; Coelingh Bennink et al., 2008a). Human maternal plasma levels increase during pregnancy to achieve a plasma concentration ranging from 0.4 to 1.2 ng/mL towards the end of gestation, while foetal plasma levels have been reported to be over 10 times higher than maternal plasma levels at parturition (Coelingh Bennink et al., 2008b). Being a natural estrogen, tolerated in very high concentrations in foetal and maternal tissue, E4 was considered an attractive candidate for use in CHCs.

Critical elements in the development of an E4-based combined oral contraceptive (COC) included the identification of a regimen that includes the proper type and dose of progestin, leading to a combined product demonstrating:

1. strong suppression of ovarian function, and therefore good contraceptive efficacy;

2. predictable and acceptable vaginal bleeding profile;

3. good overall safety and tolerability; and

4. less pronounced effects on metabolic parameters than currently available CHCs.

About the product

Drovelis contains a new oestrogen, estetrol (E4), not previously included in any combined hormonal contraceptive (CHC) or any other product. It also contains the well-known progestagen drospirenone (DRSP).

Combined hormonal contraceptives are well established since long and their primary mode of action is inhibition of ovulation.

The claimed indication is '*Oral contraception*' with the additional wording, which is standard for CHCs, that '*The decision to prescribe Drovelis should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Drovelis compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).*'

The posology follows a 24/4-day cyclic regimen; one film-coated tablet is to be taken daily for 28 consecutive days. Each pack starts with 24 pink active tablets, followed by 4 white placebo tablets. The next pack is started immediately after finishing the previous one, without a break in daily tablet intake and irrespective of presence or absence of bleeding. Withdrawal bleeding usually starts on day 2-3 after starting the white placebo tablets

and may not have finished before the next pack is started.

Type of Application and aspects on development

The clinical development programme started with four clinical trials conducted to identify the optimum combination of estetrol (E4) and progestogen in terms of the dose of E4 and the type of progestogen.

When the dose and progestogen had been decided, the contraceptive efficacy, bleeding control and safety of the chosen 3 mg DRSP/15 mg E4 (monohydrate)/ combination was studied in two pivotal Phase 3 studies; MIT-Es0001-C301 and MIT-Es0001-C302. These are both multicentre, open-label, single-arm studies. Study MIT-Es0001-C301 was performed in Europe and Russia and MIT-Es0001-C302 was performed in the US and Canada.

Overall, the Scientific advice from the CHMP has been followed.

For hormonal contraceptives, the EMA guideline "EMEA/CPMP/EWP/519/98 Rev 1" from 2005 is applicable for this product. This guideline has overall been followed.

A Phase 3 study in 12- to 17-year olds is planned as part of the PIP (study number ES-0001-C401). Date of completion is December 2021.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a combination product containing two film-coated tablets: one active tablet and one placebo. Each pink active tablet contains 3 mg drospirenone and estetrol monohydrate equivalent to 14.2 mg estetrol as active substances. Each white placebo tablet does not contain any active substance(s).

For the pink active film-coated tablets, the other ingredients are:

Tablet core: Lactose monohydrate, sodium starch glycolate, maize starch, povidone K30, magnesium stearate (E470b);

Tablet coating: Hypromellose (E464), hydroxypropylcellulose (E463), talc (E553b), cottonseed oil, hydrogenated; titanium dioxide (E171); iron oxide red (E172)

For the white placebo film-coated tablets, the other ingredients are:

Tablet core: Lactose monohydrate, maize starch, magnesium stearate (E470b);

Tablet coating: Hypromellose (E464), hydroxypropylcellulose (E463), talc (E553b); cottonseed oil, hydrogenated; titanium dioxide (E171).

The product is available in transparent PVC/aluminium blister containing 28 film-coated tablets (24 pink active tablets and 4 white placebo tablets), as described in section 6.5 of the SmPC.

2.2.2 Active substance - Estetrol monohydrate

General information

The chemical name of estetrol monohydrate is (8R,9S,13S,14S,15R,16R,17R)-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,15,16,17-tetrol monohydrate corresponding to the molecular formula $C_{18}H_{24}O_4.H_2O$. It has a molecular mass of 322.40 g/mol and the following structure:

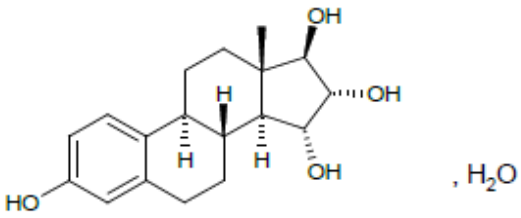


Figure 1: Estetrol monohydrate structure

The chemical structure of estetrol monohydrate was elucidated by a combination of elemental analysis, IR, ATR-IR, ^{1}H-NMR, ^{13}C-NMR (including NMR spectra: ^{1}H, ^{13}C{1H}, H-H COSY, HSQC (multiplicity edited), HMBC (double low pass filter) and 2D ROESY.), HR/MS and UV. The solid state properties of the active substance were measured by single crystal X-ray diffraction analysis and TGA-DSC/MS.

Estetrol monohydrate is a micronised white to off-white crystalline solid, poorly soluble in water and aqueous solutions. Estetrol monohydrate is slightly hygroscopic.

Estetrol monohydrate exhibits stereoisomerism due to the presence of seven chiral centres. Estetrol monohydrate crystallises as a pure enantiomer. Enantiomeric purity is controlled routinely by specific optical rotation. During the procedure adequate information has been provided by the ASMF holder confirming that interconversion of the stereo-centres present in the active substance does not take place during storage.

Polymorphism has been observed for estetrol monohydrate. Several forms have been identified as supported by experimental data. A detailed discussion of the polymorphic forms has been provided, substantiating that only one polymorph is manufactured by the ASMF holder. Polymorphism is controlled in the active substance specification by high resolution XRPD. During the procedure data has been provided demonstrating that the polymorph of the active substance is stable also during storage.

Although estetrol is a natural recurring molecule synthetised in the liver of the foetus, it is considered to be a new active substance as it has not been previously authorised in the European Union and it does not expose the patient to the same therapeutic moiety as an already authorised active substance since it is not a derivative or metabolite in the target population.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Estetrol monohydrate is synthesised using commercially available well-defined starting materials with acceptable specifications.

The description of the manufacturing process and in-process controls was updated with further details during the procedure. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Estetrol monohydrate is packaged in double polyethylene bags, which comply with the EC directive 2002/72/EC and EC 10/2011 as amended, placed in a polyethylene drum.

Specification

The active substance specification includes tests for: appearance (visual), identification (IR, HPLC, XRPD), assay (HPLC), purity (HPLC), residual solvents (GC), specific optical rotation (Ph. Eur.), water content (KF), sulphated ash (Ph. Eur.), elemental impurities (ICP-MS), particle size distribution (laser granulometry), microbiological test (Ph. Eur.).

During the procedure, the specification tests applied by the finished product manufacturer have been brought in line with those applied by the active substance manufacturer; the test limits have been tightened, in line with batch data and stability data, and are compliant with regulatory requirements.

Limit for elemental impurities and limits for potentially genotoxic impurities, set in line with ICH Q3D and ICH M7 respectively, are considered safe and accepted.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Adequate validation data has been provided for the identity test by XRPD. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from four commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three full scale batches of active substance from the proposed manufacturer stored in the intended commercial container closure system for up to 36 months under long term conditions (25 ºC / 60% RH), for up to 36 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The parameters tested are the same as for release, unless otherwise justified as discussed in the finished product pharmaceutical developmentThe analytical methods used were the same as for release and were stability indicating.

No significant changes were observed in any of the monitored parameters and all tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on samples of the active substance. Results on stress conditions (heat and heat-humidity on the dry active substance and acidic, alkaline and oxidative conditions on the active substance in solution) were also provided on samples of the active substance. No significant degradation was detected under heat, heat-humidity, acidic and light induced photodegradation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period with no special storage conditions, when stored in the proposed container.

Active substance - Drospirenone

General information

The chemical name of drospirenone is (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimetylspiro-[17H-dicyclopropa[6,7:15,16]cyclopenta[a]phenantrene-17,2'(5'H)-furan]-3,5'(2H)-dione corresponding to the molecular formula $C_{24}H_{30}O_3$. It has a molecular mass of 366.501 g/mol and the following structure:

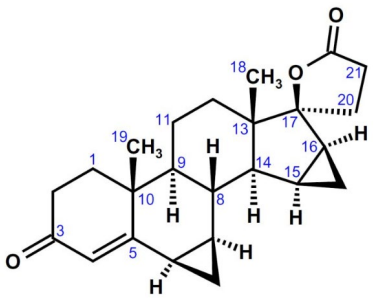


Figure 2: Drospirenone structure

The active substance is a white or almost white powder, it is practically insoluble in water, sparingly soluble in methanol, freely soluble in some organic solvents. Drospirenone is slightly hygroscopic. It is degraded in acidic media.

Drospirenone exhibits stereoisomerism due to the presence of 10 chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation, performed as per Ph. Eur. Micronised drospirenone is used in the finished product.

Polymorphism has not been observed for drospirenone.

As there is a monograph of drospirenone in the European Pharmacopoeia, the proposed suppliers of the active substance have been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for micronised drospirenone which have been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability for the proposed suppliers. The manufacturers responsible for the synthesis and the micronisation of drospirenone are listed in the CEP.

Drospirenone from the proposed suppliers is packaged in double polyethylene bags, which comply with the EC directive 2002/72/EC and EC 10/2011 as amended, placed in a fibre drum, or in a polypropylene container or in a multilayer aluminium bag (polyester/aluminium/polyamide/polyethylene) placed in a cardboard box.

Specification

The active substance specification includes tests for appearance (visual inspection), identification (specific optical rotation and IR, both Ph. Eur.), related substances (Ph. Eur.), loss on drying (Ph. Eur.), assay (Ph. Eur.) residual solvents (GC), particle size distribution (laser diffraction) and elemental impurities (ICP-MS).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents, particle size and elemental impurities in line with the additional tests listed in the CEP. All additional methods have been adequately validated and described according to ICH Q2.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Altogether batch analysis data from eight full scale batches of active substance from the manufacturersare provided. The results are within the specifications and consistent from batch to batch.

Stability

Retest period has been established based on the retest period state of the CEP or based on stability results.For one manufacturer stability data from three full scale batches of active substance stored in the intended commercial closure for up to 60 months under intermediate conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided The stability results justify the proposed retest period with no specific storage condition in the proposed container.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable.

2.2.3 Finished medicinal product – Active tablet

Description of the product and Pharmaceutical development

The active tablets are pink, round, biconvex film-coated tablets, with a drop-shaped logo embossed on one side. The tablet has approximately a diameter of 6.1 mm and a thickness of 2.8 mm.

The quality target product profile (QTPP) was defined as an immediate release dosage form with an adequate shelf life in its primary container closure system.

The formulation and manufacturing development have been evaluated through the use of risk assessment (RA) to evaluate the impact that each active substance attribute could have on the finished product critical quality attributes (CQAs).

During the RA, adequate argumentation has been provided confirming the polymorphic form of estetrol is stable during the manufacturing of the finished product and during storage. No polymorphism has been observed for drospirenone. Both substances are micronised and their specifications include limits for particle size. It was concluded that none of the active substance parameters, when used at the proposed specification, had a significant impact on the CQAs of the product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, when applicable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. The compatibility of the active substances with the excipients has been demonstrated. No incompatibilities were observed. Functionality Related Characteristics (FRC) of the excipients having a potential impact on the CQAs have been assessed

A RA of manufacturing process development with relevant risk mitigation has been provided and the critical process steps have been identified and justified during the procedure. No major changes of the process have been performed during development. Issues related to scale up have been satisfactorily addressed during the procedure.

The different formulations used during clinical studies have been well described. For the early phase II studies, 'mono' tablets including one of the active substances were used but the rest of the formulation was very similar to the final formulation. For the remaining phase II and all phase III clinical studies, combination tablets manufactured using the formulation intended for marketing were used.

The development of the QC dissolution method is clearly described. The proposed dissolution limits have been justified . The discriminatory power of the dissolution method has been satisfactorily demonstrated.

The primary packaging is transparent PVC/aluminium blister. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: sieving, dry blending, granulation, final blending), compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

During the procedure, the descriptions of the manufacturing steps has been integrated with the relevant details. The in-process controls are adequate for this type of manufacturing process.

Three consecutive production scale batches have been fully validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), average mass (in-house), water content (Ph. Eur.), identity for both active substances (HPLC and UV), uniformity of dosage units for both active substances (Ph. Eur.), assay for both active substances (HPLC), dissolution of both active substances (Ph. Eur.), related substances of both active substances (HPLC) and microbiological quality (Ph. Eur.).

Tests and limits have been justified in line with current regulatory guidance and pharmacopoeial requirements. The limits for impurities are set in accordance with ICH Q3B.

The dissolution limits have been fully justified during the procedure as discussed in the pharmaceutical development section.

Based on a RA on residual solvent, the control of residual solvent at the level of the active substances only is justified.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested to address a MO) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three full scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three full commercial scale batches of finished product stored for up to 48 months under long term conditions (25 ºC / 60% RH), for up to 48 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, assay, related substances, dissolution and microbiological quality. The analytical procedures used are stability indicating. All tested parameters were within the specification for all the three storage conditions.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. It was concluded that the tablets are adequately protected from light in the proposed container closure system as no degradation was observed.

The proposed hold times of compressible mixture of 1 month, when stored in stored in PE-bags in PE-container, tablet cores of 3 months and bulk film-coated tablets of 12 months are acceptable as supported by data.

Based on available stability data, the proposed shelf-life of 4 years, with no specific storage conditions, as stated in the SmPC (section 6.3) are acceptable.

Finished medicinal product – Placebo tablet

Description of the product and Pharmaceutical development

The placebo tablets are white to off-white, round, biconvex film-coated tablets, with a drop-shaped logo embossed on one side. The placebo tablet has approximately a diameter of 6.1 mm and a thickness of 2.8 mm.

All excipients are well known pharmaceutical ingredients and the quality of their components is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The aim of the pharmaceutical development of the placebo tablet was to develop an inert film-coated tablet with a simple composition, using well known and easy to handle manufacturing steps.

The formulation used during clinical studies is the same as that intended for marketing.

The primary packaging is transparent PVC/aluminium blister. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: dispensing, dry blending, compression (tableting), film-coating and packaging. The process is considered to be a standard manufacturing process.

A process validation has been carried out on three consecutive commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this a placebo tablet: appearance (visual), average mass (in-house), loss on drying (Ph. Eur.), disintegration (Ph. Eur.), identity (HPLC), microbiological quality (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested to address a MO) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three full scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three full commercial scale batches of finished product stored for up to 48 months under long term conditions (25 ºC / 60% RH), for up to 48 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, loss on drying, disintegration, and microbiological quality. The analytical procedures used are stability indicating. All tested parameters were within the specification for all the three storage conditions.

The proposed hold times of compressible mixture of 1 month, when stored in stored in PE-bags in PE-container, tablet cores of 3 months and bulk film-coated tablets of 12 months are acceptable, as supported by data.

Based on available stability data, the proposed shelf-life of 4 years, with no specific storage conditions, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4 Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product (both active and placebo tablet) has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor recommendations having no impact on the Benefit/Risk ratio of the product, which pertain the placebo tablet. . These points are put forward and agreed as recommendations for future quality development.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6 Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends two points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The combined oral contraceptive (COC) contains 15 mg of the new chemical entity E4 as the estrogen, as well as 3 mg of the progestogen drospirenone (DRSP), which is already used at this dosage in approved COCs.

Non-clinical studies with E4 alone were performed, to characterize its pharmacological properties, pharmacokinetic characteristics and safety profile. In addition, a number of publications on pharmacological characteristics of E4 have been included. DRSP is the progestogenic component of several COCs with ethinylestradiol (EE), including Yasmin (containing 3 mg DRSP/30 µg EE), Yasminelle and Yaz (containing 3 mg DRSP/20 µg EE). DRSP (4 mg daily) is also the component of the progestin-only birth control pill Slynd/Slynda. Data on pharmacological properties, pharmacokinetic characteristics and safety profile of DRSP from published sources have been included.

The use of COCs in the prevention of pregnancy is highly effective and long-established. COCs are however also associated with side effects, several of which are related to the estrogenic component. E4 was selected for development as a promising candidate to replace the currently available estrogens in COCs in order to reduce those side effects while retaining the contraceptive efficacy.

In establishing the program of pharmacokinetic and toxicology studies with E4, ICH guidance M3(R2), FDA Guidance for Industry on nonclinical evaluation of drug or biologic combinations (2006) and the EMA Guideline on the nonclinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005, 2008) were considered. In addition, guidance applicable to individual types of studies was taken into account.

Feedback from regulatory authorities was considered in the program and design of studies where applicable and relevant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The relative binding affinity (RBA) of E4 for human oestrogen receptors ERα and ERβ versus estradiol (E2) was between 1% and 4%, and in a transactivation assay around 0.4%. The RBA versus ethinylestradiol (EE) in the transactivation assay was 0.14% and 2.1%, respectively. E4 showed no antagonistic activity on either receptor in this assay. Activation of gene transcription by E4 was shown to be mediated via the oestrogen-responsive element (ERE).

Crystal structures of ERα-ligand binding domain complexed with E4, E2 and E3 (estriol) were reported to be similar and the binding affinity, determined by time-resolved fluorescence resonance transfer, of SRC3 for ERα-ligand complex was in the same order of magnitude for the three oestrogens. The pattern of ERα coregulators recruitment induced by E4 was highly similar to that elicited by E2, but E4 potency was lower. Data indicate that E4 has lower binding affinity for ERα as compared to E2, but still forms a complex with this receptor that binds to SRC3, almost as well as does the complex with E2.

The metabolites E4-3-glucuronide and E4-16-glucuronide showed weak oestrogenic activity with a potency approximately 3800 and 600 times lower than the potency of E4 in the ERα transactivation bioassay, respectively, and 400 times less in the ERβ bioassay for the E4-16-glucuronide (the E4-3-glucuronide did not produce a full dose response in the ERβ bioassay).

E2 (8 or 80 µg/kg/day) and E4 (1 or 6 mg/kg/day) given by the subcutaneous route for 3 weeks caused comparable increases in vaginal weight, epithelial height, epithelial proliferation, and lubrication in ovariectomized C57BL/6J mice. These vaginal responses to E4 were completely abolished in ERαAF2^{0}mice, lacking the Erα activation function AF2, indicating that the effects were entirely mediated by nuclear ERα activation.

In ovariectomized C57BL/6J mice, E4 (1 mg/kg) increased uterine luminal epithelial and stromal height and induced uterine epithelial proliferation. Its potency was ~1% of the potency of E2. E2-responsive genes in the uterus also responded to E4, with a potency 1/100 for most upregulated genes and 1/3 to 1/10 for most downregulated genes, as compared to E2.

E4 stimulated the growth of mammary gland epithelial ducts in prepubertal ovariectomized mice with a lower potency than E2. Progesterone receptor (PGR) proteins were expressed in the mammary epithelium of E4-treated mice, but not in ovariectomized (OVX) untreated mice and PGR mRNA was shown to be overexpressed under E4 treatment. In addition, the pure ERα antagonist ICI 182 780 completely blocked the elongation of the ductal tree induced by E4. These findings suggest that the epithelial growth stimulation was ERα-mediated. E4 was also shown to partially antagonize the effect of E2.

In a modified Allen-Doisy test in ovariectomized Sprague-Dawley rats, E4 caused a dose-related vaginal cornification, reduced terminal body weight and enhanced uterus weight. Its oestrogenic potency was higher after oral than after subcutaneous administration and was estimated to be 1/20th of the potency of EE.

When administered by oral gavage over the 4-day period of the oestrus cycle to female Sprague-Dawley rats, E4 inhibited ovulation with an ED50 of approximately 0.2 mg/kg bid. The anti-ovulatory potency of E4 was about

1/20th of that of EE and was also lower than the potency of E2. In New Zealand White rabbits, E4 inhibited ovulation and implantation with respective oral ED50s of 0.7 mg/kg bid and 0.06 mg/kg bid.

Secondary pharmacodynamic studies

Off-target receptor interactions
E4, at 10 µM, showed no interactions with a panel of 130 drug targets (receptors, transporters, ion channels) other than with its primary targets, the ERα and ERβ receptors. It might be noted that E4 did not bind to the progesterone, androgen or glucocorticoid receptors.

Studies in relation to breast cancer risk
E4 enhanced proliferation of normal human breast cells and MCF-7 breast cancer cells. Its potency towards normal breast cell proliferation was 1% of the potency of E2. Both nuclear (transcriptional activation) ERα activation and extra-nuclear (membrane-initiated steroid signalling (MISS)) pathways were involved. E4 also enhanced T47-D breast cancer cell migration and invasion, but with less potency than E2. The effect of E4 on breast cell proliferation and migration could be blocked with the anti-oestrogens ICI 182 780 and/or tamoxifen. E4 was also shown to attenuate the effects induced by E2 on breast cell proliferation, migration and invasion.

In vivo, E4 stimulated tumour growth in immunodeficient ovariectomized mice subcutaneously implanted with MCF-7 breast cancer cells with a ~3 times lower potency than E2 (growth at a dose of 10 mg E4/kg/day was similar to growth at 3 mg/kg/day E2), and partially antagonized E2-induced tumour growth in a dose-dependent manner. E4 inhibited the development of chemically induced mammary tumours in the dimethylbenz(a)anthracene (DMBA)-mammary tumour model in female Sprague-Dawley rats and seemed to inhibit tumour development as effectively as ovariectomy and the anti-oestrogen tamoxifen at high doses. E4 at 10 mg/kg/day even caused regression of existing tumours in this model.

Studies in relation to coagulation risks
The level of Sex Hormone Binding Globulin (SHBG) has been suggested to be a predictive marker for the risk of venous thromboembolism. E4 showed no affinity for human Sex Hormone-Binding Globulin (SHBG) and did not induce SHBG or corticosteroid-binding protein (CBG) production in ERα-expressing Hep89 cells. Both E4 and E2 caused a dose-dependent increase of the expression of tissue plasminogen activator (tPA), urokinase-type plasminogen activator (uPA) and tissue plasminogen activator inhibitor 1 (PAI-1) in HUVEC cells. E4 had a lower potency than E2 and antagonized the effects induced by high concentrations of E2 but did not impair the effects induced by low concentrations of E2.

Following chronic treatment, ovariectomized female mice exhibited a prolonged tail-bleeding time and were protected from arterial and venous thrombosis. In addition, E4 treatment decreased ex vivo thrombus growth on collagen under arterial flow conditions. In hematopoietic chimera mice with implanted bone marrow cells deficient for nuclear ERα, E4-induced protection against thromboembolism was significantly reduced, while the increased tail-bleeding time was not impacted by this deletion. Indicating that nuclear ERα activation contributes to the protective action of E4 against thromboembolism but it is not involved in the effect of E4 on primary haemostasis.

Studies on vascular effects
E4 induced rapid nitric oxide (NO) release, and endothelial nitric oxide synthase (eNOS) activation and expression in HUVEC cells with less potency compared with E2. The effect was inhibited by the ER antagonist ICI 182 780. E4 also attenuated E2-induced NO synthesis. E4 did not affect eNOS activation or NO production in mouse aorta *in vitro* but did antagonize E2-induced stimulation in this model. E4 was thus found, in rat, mouse

and human tissue, to have the capacity to inhibit the E2-induced vascular eNOS expression and NO release, which has a protective function in the cardiovascular system. Based on available literature, clinical safety concerns related to an inhibition of estrogen-induced eNOS activity and NO release in the presence of E4 are not expected since estrogens are not the major drivers of NO release supporting vasodilation and endothelial function, which is more stringently regulated by shear stress, temperature lowering and neurohumoral mediators. In addition, E4 is also shown to be able to induce vasodilation via an ER-dependent and NO-independent mechanism. E4 caused vasorelaxation of rat arteries with a lower potency than E2. The effect of E4 on vasorelaxation was mediated by both an endothelium-dependent (involving ERs) cGMP-mediated mechanism and an endothelium-independent mechanism involving inhibition of smooth muscle cell Ca2+ entry and contraction. E4 also reduced atheroma deposits in the aortic sinus in ERα+/+/LDLr /- ovariectomized mice, possibly via an ERα-dependent mechanism but had no effect on endothelial healing in ovariectomized C67BL/6J mice following carotid electric injury. However, E4 abolished the accelerated endothelial healing induced by E2 in this model. In an experimental model of femoral artery injury, E4 prevented neointimal hyperplasia to the same extent as E2.

E4, like E2, protected female ovariectomized mice against AngII-induced hypertension. The hypertensive effect of Ang II was significantly more exacerbated in ovariectomized mice or in mice lacking ERα, showing that the beneficial effect of endogenous oestrogen is ERα-dependent. Taken together, these data suggest potential vaso-regulatory properties of E4, albeit to a lower extent than E2.

Safety pharmacology programme

E4 was devoid of effects in a Functional Observation Battery in conscious female Sprague-Dawley rats up to and including a single oral dose of 15 mg/kg (~30 times clinical AUC). A slight decrease of rectal temperature at 1- and 2-hours post-dose was noted at 150 mg/kg, possibly explained by a slight increase in this parameter at these time points in the control group.

Compared to vehicle control, E4 at a concentration of 28.17 µM (~500x clinical Cmax) decreased hERG tail current amplitude by 7.1%, while the positive control E-4031 decreased hERG tail current amplitude by 83.6%. The effect on hERG is not considered to be of any toxicological significance.

E4 had no effect on heart rate, blood pressure or electrocardiogram parameters and did not induce arrhythmia in conscious telemetered female cynomolgus monkeys, at single oral dose levels up to and including the highest tested dose of 100 mg/kg (with 1 mg/kg giving an exposure somewhat higher than clinical AUC).

E4 did not affect respiratory parameters in conscious female Sprague-Dawley rats at single oral dose levels up to and including the highest tested dose of 150 mg/kg (more than 800 times clinical AUC).

The non-clinical pharmacological and safety-pharmacological characterization of estetrol is considered to be sufficient.

Drospirenone is a well-known compound and the non-clinical data presented regarding primary and secondary pharmacology as well as safety pharmacology is considered to be sufficient.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies with E4 have not been performed. Such studies were not considered warranted in view of the high selectivity of E4, its weak estrogenic potency compared to E2 and EE, and the well-established clinical profile of the latter compounds in COCs.

No publications have been consulted regarding pharmacodynamic drug interaction studies with DRSP. According to the Yasmin Prescribing Information (2017), Yasmin should not be used in subjects at risk for hyperkalaemia in view of the anti-mineralocorticoid activity of DRSP. According to the Yasmin Prescribing Information (2017) and the Yasmin Summary of Product Characteristics (2018), Yasmin is contra-indicated in subjects with renal impairment and serum potassium should be monitored in subjects on concomitant potassium-enhancing medication or strong CYP3A inhibitors. There is previous clinical experience with other products containing drospirenone and its pharmacodynamic drug interaction is being addressed in the SmPC.

2.3.3. Pharmacokinetics

Studies has been performed in female mouse, rat, monkey and rabbit (absorption and metabolism) to characterize the pharmacokinetic properties of E4, using validated LC-MS/MS assays for E4 and a validated UPLC-MS/MS method for DRSP in a 13-week repeat-dose toxicity study with the combination of E4 and DRSP.

Drospirenone

In view of the well-established use and proven clinical efficacy and safety of DRSP, pharmacokinetic studies with DRSP alone or with E4 and DRSP in combination have not been conducted, except for toxicokinetic evaluations in a 13-week oral repeat-dose toxicity study with E4/DRSP in female monkeys which included a DRSP-only group. Further pharmacokinetic data on DRSP were derived from publications on *in vitro* and/or clinical studies, as no data on pharmacokinetics in animals were found. This is acceptable.

Estetrol

Absorption

Oral bioavailability of E4 relative to the subcutaneous route of administration was estimated to be 70% or more in rats.

Tmax was 0.5 hour in mice and rats, and between 0.5 and 1.5 hours in cynomolgus monkeys. Both Cmax and AUC0-last increased with an increase in dose. Although there was some variability between studies within the same species, systemic exposure to E4 showed dose proportionality up to dose levels of 30 mg/kg/day in mice, 50 mg/kg/day in rats and 30 mg/kg/day in monkeys. At comparable dose levels, systemic exposure to E4 in Wistar rats after 13 weeks of dosing tended to be slightly lower (in terms of AUC) than that in Sprague-Dawley rats.

In mice and rats at dose levels up to 10 mg/kg/day and 15 mg/kg/day, respectively, AUC0-last was generally similar after single and multiple dosing, suggesting a lack of accumulation in plasma. Above these dose levels, AUC0-last was slightly lower after repeated administration compared to the first dose. In monkeys, AUC0-last tended to be slightly higher after repeated administration than after the first dose.

Plasma half-life of elimination (T1/2) was 1.5 – 3 hours in mice, 2 – 6 hours in rats and 10 – 19 hours in monkeys. In monkeys, plasma-concentrations-versus-time curves showed evidence of a second peak, suggesting the E4 undergoes enterohepatic circulation.

In mated/pregnant Wistar rats and pregnant New Zealand White rabbits, Tmax was 0.5 hour and between 0.5 and 3.0 hours respectively. Exposure to E4 was essentially dose-proportional up to 10 mg/kg/day in rats and 0.45 mg/kg/day in rabbits. At dose levels of 10 mg/kg/day and higher in rats and at 0.45 mg/kg/day in rabbits, Cmax was lower after multiple dosing than after the first administration. At these dose levels, AUC0-last was lower after repeated administration in rats but slightly higher in rabbits compared to the first dose.

Distribution

Radioactivity was extensively distributed in tissues of female non-pigmented Sprague-Dawley rats and partially pigmented Lister Hooded rats after a single oral dose of [14C]-E4 at 15 mg/kg. The highest radioactivity concentration was found in the liver at all time points post-dose. Tissue levels of radioactivity were below the limit of quantification in all tissues except liver and thyroid gland by 48 hours in non-pigmented rats (last sampling time point) and by 7 days post-dose (liver only) in partially pigmented rats (including melanin-containing tissues). No binding to melanin was indicated.

Plasma protein binding of E4 was 45 – 67% in mouse, rat, monkey and human. There was no indication of species-related differences or of concentration dependence up to 1000 ng/mL in animal plasma and 50 ng/mL in human plasma. E4 showed no binding to human sex hormone binding globulin (SHBG) and distributed equally between plasma and blood cells in human blood at concentrations up to 1 µM.

No placental transfer or milk excretion study has been performed. It is assumed that, since transfer from foetus to the mother occurs, there will also not be a barrier in the other direction. Data suggest that E4 is already produced by the foetal liver as early as in the 9th week of pregnancy and increases with increasing pregnancy duration. In the first trimester, maternal-foetal exchanges are limited. Furthermore, foetal E4 levels at term birth are higher than maternal, and highly variable, indicating that the transport of E4 from foetal to maternal circulation largely exceeds possible transport in the other direction. It is agreed that, considering the large inter-individual variability and the wide range of E4 exposure that exist in normal pregnancy, the amount of E4 that would be transferred to the foetus after E4/DRSP intake can be considered negligible in view of the high amounts of endogenous E4. With regard to excretion in breast milk, the applicant has provided an extensive overview of non-clinical as well as clinical data on E4 and other estrogens, showing that small amounts can be excreted in breast milk. No adverse effects were observed in offspring following exposure to estrogens via lactation. In addition, the foetus at term is producing high levels of estetrol and the newborn continue to produce endogenous E4 for several weeks after birth. It is agreed that additional exposure to small amounts via breast milk can be considered negligible.

In the SmPC, it is stated that "E4/DRSP is not indicated during pregnancy" and that "if pregnancy occurs while taking E4/DRSP, further intake must be stopped". Regarding breast-feeding "the use of CHCs should not be recommended until the breast-feeding mother has completely weaned her child and an alternative method of contraception should be proposed to women wishing to breastfeed".

Metabolism

E4 was extensively metabolized in hepatocytes from mouse, rat, rabbit, monkey and human. Metabolic pathways included direct glucuronidation and sulfation, hydroxylation combined with sulfation, hydroxylation combined with methylation, and hydroxylation combined with methylation and glucuronidation or sulfation. With the exception of the 3 glucuronide (A-ring), the exact metabolite structures could not be determined. Glucuronidation and sulfation were predominant reactions in hepatocytes from all species. Only a direct glucuronide (D-ring) and a direct sulfate (unconfirmed site) were found in human hepatocytes. These metabolites were also formed by the other species, notably rat and monkey. Methylation was an important

metabolic route in rat hepatocytes. Hepatocytes from three mouse strains showed no strain differences in metabolism of E4.

The major metabolites observed in human plasma were the E4-3-glucuronide and E4-16-glucuronide (17 and 62% of radioactivity at Tmax of 0.25-0.5 hour) and an E4-glucuronide-sulfate conjugate (9% of radioactivity). In an interspecies comparison study, the two glucuronides were identified in mouse and rat. The E4-3-glucuronide was a significant metabolite in rat and mouse plasma and in mouse urine and rat bile. The E4-16-glucuronide was not found at significant levels in mouse samples or rat plasma but was an important metabolite in rat urine and rat bile. The E4-glucuronide-sulfate conjugate was only noted at minor amounts in rat bile. In vivo metabolic pathways have not been studied in monkeys. No data on the levels of the two major human metabolites in plasma, the E4-3- and E4-16-glucuronide, is thus available. Since the two glucuronides have low pharmacological activity and glucuronidation and sulfation seem to be formed via direct reactions they are considered to be of no toxicological concern.

Excretion

After a single oral dose of 15 mg/kg to mice or rats, excretion was complete by 7 days post-administration, with the main part of the dose recovered in faeces (67% in mouse, 87% in rat).

2.3.4. Toxicology

The Applicant has developed a combined oral contraceptive (COC) containing 15 mg of the new chemical entity estetrol monohydrate (E4) as the oestrogen, as well as 3 mg of the progestogen drospirenone (DRSP), which is already used at this dosage in approved combined oral contraceptive products and will not be assessed here. E4 has been evaluated in a comprehensive set of nonclinical toxicity studies with the active substance administered by the oral route in mice, rats, rabbits and monkeys. Further, as E4 is combined with DRSP in the present combination product, a 13-week combination study in cynomolgus monkey has been performed using oral administration to evaluate potential new toxicities arising when the substances are combined.

The program of toxicology studies undertaken with E4 comprises single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity, together with supplementary studies to investigate the generation of reactive oxygen species (ROS) induced by the test item. These studies were supported, as necessary, by integrated TK monitoring. E4 was rapidly absorbed after oral administration and showed no or limited plasma accumulation after repeated administration to the animal species used in toxicology studies. Further, exposure was roughly proportional in all studies and with half-lives of 2-6 hours in rats and mice, and 10-19 hours in monkey.

The toxicity profile of E4 is mainly driven by the estrogenic properties of the substance with changes in reproductive tissues, lymphoid tissues, liver (rats), adrenals and pituitary (monkey). In addition, E4 and DRSP in combination induced reversible but adverse hyperglycaemia in female monkeys. Hyperglycaemia is a known risk for oestrogen/progestogen combinations, and the risk with this new combination is not different in that respect based on the non-clinical studies. Most changes displayed evidence of reversibility when the treatment was stopped, but full recovery was not always reached. Of particular importance are the cardiac changes reported, consisting of interstitial fibrosis in association with minimal vacuolation of the cardiomyocytes in two female monkeys receiving the combination treatment.

Overall, the general toxicities seen with E4 are consistent with the known toxicities of other oestrogens.

Single dose toxicity

A single escalating dose study in female cynomolgus monkey identified a NOAEL of 1000mg/kg. The only findings observed were emesis in one female at the 1000 mg/kg dose and decreased levels of alkaline phosphatase reaching significance at a dose level of 1000 mg/kg.

Repeat dose toxicity

Repeated-dose toxicity has been evaluated in Sprague-Dawley (SD) rat and Cynomolgus monkey in studies of up to 6 and 9 months respectively. Further, as carcinogenicity studies were performed in CD1-mouse and Wistar rats, repeated-dose toxicity was also evaluated up to 13 weeks in these strains.

Mortalities: In the 26-week study in SD rats, one mortality occurred in the 15mg/kg/day group for reasons of poor clinical condition. The cause of moribund condition was considered by the Study Pathologist to be related to gavage procedure and a relationship to the treatment was excluded.

Four monkeys died prematurely in the 13-week combination toxicity study.

Three monkeys receiving the highest dose of the combination were sacrificed early for ethical reasons on study day 45. Severe hyperglycaemia and associated changes were considered the probable cause. Based on the documentation presented, including that glucose levels led to the temporary interruption of dosing in some surviving animals, this conclusion is agreed with.

One female was found dead on study day 36, with findings that included fibrosis of the myocardium with chronic inflammation of epicardium at the apex. Fibrosis in the apex was also noted in high-dose animals at necropsy, suggesting that the findings may be related to the fibrosis noted in other animals. Additional data of the female that died on study day 36 showed that the fibrosis may well relate to a gavage related error followed by thoracic inflammation. The fibrosis in the heart at apex and within the ventricles and septum in the absence of cardiomyocyte vacuolation or hypertrophy was therefore in this animal likely an extension of this inflammation rather than a direct effect of the test substance. However, this uncertainty does not translate into a concern that the observed cardiac findings is of clinical relevance.

Bodyweight: Oestrogens exert anti-obesity effects in women and female mammals, and oestradiol replacement in rodents prevents obesity by decreasing food intake and increasing energy expenditure. It was therefore surprising to note that the CD-1 mice in the 4- and 13-week studies consistently showed dose-relatedly increased body weights with E4 treatment. There is no reasonable explanation (food consumption included) except to conclude that oestrogens (E4 included) administered to experimental animals yields considerable interspecies variation in physiological responses. In rats and monkeys, expected reductions in bodyweight were consistently noted down to adverse levels. No data is available on monkey food-consumption which makes the relation between bodyweight and food-consumption speculative.

Reproductive organs and genitals: Given that the intended indication for the product is anticonception, it is no surprise that E4 induces oestrous cycle arrest in all species evaluated, including effects associated with exaggerated estrogenic effects. Changes in weights of reproductive tissues, generally accompanied by macroscopic and/or microscopic observations, were found in all species evaluated. Ovaries, oviducts, uterus, vagina, mammary gland and pituitary gland displayed microscopic changes reflecting estrogenic responses. The findings were overall considered non-adverse and showed recovery. However, in the 39-week study in cynomolgus monkey, treatment-related changes in the cervix, including chronic inflammation in the lamina

propria is considered adverse at 3 and 10mg/kg/day. This finding was not evident in the 13-week combination study at any dose-level.

Lymphoid organs: Lymphoid atrophy was noted in all species evaluated. Thymus weight was reduced in all species, associated with minimal to severe lymphoid atrophy. Whereas thymic atrophy is a known effect of oestrogens, the finding was considered adverse in some studies where marked lymphoid atrophy was evident. No evaluations of immune function have been undertaken. While acceptable, such evaluations would have improved the possibility to make a functional evaluation of the lymphoid atrophy. However, no clear effects on immune function have been reported from the clinical studies.

Adrenals: In the mouse 13-week study, subcapsular spindle cell hyperplasia including increased vacuolation/degeneration of the x zone was noted dose-dependently from 0.3 mg/kg/day. In the rat, adrenal weights were increased in all studies. In the 4-week study, dose-related congestion of the cortex and zona reticularis cell hypertrophy (minimal-marked) was noted associated with blood vessel expansion/dilation. This correlated with increased adrenal weights. At recovery, congestion (minimal-slight) was still noted in one female each from the 50 and 150 mg/kg/day groups. In the 26-week rat study at doses at and above 1.5 mg/kg/day, dose-related cortical hypertrophy (primarily seen in the reticular layer of the adrenal glands was evident, along with capillary blood vessel dilation and cystic degeneration. At recovery, cortical hypertrophy and minimal cystic degeneration remained in 1/6 and 2/6 of treated animals. These effects were considered adverse from 5mg/kg/day in the rat. In monkeys, complex changes consisting of dose-dependent but variable association of hypertrophy/vacuolation of the zona glomerulosa (minimal-slight) and zona fasciculata (minimal-slight) and atrophy of the zona reticularis (minimal-marked) evidenced that adrenals are target organs of toxicity in all species tested. Since cells in the zona reticularis synthesize oestrogens, a negative feedback by E4 may have caused atrophy and lower weights.

Liver: In mice and rats, increased liver weights and hepatocellular hypertrophy was evident and histopathology findings included hepatocellular hypertrophy (minimal-moderate) in both species. In the rat, hepatocellular microvacuolation (minimal to moderate) was seen in the 26-week study without clear dose-relation. However, the rats administered the highest dose had slightly higher incidence and severity compared to the lower dose groups. However, given that no degeneration was reported, this change may reflect a cellular adaptation, rather than a degenerative change. In the monkey, liver-weights were increased, and a decreased hepatic glycogen content was seen. This may be related to reduced food-intake and bodyweight. Liver is a known target organ of oestrogen toxicity, and oestrogens modulate liver lipid metabolism so liver involvement after oestrogen administration is expected.

Pituitary: The pituitary gland shows increased weight hyperplasia/hypertrophy of eosinophil cells across studies. This is likely an oestrogen dependent effect, as prolactin-induced cell hyperplasia has previously been shown to result from oestrogen exposure.

Heart: In the female monkey found dead during the study, fibrosis of the myocardium with chronic inflammation of epicardium at the apex were evident findings. Further, interstitial fibrosis (minimal) was found in ventricles/septum of the three prematurely sacrificed animals, which in two cases was associated with vacuolation and hypertrophy of cardiomyocytes. The minimal interstitial fibrosis associated with vacuolation and hypertrophy of cardiomyocytes may be treatment related, but finally considered that this was not the case based on the minimal and discrete findings.

In the NHP repeat-dose study with the combination of E4 and DRSP, microscopic cardiac changes were observed. Three animals at 10/2 mg/kg/day E4/DRSP presented minimal focal interstitial fibrosis in the ventricle(s)/septum of the heart, with two animals showing vacuolation in cardiomyocytes. Four animals

(including two of the animals prematurely sacrificed) in the highest dose combination regimen also showed ventricle(s)/septum-related interstitial fibrosis and cardiomyocyte vacuolation. The Applicant did not consider the cardiac effects in the current study adverse, because the microscopic changes were minimal, not related to macroscopic changes and not found in recovery animals. This rationale can be followed, as the changes have not led to an impact on blood pressure or ECG parameters in the current study.

Microscopic cardiac abnormalities were not observed (or at least not evaluated with specific histological staining) in mice and rats. The Applicant stated that the microscopic changes in the heart in NHP treated with E4/DRSP are likely background findings. When assessing the estetrol-related microscopic data of NHP in the repeat-dose toxicity studies, it was noted that immune cell infiltrates and interstitial fibrosis at the apex occurred in all treatment groups, including controls, and thus are likely a background finding in (Mauritian-origin) cynomolgus monkeys. Interstitial fibrosis in the ventricle(s) and/or septum did also occur in a few control animals in the estetrol only-studies, but not in the control animals from the E4/DRSP combination study. Haemorrhages only occurred in animals prematurely sacrificed in the highest dose of E4/DRSP combinationand may be related to agonal changes prior to death and/or a response to stress, such as chronic poor condition or acute hyperglycaemia.

Although it is agreed with the Applicant that interstitial fibrosis in NHP is likely a background finding, the incidence and severity of the microscopic changes in the heart (primarily left ventricle/septum instead of only the apex in control animals) of E4/DRSP-treated animals at ≥10/2 mg/kg/day was higher than in control animals. An expert review on the observed cardiac findings concluded that the animals showed signs of spontaneous cardiomyopathy. This pathology resembles HCM in humans, and thus is thought to have a genetic background. Although oestrogens may have a cardiotrophic effect, it is questionable whether estetrol has acted as a hypertrophic factor in the treated monkeys. It is more plausible that hyperglycaemia and/or chronic poor condition in animals dosed with ≥10/2 mg/kg/day E4/DRSP has resulted in secretion of catecholamines, as features of spontaneous cardiomyopathy in NHP are suggestive of stress-induced disease. Thus indirectly, estetrol (with drospirenone) appears to have increased the incidence/severity of the cardiac changes observed in cynomolgus monkeys. The Applicant solely focused on the fact that cardiac changes can be background findings in NHP and did not further discuss this potential relation of estetrol (alone or in combination with progestogens) with an increase in the incidence/severity of the observed microscopic cardiac changes in NHP. In the clinic, no changes in heart function (ECG) have been observed in estetrol-treated humans. Nevertheless, some women can have certain risk factors (genetically, environmentally, etc.) that may increase the change of developing cardiomyopathy. The Applicant has described the cardiac changes in E4/DRSP animals, including the evaluation whether these changes should be considered treatment-related or not:

- The interstitial fibrosis observed in the cardiac apex should be considered normal background, as it was also found in control animals. This can be endorsed.
- The changes observed in the 10/2 dose level of E4/DRSP were not considered treatment-related, because the changes were very delimited/focal and not related to other changes. However, as these ventricular changes (primarily interstitial fibrosis) were not observed in control animals and the interstitial fibrosis was associated with cardiomyocyte vacuolation in 2 treated animals, the conclusion of the Applicant and the NOAEL for cardiac changes set at this dose level is not fully agreed.
- The changes observed in the 30/6 dose level of E4/DRSP were considered treatment-related, but not adverse, because these changes were not found in recovery animals. This is not fully endorsed, as 1 of the 2 recovery animalsshowed ventricular changes.
- The Applicant stated that no microscopic ventricular changes (or functional changes) have been observed in animals treated with E4 alone. To be correct, cardiomyocyte vacuolation was observed in the 39-week study. However, no dose-relation was seen why this was not considered E4 related by the Applicant. It

should be noted that no Masson's staining for interstitial fibrosis was used in the E4 only studies, which hampers actual conclusions regarding the occurrence of ventricular changes in these studies. Nevertheless, no ventricular changes were observed in E4 alone-treated animals in the combination studies. It thus appears like the combination of high doses of E4 with a progestogen (and not E4 alone) increased the risk for development of cardiac ventricular changes in cardiomyopathy-susceptible cynomolgus monkeys.

The Applicant had some additional considerations regarding the hypertrophic cardiomyopathy-susceptibility of the cynomolgus strain (and animal age at study start), the MoA underlying this cardiomyopathy, the doses of E4 and progestogen used in the toxicity studies (compared to human exposure), and the clinically available data for E4/DRSP and other COCs. Taking these points into account, the Applicant concluded that the observed microscopic and functional cardiac changes in Mauritian cynomolgus monkeys were most likely caused by a combination of genetic abnormalities in cardiomyocyte organization and β-adrenergic receptors and the presence of high levels of catecholamines (due to stress, steroid hormones, hyperglycemia, etc.).

While the proposed explanations are plausible, they are for the most part difficult to verify. It was considered whether to request new study data in cynomolgus monkeys from a different breed (originating from e.g. China or Vietnam), to give further assurance that the findings are indeed related to a genetic susceptibility in the monkeys of Mauritian origin. However, to request a new monkey study was not considered justified both from a 3-R perspective and because even a clean study would not be able to fully exclude a cardiovascular risk with the product. Moreover, cardiac effects related to the product, but appearing years or decades after exposure would not likely be identified in a non-clinical study.

Considering that the cardiac changes observed in the E4/DSRP study occurred at exposure levels above the clinical practice and that no observation of deleterious cardiovascular effects have been observed in the clinic, the Applicant was of the opinion that the ventricular changes observed in the Mauritian cynomolgus monkeys are of no clinical relevance. However, given the rather limited number of exposed women in the clinical trials, the clinical relevance of the cardiac findings in the monkeys are still unclear. Further, due to the similarity between hypertrophic cardiomyopathy in Mauritian cynomolgus monkeys and humans with HCM, it can be considered that the use of E4/DRSP increases the risk for development of cardiac effects in females with a genetic susceptibility for HCM and other risk factors inducing this HCM. To what extent women without HCM but with other known (or unknown) risk factors are at risk cannot be decided based on the studies in the Mauritian cynomolgus monkeys.

As there, to date, are no clinical signals suggestive of cardiac effects in humans after E4/DRSP administration, further clinical follow-up is not considered warranted. In addition, no further non-clinical studies are considered justified at this point.

Genotoxicity

The genotoxicity testing of E4 was not straight-forward. In the first Ames test, E4 was positive, as increased revertants were seen in the TA102 strain. A follow-up test in TA102 using the same batch, but with ethanol as solvent (instead of DMSO) was undertaken. A dose-related increase in revertants was noted (in both preliminary assay and confirmatory assay), with and without S9 mix, exceeding the 2-fold threshold at and above 2500 µg/plate, why the conclusion was that E4 is mutagenic. A third Ames test was performed with E4, in which two assays were performed. One assay used the direct plate incorporation method and the other was performed according to the pre-incubation method. The first assay did not pass the study requirements and was therefore not considered valid. The second study showed no increase in revertants in E4 treated plates compared to vehicle control. It was unclear why this study was negative whereas two previous GLP-compliant studies showed

that E4 is mutagenic both in absence and presence of S9-mix. The Applicant was therefore asked to discuss the Ames tests and why two independent positive results in one laboratory was followed by a clearly negative result in a second laboratory. According to the Applicant, and in accordance with an expert statement, differences in TA102 strain sensitivity may be a possible explanation for the different results noted in the three tests. As TA102 carries the *his* mutation on the multicopy plasmid pAQ1, it was agreed that different copy numbers can potentially give a change in sensitivity to mutagens. However, there were no data available to show that there were in fact differences in pAQ1 copies between the tester strains in the studies. It was therefore not possible to further evaluate the hypothesis.

It was also agreed that ROS induction is less likely to cause the effects, and thus also the differences in effects. Therefore, and overall, the Ames test studies suggest a not fully reproducible mutagenic activity in the strain TA102 perhaps via a cross-linking mode of action.

Two mouse lymphoma assays were performed to evaluate the potential of E4 to induce gene mutations in mammalian cells. Both studies showed increased mutation frequencies in cells treated with E4. In the first study, increased frequencies were only noted in the highest dose without S9 mix and was not considered positive due to lack of dose-response. In the second study, mutation frequency was dose-relatedly increased with and without S9 but did not exceed the GEF threshold and was therefore not considered positive.

The result of the lymphoma assays is considered equivocal in combination with the very unclear Ames test results.

Three *in vivo* studies have been performed with E4, one bone-marrow micronucleus test and two comet assays evaluating effects in liver and duodenum. While the micronucleus test is a standard *in vivo* study in accordance with ICH S2, it is assumed that the comet assays were performed in response to the positive results resulting from 2 of the three Ames tests conducted. The liver was chosen as it is the major site of metabolism of E4, and the duodenum is an early site of contact with E4 after oral exposure. All studies were performed in SD rats at doses up to 2000 mg/kg, which is the top dose suggested in the current ICH S2 guideline.

In the micronucleus test, the mean values of MPCE and PCE/NCE ratio were not statistically different between the groups. The first comet assay performed showed a significant increase in DNA strand breaks, but only at the lowest dose tested of 2 x 500 mg/kg/day. The second study was performed at another CRO and was more focused on doses at and around 500mg/kg and used a slightly different experimental set-up which included parameters for tissue toxicity and ROS evaluations. Tail moment and tail intensity are relatively stable among groups. It is however noted that the 500 mg/kg group (which was positive in duodenum in the first study) showed more clouds. This suggests more cytotoxicity (or possibly lower sample quality) rather than genotoxicity. Collectively, the *in vivo* studies do not suggest that E4 is a genotoxicant.

The Applicant has further referenced genotoxicity studies with drospirenone which were negative.

Carcinogenicity

Two long-term (two-year) carcinogenicity studies with E4 have been performed, one using CD-1 mice and one with Wistar rats. Wistar rats were used since this strain has a lower incidence of spontaneous mammary neoplasia as compared to S.D rats. In the mouse study, The HD was set based on weight-increase in the 13-week pre-study in CD-1 mice, and it is evident that weight was a sensitive parameter with up to 33% increase in the 1mg/kg group. Neoplastic findings (tumours) were evident in uterus and cervix (from 0.25 mg/kg/day) and in mammary gland and pituitary (at the 1 mg/kg/day dose). The overall impression of the neoplasms in reproductive organs is that they are consistent with an E4 related estrogenic effect and therefore

expected. Further, increased mammary hyaline duct content, galactoceles, hyperplasia and neoplasia are consistent with direct effects of estetrol and/ or secondary to increased prolactin secretion. The increased neoplasias noted in the pituitary (increase in hyperplasia, adenoma and carcinoma of the pituitary pars distalis) have been shown to be prolactinomas suggesting that they too are related to an estrogenic effect. The dose-level of 0.125 mg/kg/day was not carcinogenic in this study.

In the rat, E4-induced proliferative and non-proliferative effects were noted in genital tract, liver, spleen, mammary gland, adrenal cortex, mesenteric lymph node and thymus. Although there were no differences in overall mortality between treated and control groups, the percentage deaths or premature sacrifices caused by pars distalis adenomas was higher in treated groups compared with controls. These adenomas correlated with pituitary enlargements noted macroscopically and also with increased ventricular dilatation and compression of the brain. It has previously been shown in SERM-studies that this tumour is driven by oestrogens.

The only neoplastic observation presented is an increase in mammary adenocarcinoma noted at 0.8 mg/kg which was accompanied by mammary gland acinar cell hyperplasia already from the lowest dose. Oestrogen and prolactin are known as important drivers of these tumours in the rat. It is also noted that pituitary tumours were also noted in the mouse carcinogenicity study. Given the increased pituitaries it is possible that prolactin levels were increased. It is to this end strange that such an apparent factor has not been evaluated within the present study, as it could have given more clear data on this. Overall small effects were noted on haematology and blood biochemistry parameters with effects mainly on increases in reticulocytes count, triglyceride levels and alkaline phosphatase and decreased cholesterol. The blood biochemistry changes are similar to the findings in the 13-week study, but there doses up to 6mg/kg were used.

Except for the mammary gland hyperplasia noted already at 0.08mg/kg, non-neoplastic proliferative findings (i.e. hyperplasias) were noted from 0.27mg/kg/day uterus, ovaries and liver. Non-proliferative findings reported are overall involving lymphoid and oestrogen sensitive organs and are reflective of the findings already noted in the 13-week study in Wistar rats. From this study, it can be concluded that E4 is carcinogenic and produced mammary gland adenocarcinoma at 0.8 mg/kg/day.

Overall, it can be concluded that E4 is carcinogenic in mice and rats. Oestrogen-containing combined oral contraceptives are classified as Group 1 by IARC, and this combination is not different in that respect.

Reproduction Toxicity

Modified segment I study: The E4 exposure of rat females led to a reversible decrease in oestrus-cycling females from 0.5mg/kg/d. There were no clear signs of reduced fertility or disturbed early embryogenesis (e.g. fertility index, gestation index). Exposure to E4 led to an overall decrease in food intake (-10%, 1.5mg/kg/d) and body weight (-4% to -7% from 0.50mg/kg/d) that was most evident during the first 1-2w of exposure. The food intake and body weight reduction effects were not evident during the recovery phase (although there was a +50% to 90% body weight gain from 0.17mg/kg/d) but seemed to become manifest again during pregnancy in both pivotal studies (reduced food intake -4.5% to -12.5% across doses and studies, reduced body weight of -6.6% to -7.2% and a trend of reduced body weight gain at ≥0.50mg/kg/d in one of the pivotal studies). Overall, the general NOAEL across studies was set to 0.17mg/kg/d and the LOAEL to 0.50mg/kg/d based on the reduction of oestrus cycling during the exposure period (first pivotal study) and reduced food intake/body weight gain (second pivotal study).

Segment II (EFD): In dose-range finding rat studies, there was total embryofoetal loss at ≥10mg/kg/d. In the pivotal rat study (exposure period Gd6-Gd17, 0.30 to 3.0mg/kg), several animals (n=4/24) were sacrificed

early at the high dose (3.0mg/kg/d) due to abortions/poor clinical conditions. At the high dose, there was also an overall clear reduction of dams with live foetuses (42%). There was a significant increase of external limb malformations (severe flexed or malrotated ankle joint, shortened limbs), skeletal malformations (bent radius, thickened forelimb humerus, bent pectoral scapula) and variations (nodulated or kinked ribs, un-ossified sternebrae) and a general increase of number of litters with malformed foetuses from the middle dose (1.0mg/kg/d). There was also a trend (stat. non-sign.) of increased mean of pre- and post-implantation loss and number of foetuses per female with increasing dose. The was a reduced body weight gain (+16.5 to +17.5% compared to control +20.5%) from the middle dose (1.0mg/kg) which correlates with trends of reduced food intake and mean body weight. At Gd20, there was a significant mean body weight (corrected for uterus weight) reduction and enlarged and thickened placenta at the highest dose. The overall maternal and embryofoetal NOAEL was 0.30mg/kg/d and the LOAEL was 1.0mg/kg. No toxicokinetic measurements were conducted in the pivotal rat EFD study, but a non-pivotal Rat EFD study covered the same doses and gave a NOAEL Cmax (Gd17) of 6825pg/mL, a NOAEL AUC0-t (Gd17) of 9330pg x h/mL, a LOAEL Cmax (Gd17) of 20878pg/mL and an LOAEL AUC0-t (Gd17) of 37656pg x h/mL.

In the rabbit pivotal study (exposure period Gd6-Gd18; 0.05 to 0.45mg/kg/d), there some minor adverse clinical signs (hair loss) in the females from the middle dose (0.15mg/kg/d) and more adverse signs at the high dose of 0.45mg/kg/d (emaciated appearance, absence of faeces). There was a general reduction of main study females with live foetuses from the middle dose (n=9/20 at 0.15mg/kg/d and n=2/20 at 0.45mg/kg/d) due to abortion/total resorption (with an stat. sign. increase of late gestation resorptions at the high dose). There was also an increase of post-implantation loss (+37.4%) at the high dose. There was no clear exposure-dependent increase in embryo-foetal anomalies (malformations/variations) except an increase in supernumerary 13th ribs (a variation) from the middle dose (around +65% to +71%) although the teratological assessment is complicated by there being less females with live foetuses at the middle dose and especially the high dose. The 13^{th} rib observation is considered to be of unlikely relevance for human extrapolation. There was a general reduced maternal food intake from the middle dose (also transiently before Gd10 at the low dose of 0.05mg/kg/d) spanning -36% to -74%, a reduction in mean body weight (-7% at 0.15mg/kg/d and -13% at 0.45mg/kg/d) and a reduced body weight gain during the exposure period (Gd6-Gd18) followed by an increased gain during the recovery period (Gd19-Gd24). There was a non-significant trend of reduced gravid uterus weight from the middle dose (-12% to 24%). The stroma of the endometrium was slightly more prominent plus minimal atrophy of the endometrial epithelium at the high dose (n=4-5/8 observed animals) plus some minimal focal haemorrhagic ovary cysts (n=2/8 observed animals) at the high dose. There was weak dose-accumulation of E4 during the exposure period at the lowest dose (Cmax 1.2x, AUC0-t 1.63x) that was reduced with increasing doses. The overall maternal and embryofoetal NOAEL is 0.05mg/kg/d (Cmax 925pg/mL, AUC0-t 6835pg x h/mL) and LOAEL 0.15mg/kg/d (Cmax 3816pg/mL, AUC0-t 24477pg x h/mL).

Based on a clinical AUC of 59100pg x h/mL (clinical study MIT-Es0001-C103), the exposure margins to the EFD NOAELs are: I) rat EFD NOAEL AUC exposure margin between 0.15x (the fraction between animal AUC0-6h and human AUC0-24h and likely misrepresentative) and 0.63x (the fraction between 4xAUC0-6h and human AUC0-24h), II) rabbit EFD NOAEL AUC exposure margin 0.41x (rabbit AUC0-t from 24h post-dose sampling vs human AUC0-24h. The Applicant has not provided any discussion on exposure margins for the EFD data, but using these rough estimates, there is no human exposure margin for the non-clinical observations.

Segment II+III: In the modified segment III rat study (exposure period Gd6-Gd18+PND1-PND21 with recovery up to PND116 in males, doses 0.17 to 1.5mg/kg/d), there was an increase of F0 female mortality/pre-termination deaths partly due to reduced survival during delivery, partly to the finding of dead litters after delivery. At the high dose (1.5mg/kg/d), there was several adverse clinical signs among females after delivery (e.g. cold to the touch, pallor of extremities, hypoactivity, prostration, blood in the bedding). At

the high dose, there was a clear reduction of females with live born offspring (control n=20 compared to high dose n=11, total live control pups n=197 vs high dose pups n=54) and the gestation index was reduced to 64.7%. The increase in F0 female and F1 offspring mortality was greatest around delivery and the first days after delivery (more cannibalized pups or intact pups found dead at PND4) but not afterwards (no difference in lactation index).

Exposed F0 females demonstrated clearly reduced food intake (-15% to -26%) from the middle dose (0.50mg/kg) during pregnancy and in the lactation phase at the high dose (-21% to -28% at 1.5mg/kg/d). This corresponded to a reduced body weight gain (>10%) during pregnancy (but without clear difference in mean body weights) but not during the lactation period (yet with a reduced mean body weight of -9% to -10%) from the middle dose (0.50mg/kg/d). Pre-weaning F1 offspring did not demonstrate any clear change in mean body weight or body weight gain. Instead, this was observed post-weaning in males with a reduction in food intake (-6% to -9%) from the middle dose, a reduced mean body weight (-6% to -10%) from the middle dose throughout recovery and a reduced body weight gain primarily between PND36 to PND57 from the middle dose (the overall weight gain across the recovery period was still reduced compared to controls). No food intake/body weight differences were observed in F1 pregnant females (termination at Gd15).

There were no exposure generated differences in morphological landmarks and behavioural development (motoric and reflex development, cognitive development). With regard to F1 animal sexual development, there were no E4 effects on prenatal, pre-weaning or post-weaning sexual maturation landmarks (sex-ratio, anogenital distance, balanopreputial separation or vaginal opening) nor on F1 female pairing, mating or fertility (e.g. mean number of corpora lutea, pre- and post-implantation loss). The overall F0 maternal and F1 offspring NOAEL is 0.17mg/kg/d and the LOAEL is 0.50mg/kg/d.

Toxicokinetic data

The toxicokinetics of E4 was evaluated in oral gavage studies in CD-1 mouse, SD rat, Wistar rat and Cynomolgus monkey of up to 39-weeks. Further, 13-week combination study with drospirenone has been performed in cynomolgus monkey.

Interspecies comparison

Steady-state exposure (AUC, Cmax) of E4 and DRSP upon repeated administration of E4/DRSP 15/3 mg tablets to healthy female subjects (age 18-50 years per protocol) has been determined in clinical study MIT-Es0001-C103. Exposure ratios have been calculated versus steady-state human exposures (AUC0-24: 59.1 and 519 ng.hr/mL for E4 and DRSP, respectively; Cmax: 17.9 and 48.7 ng/mL for E4 and DRSP, respectively).

Study	**NOAEL (mg/kg/day)**	**Animal exposure at steady state AUC0-last (ng.h/mL)**	**Cmax (ng/mL)**	**Safety margin: ratio animal/human exposure (AUC*)**	**Safety margin: ratio animal /human exposure (Cmax*)**
CD1 Mouse , GLP, 13 weeks	1	87.267.3	45.639.4	1.481.14	2.202.55
Wistar Rat , GLP, 13 weeks	0.6	57.6	25.1	0.97	1.40

SD Rat , GLP, 26 weeks + 8-week recovery	1.5	196	56.8	3.32	3.17
Cyno Monkey , GLP (except hormone measurements), 4 weeks	5	1153	348	19.51	19.44
Cyno Monkey , GLP 13 weeks with 4-week recovery	3	363.4	121.3	6.14	6.79
Cyno Monkey , GLP 39 weeks with 6-week recovery	1	123	33.0	2.08	1.84
Cyno Monkey , GLP 13 weeks with 4-week recovery	E4: 3	483	173	8.2	9.66
	DRSP: 0.6	630	105	1.2	2.16
Carcinogenicity CD-1 mouse (Neoplasm)	0.125	4.60	3.75	0.08	0.21
Carcinogenicity SD Rat (Neoplasm)	0.27	18.8	9.99	0.32	0.56

*Based on AUC0-24: 59.1 and 519 ng.hr/mL for E4 and DRSP and Cmax: 17.9 and 48.7ng/ml, respectively in clinical study MIT-Es0001-C103

Margins of toxicity are considered to be low, but they are acceptable, considering that the toxicities identified in the programme are clinically well-known from other COC products.

Local Tolerance

Local tolerance for E4, DRSP and the combination was evaluated in the repeat-dose oral toxicity studies. Separate local tolerance studies were not performed. The approach is acceptable, given that oral gavage administration has been used in the non-clinical program, and that oral dosing is the intended clinical route of administration.

Other toxicity studies

Dependence

It was taken into consideration in the safety pharmacology study. According to the Applicant "*Estetrol was devoid of effects on central nervous system in female rats up to and including a dose of 15 mg/kg"*. The absence of a specific dependence study is endorsed.

Phototoxicity

In line with ICH S10, it was considered justified not to perform further phototoxicity testing as E4 displays relatively weak distribution to light exposed tissues and shows no prolonged retention in melanin-containing structures. In addition, no symptoms of phototoxicity have been observed in any of the animal studies.

2.3.5. Ecotoxicity/environmental risk assessment

Drovelis has two API: estetrol (E4) and drospirenone (DRSP). With regard to the latter, a letter of access to the Environmental Risk Assessment dossier for the DSRP (3mg) containing medical product has been provided and no new assessment has been conducted.

With regard to E4, it is by definition an oestrogen receptor agonist and therefore also considered an endocrine active substance. As such, a phase II assessment is required independent of the PECsw value. That being said, the standard phase I PECsw for E4, correcting for the molecular weight of hydrate, is 0.071µg/L (triggering a Phase II assessment). A SimpleTreat modelling of WWTP/STP impact on E4 effluent levels indicated that 99.3% of E4 moves into the surface water.

The log Kow (1.65) does not trigger a PBT assessment. The E4 ERA shows that E4 is not readily biodegradable in sludge (based on an OECD TG301B study). The adsorption coefficient (Kd) for E4 is between ~1 and 2.8L/kg in soils (Kd 0.96-2.77L/kg) and ~19L/kg (Kd 18.99-19.23L/kg) in activated sludge while the organic carbon-water partition coefficient (Kfoc) is between 88 and 147L/kg for soils and 35-36L/kg for sludge (based on an OECD TG106 study) with the Kfoc outcomes being considered more relevant (based on a TIER3 study).

As such, E4 is unlikely to be deposited on agricultural land via sludge in any substantial amount. In water-sediment systems (i.e. OECD TG308), more than 10% of E4 shifts to the sediment within 14d. The E4 half-life range is between ~3.3d and 15d at 20◦C (empirical) and 8.1d-25.7d at 12◦C (predicted). Among aquatic toxicity model organisms, fish (Japanese medaka) is most sensitive to E4 exposure (fish full-life cycle, OECD TG240). The concentration response for the most sensitive endpoint, hatching, was non-monotonic with statistically significant effects compared to controls in the three middle concentrations but not the lowest and highest concentration (C1: 0.00069mg/L with hatching at 91%, C2: 0.0029mg/L [hatching 36%], C3: 0.0087mg/L [hatching 72%], C4: 0.031mg/L [hatching 34%] and C5: 0.099mg/L [83%]). For changes in vitellogenin levels in Japanese medaka, the NOEC is 0.0087mg/L and LOEC 0.031mg/L. There were no effects on activated sludge after 3h exposure (NOEC 1000mg/L, OECD TG209). The pivotal sediment-dweller (*Chironomus riparius*) NOEC was 1000mg/kg (OECD TG218) but several validity criteria in the study were not met. The emergence in the control groups were 66% (control) and 80% (solvent control) with 70% being a validity criterium. The emergence in control groups occurred between 18 and 28 days (control) as well as between 18d and 27d (solvent control) whereas the validity range is between 12d and 23d. Also, the temperature varied by more than 1ºC across the duration of the test. Instead, the dose-range fining study will be used (giving a NOEC of 9.1mg/kg; corrected to an organic carbon content of 10%).

The proposed E4 PECsw is 0.0312ug/L based on a refined Fpen of 0.0044.. The Applicant is committed to submit an updated ERA with this PECsw as a basis. For the surface water compartment, this is stated to give a risk quotient of < 1, but the final conclusion can only be made with the submission of the updated ERA.

Table 1. Summary of main study results

Substance (INN/Invented Name): *Estetrol monohydrate (E4)*			
CAS-number (if available): 15183-37-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD TG107	Log Kow (pH 7) = 1.65	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	1.65	*not B*
	BCF		
Persistence	DT50 or ready biodegradability	DT50 water: 8.1d – 25.7d DT50 sediment: 8.7d – 14.3d Not readily biodegradable	See OECD TG301B and TG308 results.
Toxicity	NOEC	0.69µg/L	T (FFLC study)
PBT-statement :	E4 is considered not PBT, nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
Default PECsw (Phase I)	0.071	µg/L	> 0.01 threshold (Y)
Other concerns	Candidate EAS		(Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	<u>*Soils*</u> *Ads* *Kd : 0.9632 - 2.7663* *Kdoc : 88-147* *Kf : 1.03 – 3.18* *Kfoc : 88-147* *Des* *Kd : 1.401 – 6.4428* *Kdoc : 176-227* *Kf : 1.42 – 6.32* *Kfoc : 176-227* <u>*Sludge*</u> <u>*Ads*</u> *Kd : 18.99 – 19.23* *Kdoc : 35 - 36* *Kf : 13.12* *Kfoc : 35-36*	Study with 3 soils and 2 sludges. E4 is not significantly adsorbed to sewage sludge.
Ready Biodegradability Test	OECD TG301B	Not readily biodegradable ThCO2 = 3% (<60%)	28 days
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	<u>*Whole system*</u> DT_{50} (20°C) = 3.99d – 7.3d (CAKE) <u>*Water*</u> DT_{50} (20°C) = 3.32d – 4.33d (1comp) DT_{50} (20°C) = 3.81d – 12.08d	Aerobic-only study with two water-sediment systems. Two transformation products (WS2

		(2comp) DT_{50} (12°C) = 8.1d – 25.7d *Sediment* DT_{50} (20°C) = 7.18d – 15.3d (1comp) DT_{50} (20°C) = 4.09d – 6.71d (2comp) DT_{50} (12°C) = 8.7d – 14.3d >10% E4 in sediment by d14, levels decrease to <10% thereafter. Ultimate degradation: 8-15%			and WS3) mainly in water. DT50 between 4.22d-11.9d. Calculations with 1 and 2-compartment models.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test /*P. subcapitata*	OECD TG201	Biomass NOEC EC50 Yield NOEC EC50 Growth rate NOEC EC50	 100 >100 100 >100 100 >100	 mg/L mg/L mg/L mg/L mg/L mg/L	Exposure: 72h
Daphnia sp. Reproduction Test	OECD TG211	Reproduction NOEC LOEC Length NOEC LOEC Mortality NOEC LOEC	 11.5 >11.5 11.5 >11.5 11.5 >11.5	 mg/L mg/L mg/L mg/L mg/L mg/L	Exposure: 21d
Fish full-life cycle (FFLC) /Japanese Medaka (*O. latipes*)	OECD TG240	F0 endpoints NOEC LOEC F1 endpoints NOEC LOEC F1 vitellogenin NOEC LOEC F2 endpoints NOEC LOEC	 99 >99 0.69 2.90 8.70 31.0 99 >99	 ug/L ug/L ug/L ug/L ug/L ug/L ug/L ug/L	*Most sensitive endpoint: F1 hatching.*
Activated Sludge, Respiration	OECD TG209	NOEC	1000	mg/L	No inhibitory

Inhibition Test					effect
Phase IIb Studies					
Sediment-dwelling organism	OECD TG218	NOEC $NOEC_{OC10}$	10 9.1	mg/kg mg/kg	*C. riparius*

Shortly, DRSP is a previously assessed substance, it is considered an endocrine active substance and therefore a substance of potential environmental concern. It is not readily biodegradable, considered very persistent (vP) in a water:sediment simulation study and there is a potential for accumulation in for sediment. The substance meets the T-criterion and the vP criterion but does not meet the B-criterion based on a bioconcentration study in fish, hence DRSP is not PBT, nor vPvB. The DRSP PECs are 0.015ug/L (PECsw), 0.00375ug/L (PECgw), 0.015ug/L (PECstp) and 9.5ug/kg dw (PECsed) while the corresponding PNEC values are ≤0.023ug/L (PNECsw), 60ug/L (PNECgw), ≥940ug/L (PNECstp) and 5260ug/kg dw (PNECsed). This gives risk quotients below 1 (or 0.1. for sewage microorganisms). As such, the provided DRSP ERA does not identify any environmental risks from DRSP but the most sensitive PNEC of ≤0.023ug/L is based on a LOEC value making the RQ for surface water inconclusive (see discussion).

Table 2. Summary of main study results

Substance (INN/Invented Name): *Drospirenone (DRSP)*			
CAS-number (if available): 67392-87-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD TG117	Log Kow (pH 7) = 3.1	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.1	*not B*
	BCF	average 96.5L/kg	OECD TG305 study
Persistence	DT50 or ready biodegradability	DT50 = 19d (20°C) DT50 = 40.6d (12°C) Not readily biodegradable	No DT50 at 12C in original ERA. Calculated by assessor.
Toxicity	NOEC or CMR	<0.23μg/L	T
PBT-statement :	Drospirenone is considered not PBT, nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
Default PEC surface-water	0.015	μg/L	> 0.01 threshold (Y)
Other concerns	Candidate EAS		(Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	*Sludge ads* *Kfoc : 754-767*	Study with 2 sludges.
Adsorption-desorption	OECD TG121	Log K_{oc} = 3.8 K_{oc} = 6310	
Ready Biodegradability Test	OECD TG301B	Not readily biodegradable	28 days OECD TG308 necessary
Aerobic and Anaerobic	OECD TG308	*Water (20C)*	Aerobic-only study

Transformation in Aquatic Sediment systems		DT_{50} = 2.1d (geomean) <u>*System (20C)*</u> DT_{50} = 19d >10% DRSP in sediment by d14, Sediment shifting: 56% of radioactivity in Espel sediment at day 14; 75 % of radioactivity in Horn sediment at day 14.			with two water-sediment systems.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*P. subcapitata*	OECD TG201	NOEC	1.3	mg/L	Growth rate Exposure: 72h
Daphnia sp. Reproduction Test	OECD TG211	NOEC	0.60	mg/L	Reproduction Exposure: 21d
Fish full-life cycle (FFLC), *P. promelas*	OECD TG240	LOEC	<0.00023	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC	≥9.4	mg/L	Study less reliable because concentrations not measured. However, because the NOEC is clearly above solubility, results are used.
Phase IIb Studies					
Sediment-dweller effects	OECD TG218	$NOEC_{OC10}$	526	mg/kg	*C. riparius* *Adjusted for 10% OC*
Bioconcentration in fish	OECD TG305	BCFss ~5% lipids	94-99	L/kg	*Average 96.5L/kg* ~5% lipids Risk for secondary poisoning does not need to be assessed any further.

2.3.6. Discussion on non-clinical aspects

The pharmacological profile of estetrol is similar to the oestrogenic responses of the two reference compounds used, oestradiol and ethinyl oestradiol, but has a weaker response. The difference seen *in vitro* is larger than that seen in *in vivo* studies. Estetrol displays a selective binding to the human oestrogen receptors (ER) and binds to both ERα and ERβ, with a higher affinity for ERα compared to ERβ. The potency of estetrol *in vivo* is generally 10 to 20 times lower than the potency of ethinyl oestradiol (EE) and is also lower than the potency of E2. In general, the difference in potency seem to be similar for both wanted and unwanted effects. The lower potency of oestradiol seems to be reflected also by the clinical dose chosen (15 mg), which is at least 500 times higher compared to the dose of ethinyl oestradiol (0.02 – 0.03 mg) used in combined oral contraceptives already on the market.

Estetrol is a naturally occurring oestrogen produced by the human foetal liver and reaches the maternal circulation through the placenta. It should be noted that the physiological function of estetrol in pregnancy is

unknown but the transfer through the placenta to the maternal circulation would strongly indicate that externally administrated estetrol is also likely to reach the foetus. Based on the conditionality of its developmental expression, it seems likely that estetrol has a specific function during pregnancy in comparison to other endogenous oestrogens and it is therefore possible that the focus on comparing the pharmacological effects of estetrol using established assays for known oestrogens might be somewhat misleading. However, without further knowledge regarding the physiological function of estetrol, the performed non-clinical pharmacological programme is considered acceptable and sufficient.

The non-clinical pharmacokinetic characterisation of estetrol is in general considered acceptable and sufficient.

Information on placental transfer as well as transfer into breast milk is absent. However, it is concluded that the amount of E4 that would be transferred to the foetus after E4/DRSP intake can be considered negligible in view of the high amounts of endogenous E4, and it is also agreed that additional exposure to small amounts of E4 via breast milk can be considered negligible since the foetus at term is producing high levels of estetrol and the newborn continue to produce endogenous E4 for several weeks after birth.

The toxicology studies performed with estetrol to support the MAA for Drovelis include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity. Additional studies investigated if estetrol induced ROS. The toxicity profile of E4 is mainly driven by the estrogenic properties of the substance with changes in reproductive tissues, lymphoid tissues, liver (rats), adrenals and pituitary (monkey). Further, in the combination study in monkey with estetrol and drospirenone, reversible but adverse hyperglycemia was evident.

Mortalities were found in the studies among animals (rats and monkeys) treated with estetrol. In the 26-week study in SD rats, one mortality occurred in the 15mg/kg/day group for reasons of poor clinical condition. The cause of moribund condition was considered by the Study Pathologist to be related to gavage procedure and a relationship to the treatment was excluded. In the 13-week combination study, one female found dead on study day 36 with findings that included fibrosis of the myocardium with chronic inflammation of epicardium at the apex. The Applicant does not consider these changes to be related to treatment but rather related to trauma associated with the gavage. This is agreed. In the NHP repeat-dose study with the combination of estetrol and drospirenone, microscopic cardiac changes were also observed. Three animals at 10/2 mg/kg/day E/D presented minimal focal interstitial fibrosis in the ventricle(s)/septum of the heart, with two animals showing vacuolation in cardiomyocytes. Thus, estetrol (with drospirenone) seems to increase the incidence/severity of the cardiac changes observed in cynomolgus monkeys. The Applicant solely focused on the fact that cardiac changes can be background findings in NHP and did not further discuss this potential relation of estetrol (alone or in combination with progestogens) with an increase in the incidence/severity of the observed microscopic cardiac changes in NHP. While no changes in heart function (ECG) have been observed in estetrol-treated humans in the clinic, some women can have certain risk factors (genetically, environmentally, etc.) that may increase the change of developing cardiomyopathy. Therefore, the Applicant was asked to 1) discuss the potential mechanism of action of the observed increased incidence/severity of cardiac changes in animals treated with E4 (with DRSP) compared to control treatment and 2) elaborate whether cardiac changes can be considered a clinical risk. In addition, based on the outcome of this discussion, the Applicant was requested to provide a summary of the cardiac findings in SmPC section 5.3. In the response, the Applicant maintained that the observed microscopic and functional cardiac changes in Mauritian cynomolgus monkeys were most likely caused by a combination of genetic abnormalities in cardiomyocyte organization and β-adrenergic receptors and the presence of high levels of catecholamines (due to stress, steroid hormones, hyperglycemia, etc.). While the proposed explanations are plausible, they are for the most part difficult to verify. However, as there to date are no clinical signals suggestive of cardiac effects in humans after E4/DRSP administration, no further non-clinical

studies are considered justified at this point.

The genotoxicity testing of E4 was not straight-forward. In the first Ames test, E4 was positive, as increased revertants were seen in the TA102 strain. A follow-up test in TA102 using the same batch, but with ethanol as solvent (instead of DMSO) was undertaken. A dose-related increase in revertants was noted (in both preliminary assay and confirmatory assay), with and without S9 mix, exceeding the 2-fold threshold at and above 2500 µg/plate, why the conclusion was that E4 is mutagenic. A third Ames test was performed with E4, in which two assays were performed. One assay used the direct plate incorporation method and the other was performed according to the pre-incubation method. The first assay did not pass the study requirements and was therefore not considered valid. The second study showed no increase in revertants in E4 treated plates compared to vehicle control. It is unclear why this study was negative whereas two previous GLP-compliant studies showed that E4 is mutagenic both in absence and presence of S9-mix. The Applicant was therefore asked to discuss the Ames tests and why two independent positive results in one laboratory was followed by a clearly negative result in a second laboratory. According to the Applicant, and in accordance with the expert statement by Kirkland 2013, differences in TA102 strain sensitivity may be a possible explanation for the different results noted in the three tests. However, there were no data available to show that there were in fact differences in pAQ1 copies between the tester strains in the studies. It was therefore not possible to further evaluate the hypothesis. Still, taking the overall negative results of the in-vivo testing into account, the conclusion is reached that estetrol is not considered a genotoxicant.

Two-year carcinogenicity studies in rats and mice showed that estetrol is carcinogenic. In mice, neoplastic findings (tumours) were evident in uterus and cervix (from 0.25 mg/kg/day) and in mammary gland and pituitary (at the 1 mg/kg/day dose). In the rat, the only neoplastic observation presented is an increase in mammary adenocarcinoma which was accompanied by mammary gland acinar cell hyperplasia already from the lowest dose. Thus, overall, it can be concluded that E4 is carcinogenic in mice and rats.

DART: In the 'return-to-fertility studies, it can be noted that when E4-exposed females where mated with naïve 8w old males, there were overall fewer pregnant females and higher levels of pre- and post-implantation losses compared to when mated to naïve 13w old males (likely due to sexual immaturity among the males). The "8w-matings" demonstrated an E4 dose-response profile of increased number of pregnant females (controls n=9, 0.17mg/kg/d n=11, 0.50mg/kg/d n=15 and 1.50mg/kg/d n= 16). This increase was not observed after the "13w-matings". Overall, the general NOAEL across two pivotal 'return-to-fertility' studies was 0.17mg/kg/d and the LOAEL to 0.50mg/kg/d based on the reduction of oestrus cycling during the exposure period (first pivotal study) and reduced food intake/body weight gain (second pivotal study). The NOAEL across studies for the endpoints fertility and early embryogenesis was 1.50mg/kg/d.

For the pivotal EFD rat study, there has been a discussion on whether the observed skeletal anomalies are likely to be postnatally remodelled to a normal state. While postnatal skeletal remodelling is reported in the literature, it is yet far from clear if the conditions for such a phenomenon cover this particular context. The E4 segment II+III rat study has relatively few live pups due to delivery problems and high early life mortality (see below) at the relevant dose range and it is therefore problematic to use such data to argue that the absence of skeletal problems in those pups proves remodelling. Putative remodelling does also not address some other observed severe external malformations (limb flexure/rotational malformations) that seem to be overrepresented and the NOAEL proposal is therefore not considered acceptable. There are some indications that these malformations may be deformations that are generated in late rat gestation, possibly due to E4 effects on the uterus and placenta (e.g. external morphological findings at partus and the absence of findings in skeletal examinations). This late gestation effect in rat may be of clinical relevance for risk minimization, as it is proposed (see SmPC 4.6) that if pregnancy occurs while taking Drovelis, further intake must be stopped. The overall maternal and

embryofoetal NOAEL is considered to be 0.30mg/kg/d and the LOAEL 1.0mg/kg.

On a more general level, E4 is a novel oestrogen that may or may not be equivalent to older oestrogens but in absence of more substantial clinical evidence, it is difficult at this stage to make claims about the safety of E4 based on referring to older COC oestrogens. A small fraction of the DRSP dose is known to transfer into milk. It is reported that the infant is exposed to a maximum of 0.6% of the dose through breast feeding (about 18 µg daily). The possible effects of this have not been studied and this has been reflected in the SmPC 4.6 ("Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the breast milk and might affect the child").

In the modified segment II+III rat study, E4 exposure seems to increase the likelihood of irregular pup delivery and early offspring survival. Early exposure (prenatal and/or postnatal) does not seem to affect sexual development/maturation. The embryofoetal toxicity effects in F0 animals (and those seen in the EFD studies in rat and rabbit) are not detected in pregnant F1 females. That being said, E4 does seem to cause minor (around or less than -10%) male-specific long-lasting post-weaning changes in male food intake/body weight gain. The overall F0 maternal and F1 offspring NOAEL is 0.17mg/kg/d and the LOAEL is 0.50mg/kg/d.

ERA:

E4 has a log Kow of 1.65 and does not trigger a PBT assessment (log Kow >4.5) nor is it expected to bioconcentrate in aquatic organisms (log Kow >3). Based on FFLC E4 F1-generation hatching success data, the NOEC is 0.00069mg/L (measured) or 0.001mg/L (nominal). Although the FFLC concentration hatching response relation is not fully monotonic, considering that there are statistically significant differences in hatching in the middle concentrations (and partly supported by statistically significant changes in anal papillae at the highest concentration), and that E4 is an endocrine active substance which is expected to be effective on reproductive endpoints at very low concentrations, the lowest concentration (0.69ug/L) is chosen as the basis for the risk assessment.

The proposed E4 PECsw is 0.0312ug/L based on a refined Fpen of 0.0044 but an updated ERA remains to be submitted (the applicant is committed to submit an updated ERA with this PECsw as a basis). For the surface water compartment, this is stated to give a risk quotient of < 1, but the final conclusion can only be made with the submission of the updated ERA.

The ERA for DRSP is based on separate medical products and a Letter of Consent was provided. With regard to aquatic toxicity, it has resulted in a conclusion of potential surface water environmental risk from DRSP. This is also expressed in the SmPC 5.3.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical pharmacological and pharmacokinetic programme is in general considered acceptable.

The toxicity profile of estetrol has been characterised in the toxicology programme performed in mice, rats and monkey in doses up to 39 weeks duration. The doses chosen are considered appropriate to characterise the toxicity of estetrol and to make proper risk assessments. The adverse toxicities identified are overall related to the pharmacology profile of oestrogens, hence they can be considered established for these products. One important exception is the cardiac effects noted in the E4/DRSP combination toxicity study. The clinical relevance of the observed cardiotoxicity was thoroughly scrutinized. It was concluded that genetic susceptibility for cardiomyopathy in the monkey strained most likely was the main factor behind this effect. While it cannot be fully excluded that the combination of E4 and DRSP may also have contributed (directly or indirectly), the

margins of exposure to the NOAEL and the absence of similar observations in clinical studies provides further assurance that the clinical relevance of cardiotoxicity is limited. The genotoxicity programme was completed, and overall considered negative. Estetrol was evaluated in 2 carcinogenicity studies in rats and mice. The substance is carcinogenic in both species. This was expected, as oestrogen-containing combined oral contraceptives are classified as Group 1 by IARC. This combination is not different in that respect. One factor to consider is the similarity/dissimilarity between estetrol and other oestrogens used in COCs and what this means with regard to possible developmental toxicity effects. While there is likely an overlap with the COC oestrogens with regard to developmental risk, E4 has some novel ADME properties and there is yet insufficient evidential basis to make claims that it is equivalent to the older oestrogens. Finally, estetrol and drospirenone are both endocrine modulating substances, with the latter being classified as a potential environmental concern.

The CHMP considers the following measures necessary to address the non-clinical issues:

The applicant should provide an updated Environmental Risk Assessment with the E4 PECsw of 0.0312ug/L, based on a refined Fpen of 0.0044.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- ***GCP inspection***

A verification of GCP compliance of trials supporting the application was proposed by the CHMP as the Sponsor had not previously been inspected for a CAP MA, and since this product represents some degree of novelty (new estrogen not previously used in any other product).

A GCP inspection has been performed for the following clinical studies:

MIT-Es0001-C301: (pivotal European/Russian study), verification of selected efficacy and safety data reported in the Marketing Authorisation Application

MIT-Es0001-C302: (US/Canadian study), focus on Pharmacovigilance (safety and pregnancy cases processing, safety database, safety reporting)

The outcome of this inspection has now become available with the following conclusions:

- Quality of the data, ethical conduct and GCP compliance:

The trial was ethically conducted and all safety and efficacy data from the clinical trial site seem accurately recorded and reported in the Clinical Study Report. The data obtained at the sites inspected are reliable and can be accepted as support of the Marketing Authorisation Application submitted to the EMA for approval.

- Recommendation for the acceptability of the clinical trial data for the submitted application assessment:

Despite the deficiencies of the Sponsor quality management system, as almost all tasks were outsourced to the CRO, the data quality is acceptable and the trial has been conducted according to GCP and ethical standards, therefore the inspection team considers that data are trustworthy and can be used for the evaluation of the Marketing Authorisation Application submitted to the Agency.

It is noted that CRO sites were inspected remotely based on "Guidance on remote GCP inspections during the COVID19 pandemic". This decision has been made by the inspection team, in agreement with the CRO and was conducted in parallel for both inspections 2020/011 and 2020/012. Hybrid method (on-site and remote) was used for the inspection at the Sponsor site.

Issues related to the pharmacovigilance system are addressed in section 3.5 below.

- ***Tabular overview of clinical studies***

Table 1. Clinical studies conducted with E4 alone and E4/DRSP combinations with formulations used

Study ID	Phase, Study Type	Title	Formulation, dose (mg), treatment duration
Biopharmaceutics			
0030C A001	1 Bioequivalence	An open label, single centre, single dose, randomised, two-period, crossover two-stage bioequivalence study between two formulations of 15 mg estetrol and 3 mg drospirenone in healthy young female subjects	Combined tablet vs separate tablets E4/DRSP 15/3 mg; single dose E4 15 mg+ DRSP 3 mg, single dose
0031CA001	1 Bioequivalence	An open-label, single center, single-dose, randomized, crossover, bioavailability study between two formulations of 20 mg estetrol and 0.15 mg levonorgestrel in healthy female subjects	Combined tablet vs separate tablets E4/LNG 20/0.15 mg; single dose E4 20 mg + LNG 0.15 mg; single dose
0031CA002	1 Food Effect	A study to characterize the effect of food on the bioavailability of 20 mg estetrol/0.15 mg levonorgestrel tablets in healthy female volunteers	Combined tablet E4/LNG 20/0.15 mg; single dose
Es0001-C101	1 Food Effect	A study to characterize the effect of food on the bioavailability of 15 mg estetrol/3 mg drospirenone tablets in healthy female volunteers	Combined tablet E4/DRSP 15/3 mg; single dose
Clinical pharmacology E4 alone			
PR3050	1 Safety–PK-PD	A double-blind, randomized, placebo-controlled, single rising dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of estetrol in healthy postmenopausal volunteers.	Oral solution E4 0.1,1,10,100 mg; single dose
PR3054	1b Safety–PK-PD	A phase I, partly randomized, open-label, multiple dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of 3 dosages of estetrol, the lowest dose of 2 mg estetrol compared with 2 mg of estradiol, after daily oral administration for 28 days in healthy postmenopausal women	Oral solution E4 2, 10, 20, 40 mg; 28days E2V 2 mg; 28 days
PR3077	1b Safety–PK-PD	A phase I, double-blind, randomized, placebo-controlled, multiple dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of 4 dosages of estetrol after daily oral administration for 28 days in healthy men	Oral solution E4 2, 10 mg; 28 days E4 20, 40 mg (not tested)
MIT-Es0001-C102	1 PK -Safety	An open-label, single center, randomized, two period study to characterize the safety, tolerability and pharmacokinetics (PK) of estetrol (E4) after single and	Tablet E4 5, 15, 45; single dose

Study ID	Phase, Study Type	Title	Formulation, dose (mg), treatment duration
		multiple oral doses in healthy female volunteers	E4 15 mg; 14 days
MIT-Es0001-C105	1 Mass balance	An open-label, single dose study designed to assess the mass balance recovery, metabolite profiles and metabolite identification of [^{14}C] estetrol in healthy female volunteers	Oral solution [^{14}C] E4, 15 mg; single dose
Clinical pharmacology E4/DRSP combination, final film-coated fixed combination tablets			
MIT-Es0001-C103	1 SD&MD PK-Steady state PK, QTc	A randomized, double-blind, placebo-controlled, parallel, single center study to investigate the pharmacokinetics, safety, tolerability, and QT concentration-effect modelling of estetrol (E4) in combination with drospirenone (DRSP) after single and multiple dosing in healthy women	Combined Tablets (encapsulated) E4/DRSP 15/3 mg, 30/6 mg, 60/12 mg, 75/15 mg; 14 days
MIT-Es0001-C109	1 SD PK-Ethnic comparison	A single-center, double-blind, placebo-controlled, randomized study to compare the pharmacokinetic profile of different dosages of estetrol (E4) combined with drospirenone (DRSP) or E4 alone between Japanese and Caucasian populations	Combined tablets E4: 15 mg; single dose E4/DRSP: 5/3 mg,15/3 mg, 20/3; single dose
MIT-Es0001-C110	1 SD PK-DDI	An open-label, two-way cross-over study to determine the effect of multiple doses of valproic acid on the pharmacokinetics and safety of a single oral dose of estetrol/drospirenone in healthy female subjects	Combined tablet E4/DRSP 15/3 mg; single dose
MIT-Es0001-C106	1 SD&MD PK, tQTc	A phase 1, randomized, double-blind, multiple-dose, parallel group with a nested crossover design study to investigate the effects of therapeutic and supratherapeutic concentrations of estetrol (E4) in combination With drospirenone (DRSP) on the heart rate corrected QT interval (QTc) in healthy women	Combined tablets (encapsulated) E4/DRSP 15/3 mg, 75/15 mg; 10 days both doses
Dose selection and confirmation			
PR3081	2a PD-PK/PD-Saf	A feasibility study into the contraceptive effect of estetrol alone or combined with either progesterone or desogestrel by daily oral administration to healthy female volunteers for 28 days	E4: Oral solution; DSG tablet; P capsule. E4: 10,20 mg; 28 days E4/DSG 20/0.15 mg; 28 days E4/P 20/200 mg; 28 days
ES-C01	2a Eff/saf (df -PD)	A dose-finding study with active control group Yaz® to assess the contraceptive efficacy and the effect on liver function of 5 or 10 mg estetrol combined with either 3 mg drospirenone or 150 µg levonorgestrel, or 20 mg estetrol combined with 150 µg levonorgestrel, by daily oral administration to healthy female volunteers for 3 cycles of 24 days each followed by a 4-day treatment pause	Separate tablets E4 5 and 10 mg + DRSP 3 mg; 3 cycles (1 cycle = 28 days) E4 5, 10, and 20 mg + LNG 0.15 mg; 3 cycles (1 cycle = 28 days) Reference, combined tablet: EE/DRSP 0.02/3; 3 cycles (1 cycle = 28 days)

Study ID	Phase, Study Type	Title	Formulation, dose (mg), treatment duration
ES-C02	2b Eff/saf (df -PD)	A randomized, open-label, multicenter study to assess the cycle control of 15 mg or 20 mg estetrol combined with either 150 µg levonorgestrel or 3 mg drospirenone, compared to a combined oral contraceptive containing estradiol valerate and dienogest	Separate tablets E4 15 or 20 mg + DRSP 3 mg; 6 cycles (1 cycle = 28 days) E4 15 or 20 mg + LNG 0.15 mg; 6 cycles (1 cycle = 28 days) Reference, combined tablet: E2V 1/2/3 mg+ DNG 0/2/3 mg (Qlaira®); 6 cycles (1 cycle = 28 days)
MIT-Es0001-C201	2 Safety/PD	A single-center, randomized, open-label, three-arm study to evaluate the effect of E4 (15 mg) in combination with DRSP (3 mg) and of two reference COCs containing either EE (30 ug) and LNG (150 ug) or EE (20 ug) and DRSP (3 mg) on endocrine function, metabolic control and hemostasis during 6 treatment cycles.	Tablet (combination) E4/DRSP 15/3; 6 cycles (1 cycle = 28 days) EE/DRSP 0.02/3; 6 cycles (1 cycle = 28 days) EE/LNG 0.03/0.15; 6 cycles (1 cycle = 28 days)
MIT-Es0001-C202	2 Efficacy/PD	A single-center, randomized, open-label, two-arm study to evaluate the ovarian function of a monophasic combined oral contraceptive (COC) containing 15 mg Estetrol (E4) and 3 mg drospirenone (DRSP) and a monophasic COC containing 20 mcg ethinylestradiol (EE)/3 mg DRSP (Yaz®), administered orally once daily in a 24/4 day regimen for three consecutive cycles	Tablet (combination) E4/DRSP 15/3; 3 cycles (1 cycle = 28 days) EE/DRSP 0.02/3; 3 cycles (1 cycle = 28 days)
Phase 3, final film-coated fixed combination tablets			
MIT-Es0001-C301	3 Efficacy/safety EU/Rus	A multicenter, open-label, single-arm study to evaluate the contraceptive efficacy and safety of a combined oral contraceptive containing 15 mg estetrol and 3 mg drospirenone	Tablet (combination) E4/DRSP 15/3; 13 cycles (1 cycle = 28 days)
MIT-Es0001-C302	3 Efficacy/safety US/Can	A multicenter, open-label, single-arm study to evaluate the contraceptive efficacy and safety of a combined oral contraceptive containing 15 mg estetrol and 3 mg drospirenone	Tablet (combination) E4/DRSP 15/3; 13 cycles (1 cycle = 28 days)

DNG = dienogest, DRSP = drospirenone, DSG = desogestrel, E4 = estetrol, LNG = levonorgestrel, E2V = estradiol valerate, PD = pharmacodynamics, PK = pharmacokinetics

2.4.2. Pharmacokinetics

The Applicant has conducted several clinical studies addressing the PK of estetrol alone, as well as the clinical studies addressing the PK of estetrol with co-administration of drospirenone. In general, basic PK information of estetrol was provided/described by the Applicant and included in the SmPC.

For drospirenone, no *in vitro* PK or PD studies using human biomaterials were conducted by the Applicant. Furthermore, no DDI potential of drospirenone was investigated. Since drospirenone is already approved in other medicinal products, many PK aspects were described by referring to the available published literature. However, the Applicant has also obtained new clinical PK data for drospirenone with the co-administration of estetrol, and these are also included in the SmPC.

The PK properties of estetrol alone were established in five clinical trials. Post-menopausal women in two early clinical trials (Studies **PR3050**, **PR3054**) and men in one clinical trial (Study **PR3077**) received single or repeated doses of estetrol as a solution over a dose range from 0.1 to 100 mg. Pre- and post-menopausal women received a single ascending dose of estetrol and multiple doses of estetrol 15 mg administered as a tablet in a further clinical trial (Study **MIT-Es0001-C102**). Lastly, post-menopausal women received single doses of 15 mg [^{14}C]-E4 to assess mass balance recovery, PK, metabolite profiling and identification in a mass balance study (Study **MIT Es0001-C105**).

Three clinical trials were performed to investigate the estetrol and drospirenone combination PK profiles (study **MIT-Es0001-C103**, **MIT-Es0001-C106** and **MIT-Es0001-C109**).

Furthermore, one additional clinical DDI study with the valproic acid was also conducted (study **MIT-Es0001-C110**).

Finally, additional PK data from four Phase I biopharmaceutic clinical trials investigating bioequivalence and food effects were also obtained for estetrol/drospirenone combination (studies **0030CA001**, **Es0001-C101**) and additional "supportive" studies with estetrol /levonorgestrel combination (studies **0031CA001**, **0031CA002**).

It is worth emphasizing that Phase I clinical studies **PR3050**, **PR3054**, **PR3077** and **MIT-Es0001-C105** were conducted by administering estetrol as an oral solution, while in other clinical studies estetrol was administered in the form of film-coated tablets with or without drospirenone.

A brief tabular overview of PK studies is given in the table below:

Table 2. Studies in which pharmacokinetics is included.

Study Number	Description	Dose	Subjects
Phase 1 studies; Oral solution			
PR3050	Single rising dose	E4 0.1 mg E4 1 mg E4 10 mg E4 100 mg	Healthy postmenopausal volunteers N=32
PR3054	Multiple dose study with estetrol and estradiol (28 days)	E4 2 mg E4 10 mg E4 20 mg	Healthy postmenopausal volunteers N=49

Study Number	Description	Dose	Subjects
		E4 40 mg	
PR3077	Multiple dose study (28 days)	E4 2 mg E4 10 mg	Healthy men N=20
MIT-Es0001-C105	Mass balance study; single dose	[^{14}C]-Estetrol monohydrate 15 mg	Healthy female volunteers N=6
Phase 1 studies; Film-coated tablets			
0030CA001	Single dose bioequivalence study	E4/DRSP 15/3 mg E4 15 mg + DRSP 3 mg	Healthy young female subjects N=11
0031CA001	Single dose bioequivalence study	E4/LNG 20/0.15 mg E4 20 mg + LNG 0.15 mg	Healthy female volunteers N=28
0031CA002	Food interaction study; single dose	E4/LNG 20/0.15 mg	Healthy female volunteers N=24
Es0001-C101	Food interaction study; single dose	**E4/DRSP 15/3 mg (final formulation)**	Healthy female volunteers N=24
MIT-Es0001-C102	Single and multiple dose study	E4 5 mg E4 15 mg E4 45 mg	Healthy female volunteers N=27
MIT-Es0001-C103	Single and multiple dose study	**E4/DRSP 15/3 mg (final formulation)** E4/DRSP 30/6 mg E4/DRSP 60/12 mg E4/DRSP 75/15 mg	Healthy women N=55
MIT-Es0001-C106	Multiple dose study	**E4/DRSP 15/3 mg (final formulation)** **E4/DRSP 75/15 mg (5 * final formulation)**	Healthy women N=32
MIT-Es0001-C109	Single dose study; Study influence of ethnicity	**E4/DRSP 15/3 mg (final formulation)** E4 15 mg E4/DRSP 5/3 mg E4/DRSP 20/3 mg	Japanese healthy women N=48 Caucasian healthy women N=48
MIT-Es0001-C110	Interaction study with valproic acid	**E4/DRSP 15/3 mg (SD) (final formulation)** Valproic acid @@ mg (MD)	Healthy female subjects N=
Phase 2 study; Film-coated tablets			
ES-C01	Comparative study with Yaz®; treatment of 3 cycles of 24 days each followed by a 4-day treatment pause	- E4 5 mg + DRSP 3 mg - E4 10 mg + DRSP 3 mg - E4 5 mg + LNG 0.15 mg - E4 10 mg + LNG 0.15 mg - E4 20 mg + LNG 0.15 mg - EE/DRSP 0.02/3 mg (Jazz$^{(R)}$)	Healthy female volunteers N=24
Phase 3 study; Film-coated tablets			
MIT-Es0001-C302	Efficacy study with population PK substudy	**E4/DRSP 15/3 mg (final formulation)**	Healthy female volunteers N=1024

Overview of the PK parameters obtained with the single dose of estetrol at 15 mg (i.e. proposed therapeutic dose) is given in the table below.

Table 3. Overview of PK plasma parameters obtained in different clinical studies after single dose administration of estetrol at 15 mg with or without co-administration of drospirenone at 3 mg.

Study	GM (GM CV%)				Median (Min-Max)
	C_{max} (ng/mL)	AUC_{0-inf} (ng*hr/mL)	AUC_{0-24} (ng*hr/mL)	$t_{1/2}$ (hr)	T_{max} (hr)
	Treatment: E4 15 mg				
MIT-Es0001-C102	17.89 (57.56)	87.09 (28.24)	44.92 (28.35)	18.47 (31.66)	0.50 (0.33-1.50)
MIT-Es0001-C105	16.6 (18.7)	92.6 (15.2)	NC	31.72 (31.8)	0.25 (0.25-0.50)
MIT-Es0001-C109[a]	18.56 (39.4)	69.02 (73.3)	NC	23.79 (57.0)	0.34 (0.33-2.0)
	Treatment: E4/DRSP 15/3 mg fixed-dose combination				
0030CA001	11.34 (42.7)	73.54 (18.6)	NC	34.37 (27.0)	0.63 (0.25-1.25)
Es0001-C101	14.33 (0.75)	62.83 (0.41)	NC	NC	0.50 (0.17-1.50)
MIT-Es0001-C103	18.0 (61.3)	72.0 (31.7)	36.4 (29.9)	24.3 (39.2)	0.50 (0.50-2.00)
MIT-Es0001-C109[a]	10.1 (82.8)	80.22 (51.4)	NC	23.89 (25.1)	0.50 (0.33-2.52)

[a] Caucasian subjects, [b] $AUC_{0-\tau}$, [c] AUC_{0-24}. Values are provided as GM (GM CV%) or for T_{max} as median (min-max)
AUC = area under the plasma concentration-versus-time curve, AUC_{0-24} = AUC from baseline to 24 hours, $AUC_{0-\tau}$ = AUC during a dosage interval (τ), AUC_{0-inf} = AUC from zero to infinite time, C_{max} = maximum plasma concentration, GM CV = coefficient of variation of the geometric mean, DRSP = drospirenone, E4 = estetrol, GM = geometric mean, NC = not calculated, $t_{1/2}$ = elimination half-life, T_{max} = time to C_{max}

Analytical methods

The concentrations of E4 and DRSP in human plasma and urine were determined using validated liquid chromatography methods with tandem mass spectrometry (LC-MS/MS) or ultrahigh performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS).

Population PK

The applicant has developed a popPK model for drospirenone and a popPK model for estetrol. No claims are made from the popPK models in the SmPC and the models do not raise any concerns.

Absorption

Results from all clinical trials (with PK data) imply that following an oral administration, estetrol is rapidly absorbed from the gastrointestinal tract with C_{max} observed within 1 hour. It is worth emphasizing that after the initial absorption phase, lower secondary reabsorption peaks were observed indicating the enterohepatic recycling. No PK data were obtained in human subjects following intravenous administration of estetrol, and therefore no data about the (absolute) bioavailability are available. In the mass-balance study, 69% of administered radioactivity was recovered from urine which implies that the absolute bioavailability is at least 69%.

Initial Phase I studies used estetrol as an oral solution (Study PR3050, PR3054, PR3077, MIT-Es0001-C105) while in the remaining clinical trials drug was administered as film-coated tablet (FCT). The rate of absorption was slower with the tablet formulation compared to the oral solution. The difference was however limited, with T_{max} for estetrol observed after 0.5 hour for the oral solution and within 0.5 to 1 hour for the film-coated tablets.

In vitro findings implied that estetrol acts as a P-gp and BCRP substrate. Co-administration of drugs that affect the activity of P-gp and BCRP is however unlikely to result in a clinically relevant drug interaction with estetrol.

The Applicant has conducted one clinical study **Es0001-C101** to characterise the effect of food on the bioavailability of 15 mg estetrol/3 mg drospirenone tablets. C_{max} of estetrol and DRSP following oral administration of a single estetrol/DRSP 15/3 mg tablet in fed conditions was lower than in fasted conditions, and it was outside of the standard BE acceptance criteria. The median estetrol T_{max} under fasted conditions was 0.50 h versus 0.75 h under fed conditions, and for DRSP it was 1.23 and 1.67 h, respectively. However, the extent (AUC) of estetrol and DRSP absorption following oral administration of a single estetrol/DRSP 15/3 mg tablet in fed conditions was equivalent to the one in fasted conditions. Importantly, clinical studies have demonstrated adequate efficacy and safety at these exposure levels with estetrol. Therefore, present SmPC 4.2 text suggests that the drug can be taken every day at about the same time, if necessary, with a little liquid.

Distribution

The apparent volume of distribution determined after oral administration (V/F) of estetrol 15 mg alone and in combination with DRSP 3 mg was high (range GM V/F for estetrol 15 mg, 4450 to 7460 L) indicating that estetrol is widely distributed in tissues with only a limited amount in plasma. This is consistent with the quick distribution and slow terminal elimination phase observed in the PK profile of estetrol. PK profiles of estetrol indicated secondary peaks which implied entero-hepatic recirculation. This may be due to intestinal reabsorption of estetrol following biliary excretion of estetrol (or estetrol-glucuronide which can undergo bacterial hydrolysis to estetrol in the gut).

Study denoted as **ES-T33** investigated the *in vitro* binding of estetrol to plasma proteins from female mouse, rat, monkey and human by implementing the Equilibrium Dialysis (ED) technique. The protein binding of estetrol ranged between 44.8 and 67.2% in plasma from mouse, rat, monkeys and human. Plasma protein binding in human ranged from 45% to 50.4 %. There was no clear concentration dependence of plasma protein binding for any of the species evaluated. Furthermore, no species differences in the extent of plasma protein binding was apparent.

No *in vitro* study with DRSP was conducted by the Applicant. Based on the provided literature, the plasma protein binding of DRSP ranges from 95 to 97%, with a majority bound to albumin, and 3 to 5% circulating freely or unbound (Schindler et al., 2003).

Elimination

Following administration of a single oral solution of 15 mg [^{14}C]-estetrol, approximately 69% of the total recovered radioactivity was detected in urine, and 21.9% in faeces (**MIT-Es0001-C105** Study). No parent compound was detected in urine. Main metabolites quantified in urine were estetrol-3-glucuronide and estetrol-16-glucuronide. The low recovery of radioactivity in faeces over the first 24 hours post-dose suggests that absorption of [^{14}C]-estetrol was high, with relatively few (<2.5%) unabsorbed drug related material recovered in faeces within this time.

Following dosing, estetrol and total radioactivity were rapidly absorbed. The geometric mean apparent terminal half-life for estetrol was 31.7 h. Metabolic burden following dosing of [^{14}C]-estetrol was high, with exposures of estetrol (parent) accounting for only 15.8% of circulating total radioactivity.

The observed geometric mean renal clearance for estetrol was low at only 8.10 mL/min. However, the renal clearance for total radioactivity was much higher at 273 mL/min, suggesting an overall net secretion when compared to the glomerular filtration rate of 125 mL/min.

Table 4. Study MIT-Es0001-C105. Mean recovery of total radioactivity in urine and faeces following a single oral dose of 15 mg [14C]-estetrol (N= 6).

Collection period (hrs)	Urine			Feces		
	%Ae	CV%	N	%Ae	CV%	N
-12-0	0.0	-	6	0.0	-	5
0-6	21.737	16.3	6	2.428	178.7	6
6-12	5.597	68.7	6			
12-24	10.187	23.7	6			
24-48	12.857	22.5	6	3.878	113.2	6
48-72	7.252	20.9	6	7.573	47.2	6
72-96	4.800	34.1	6	3.418	44.5	6
96-120	2.742	28.5	6	2.092	67.4	6
120-144	1.602	45.5	6	1.072	93.1	6
144-168	0.965	64.5	6	1.038	96.5	6
168-192	0.568	62.9	6	0.500	62.0	6
192-216	0.332	77.4	6	0.402	90.8	6
216-240	0.205	82.9	6	0.215	125.9	6
240-264	0.130	68.4	3	0.220	90.8	3
264-288	0.220	-	1	0.080	-	1
288-312	0.160	-	1	0.190	-	1

%Ae = amount excreted expressed as percentage of the dose of total radioactivity administered, CV = coefficient of variation, N = number

For the majority of estetrol administered orally to women, after conjugation, urine excretion is the predominant route of elimination (Studies ES-C01, MIT-Es0001-C105). The terminal elimination half-life was generally estimated between 20 and 30 hours. Under the steady-state conditions, the GM elimination half-life (CV%) was calculated to be 24.3 hours (26.3) (Study **MIT-Es0001-C103**).

Excretion of DRSP is nearly complete after 10 days with very small amounts excreted unchanged in urine and faeces (Krattenmacher, 2000). At least 20 different metabolites are observed in urine and faeces. Less than 10% of the metabolites in urine are freely extractable, while about 38% to 47% are excreted as glucuronide- and sulfate-conjugates. In faeces, about one-third of the metabolites are freely extractable and about 17% to 20% are excreted as glucuronides and sulphates. The t1/2 is about 30 to 40 hours (Martindale, 2019). This was confirmed by results of study MIT-Es0001-C103; after oral administration of E4/DRSP 15/3 mg fixed-dose combination, plasma DRSP levels decreased with a t1/2 of 34.2 hours.

Moreover, the Applicant has conducted several *in vitro* studies addressing different aspects of the metabolism of estetrol by using different *in vitro* systems such as cryopreserved hepatocytes, human liver microsomes and individual recombinant enzymes. Study 0031-102 which was designed to obtain the information on major cytochrome P450 enzymes, indicated no involvement of these enzymes in the metabolism of estetrol. Study 0031-106 investigated potential involvement of UGT enzymes in the metabolism of estetrol by using human liver microsomes as well as recombinant rUGT enzymes expressing single human UGT enzymes. Both *in vitro* systems identified UGT2B7 as the key enzyme catalysing glucuronidation of estetrol. Study PR3099 investigated the ability of seven isoforms of human cytosolic sulfotransferase (SULT) to catalyse the sulphation of estetrol, namely SULT1A1, 1A3, 1B1, 1E1, 1C2, 2A1, and 2B1b. SULT1E1 was the dominant sulfotransferase isoform that catalyses formation of a direct sulphate i.e. estetrol-3-sulphate *in vitro*. Overall, based on all the conducted *in*

vitro studies, it appears that estetrol undergoes phase 2 metabolism to form glucuronide and sulphate conjugates.

Dose proportionality and time dependencies

Dose-proportionality

Overall, estetrol appeared to demonstrate a dose-proportional PK. Estetrol exposure in plasma was increasing with increasing doses, both after single (SAD) and repeated (MAD) dosing. It is worth emphasizing that Phase I clinical studies PR3050, PR3054, PR3077 were conducted by administering estetrol as an oral solution, while in other clinical studies described in this section, estetrol was administered in the form of film-coated tablets with or without co-administration of drospirenone. In the studies where estetrol was administered as an oral solution, a more than dose proportional increase in C_{max} and approximately dose-proportional increase in AUC was observed. In the studies conducted with film-coated tablets, a generally better dose-proportionality in terms of both C_{max} and AUC was observed.

Accumulation ratio R_{AC} of estetrol observed with once daily dosing at the proposed therapeutic dose of 15 mg was about 1.6.

Co-administration of drospirenone did not seem to influence the PK properties of estetrol.

Studies PR3050 and PR3054 included only post-menopausal women, and PR3077 study included only men (i.e. populations for which estetrol is not indicated in the present MAA), but the obtained PK parameters seemed not to differ from the target population (see also Special populations heading).

Pharmacokinetics in target population

Three clinical trials were performed to investigate the estetrol and drospirenone combination PK profiles (study MIT-Es0001-C103, MIT-Es0001-C106 and MIT-Es0001-C109).

Study MIT-Es0001-C103

This was a randomized, double-blind, placebo-controlled, parallel, single centre study to investigate the pharmacokinetics, safety, tolerability, and QT concentration-effect modelling of estetrol (E4) in combination with drospirenone (DRSP) after single and multiple dosing in healthy women. Subjects received therapeutic and supratherapeutic single and multiple doses (14 days) of E4 in combination with DRSP. Plasma PK parameters were estimated using noncompartmental analysis: T_{max}, C_{max}, AUC_{0-24}, $AUC_{0-tlast}$, AUC_{0-inf}, K_{el}, $t_{1/2}$, and R_{AC}.

Median T_{max} values ranged from 0.5 to 1.26 h (E4) and 1 to 2 h (DRSP) following single and multiple dose administrations. Geometric mean $t_{1/2}$ values were similar following single dose and multiple dose administrations and ranged from 20.2 to 24.3 h for E4 and from 28.4 to 37.1 h for DRSP.

The observed increase in E4 and DRSP exposure in terms of AUC appeared to be dose-proportional. In terms of C_{max}, the observed increase in exposure to E4 and DRSP was slightly less than dose-proportional.

The geometric mean accumulation ratio (comparing AUC after 14 days and 1 day of E4/DRSP dosing) ranged from 1.62 to 1.87 for plasma estetrol and from 2.32 to 2.58 for plasma DRSP. Similar C_{max} values were observed for estetrol between Day 1 and Day 14 for the respective doses.

Following multiple dose administrations, steady state estetrol concentrations appeared to have been reached after 5-6 days of dosing for the 15 mg E4/3 mg DRSP.

Study MIT-Es0001-C106

Overall, the main aspects of this clinical trial were the evaluation of safety parameters. The PK of E4/DRSP was assessed following administration of therapeutic (15/3 mg) and supratherapeutic (75/15 mg) multiple oral doses of E4/DRSP. Subjects in Group 1 (N = 32) received a therapeutic dose of E4/DRSP once daily for 10 days followed by a supratherapeutic dose once daily for another 10 days. Of the 32 women treated with the E4/DRSP, 30 completed the study.

Estetrol was rapidly absorbed following oral dosing with a median T_{max} of 1 hour on both Day 10 after therapeutic treatment and Day 20 after supratherapeutic treatment. A 5-fold increase in the amount of esterol administered between Day 10 and Day 20 resulted in a 5.4 -fold increase in C_{max} and a 4.5-fold increase in AUC_{0-t} from Day 10 (therapeutic) to Day 20 (supratherapeutic), which implies dose-proportionality.

DRSP was also rapidly absorbed after oral administration with a median T_{max} of 1.55 hours on Day 10 after therapeutic treatment and 2 hours on Day 20 after supratherapeutic treatment. A 5-fold increase in the amount of DRSP administered between Day 10 and Da y 20 resulted in a 5.4-fold increase in C_{max} and a 5.8-fold increase in AUC_{0-t} between Day 10 (therapeutic) to Day 20 (supratherapeutic), implying dose-proportionality.

No single dose PK was described in this study, and therefore no accumulation ratios (R_{AC}) nor time-dependency aspects are provided/available from this study.

Study MIT-Es0001-C109

This was a single-centre, double-blind, placebo-controlled, randomized study to compare the PK profile of different dosages of estetrol (E4) combined with drospirenone (DRSP) or E4 alone between Japanese and Caucasian populations.

Ninety-six female subjects (48 Caucasian and 48 Japanese) were enrolled. Each treatment group consisted of 12 Japanese and 12 Caucasian subjects (active treatment: N=10, placebo: N=2). Subjects received single doses of E4/DRSP, E4 15 mg tablets or placebo.

The overall data indicated no relevant PK differences between Japanese and Caucasian subjects.

Estetrol was quickly absorbed with a median T_{max} of 0.34 to 1.38 hours in Japanese and Caucasian subjects. In the presence of DRSP (3 mg), estetrol C_{max}, AUC_{0-t} and AUC_{0-inf} seemed to increase in a dose proportional manner for Japanese and Caucasian subjects across the dose range studied (5, 15 and 20 mg). At 15 mg, estetrol displays similar exposure for Japanese and Caucasian subjects with or without the presence of DRSP (3 mg). The geometric means ratios of "Japanese/Caucasian" for the PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were about 1.

Drospirenone was quickly absorbed with a median T_{max} of 1.00 to 1.75 hours in Japanese and Caucasian subjects. In the presence of estetrol (5, 15 and 20 mg), DRSP C_{max}, AUC_{0-t} and AUC_{0-inf} remained constant for Japanese and Caucasian subjects. The geometric means ratios of "Japanese/Caucasian" for the PK parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were about 1.

Special populations

No dedicated studies in RI and HI patients were conducted by the Applicant. This was justified by stating that other approved medicinal products which contain drospirenone are contraindicated in patients with severe RI and HI. According to the Applicant: "*Products containing DRSP are contraindicated in subjects with renal impairment and liver disease. Consequently, the sponsor intends to contraindicate the E4/DRSP COC too in renally and hepatically impaired subjects, hence specific studies with E4/DRSP in this population have not been conducted*".

Influence of age (elderly) and gender (men) are not relevant when considering the proposed indication/target population. However, it is worth mentioning that the studies PR3050 and PR3054 included only post-menopausal women, and PR3077 study included only men (i.e. populations for which estetrol is not indicated in the present MAA), but the obtained PK parameters seemed not to differ substantially from the target population.

On the grounds that the E4/DRSP COC is intended for a condition that does not occur in boys and in girls between birth and menarche, a waiver for these paediatric subsets has been granted. It is agreed with the Applicant that PK and pharmacodynamics/efficacy of E4/DRSP might be considered largely comparable between post-menarcheal adolescent girls and adult females. After regulatory consultation, the Applicant has therefore agreed to the conduct of a 6-cycle open-label clinical study to evaluate the safety, PK, compliance and efficacy of the E4/DRSP COC in post-menarcheal girls aged 12 to 17 years of age, to be completed by December 2021.

Influence of race was investigated in one clinical study MIT-Es0001-C109 (see more details above) which generally implied no differences in the PK between healthy Japanese and Caucasian women.

Pharmacokinetic interaction studies

The Applicant has conducted 4 *in vitro* studies investigating the interaction potential of estetrol with CYP and/or UGT enzymes: study **0031-100** which investigated the induction potential, and studies **PR3038**, **0031-101** and **0031-105** which examined the inhibitory potential.

Furthermore, the Applicant has conducted four *in vitro* studies addressing different aspects of interaction potential of estetrol (both as a perpetrator and/or substrate) with drug transporters. These studies were denoted as: **0031-NC017**, **0031-103**, **Es0001-NC-013**, **0031-107**.

No *in silico* studies addressing interaction potential of estetrol were conducted.

Finally, the Applicant has also conducted one clinical DDI study (**MIT-Es0001-C110**) with the valproic acid (VAL) as a perpetrator drug i.e. UGT2B7 inhibitor (main UGT isoform which catalyses biotransformation of estetrol into a direct glucuronide).

No interaction studies with drospirenone were conducted by the Applicant, apart from the comparison of estetrol PK with and without drospirenone co-administration which seemed to be unaffected. Drospirenone was introduced for medical use in 2000. In view of the well-established use and proven clinical efficacy and safety of DRSP, *in vitro* human biomaterial studies and *in vivo* clinical pharmacology studies with DRSP alone or with E4/DRSP combination to investigate potential drug interactions have not been conducted.

Based on the maximal observed concentration (C_{max}=17.9 ng/mL) in clinical studies with the proposed therapeutic dose of estetrol (D=15 mg, or 14.2 mg as estetrol anhydrous) and its estimated unbound fraction (f_u about 0.5), the concentration cut-off for the *in vitro* investigation of systemic interaction potential (according to

EMA's DDI guideline) is calculated to be **1.47 µM** (when taking into account MW=304.38 g/mol for estetrol, anhydrous). Furthermore, the corresponding concentration cut-off for the intestinal exposure is estimated to be **18.7 µM**, while the hepatic inlet exposure was **36.7 µM** (i.e. assuming f_a=1, f_g=1, k_a=0.1min^{-1}, Q=97L/h).

Most of the *in vitro* studies have included sufficiently high estetrol concentrations (as "perpetrator" drug) covering EMA's concentration cut-off values as presented above, and therefore *in vitro* perpetrator studies appeared adequate in this regard.

The presented *in vitro* data implied a generally low interaction potential with estetrol as a perpetrator drug. Based on the presented IC50 values, a small interaction signal was detected for CYP3A4 enzyme with the estimated IC50 value of about 40 µM, which was not considered as clinically relevant according to the basic model of EMA DDI guideline. When it comes to UGT enzymes, IC50 values for UGT1A9 were 95.5 and 25.8 µM, while for UGT2B7 they were 89.4 µM and 38.0 µM in microsomes and rUGTs, respectively. These values were also not considered as clinically relevant according to the basic model of EMA DDI guideline, i.e. no interaction risk. Transporter for which an inhibitory signal was detected was OAT3 (IC50 of 16.5 ± 1.5 µM), however this *in vitro* signal was not considered as a clinically relevant according to the basic model of EMA DDI guideline.

Based on the *in vitro* experiments (studies 0031-103 and Es0001-NC-013) estetrol appeared to be a P-gp and BCRP substrate. Co-administration of drugs that affect the activity of P-gp and BCRP is however unlikely to result in a clinically relevant drug interaction with estetrol.

In the *in vivo* DDI study (**MIT-Es0001-C110**) with the valproic acid as a perpetrator drug i.e. UGT2B7 inhibitor (UGT isoform that catalyses biotransformation of estetrol into a direct glucuronide), there was a statistically significant increase in the exposure of estetrol (with a 1.36-fold increase in geometric mean Cmax for estetrol, and 1.13-fold increase in $AUC_{0\text{-}inf}$). This study did not provide results about the potentially opposite DDI scenario, i.e. valproic acid as a potential victim drug and estetrol as a potential perpetrator.

Pharmacokinetics using human biomaterials

In the study denoted as **0031-104**, the Applicant has also investigated the plasma-to-blood cell partitioning ratio of 14C-estetrol in human blood samples. 14C-Estetrol was approximately equally distributed between the blood cells and plasma. The distribution was not time nor concentration dependent.

In competitive binding assays with [3H] dihydrotestosterone (DHT) or [3H]-E2 as ligands, E4 showed no binding to human sex hormone binding globulin - SHBG (Study **PR3025**).

A complete assessment for DRSP has been already done and currently available in the product information of approved products and in peer reviewed publications. Repetition of certain tests or trials is unlikely to extend the scientific knowledge about DRSP.

2.4.3. Pharmacodynamics

The clinical PD pharmacology programme of estetrol monohydrate (E4) and drospirenone (DRSP) consisted of seven studies, performed in the following order:

Initially, the safety, tolerability, (PK) and PD properties of E4 alone were analysed during two phase 1 single- and multiple-dose studies in postmenopausal women. **PR3050** E4 was a single-dose, first-in-human, double-blind, randomized, placebo-controlled, single rising dose (of E4 0.1, 1, 10, or 100 mg) study to evaluate the safety, tolerability, PK and PD of E4 in postmenopausal women. **PR3054** was a multiple-dose, phase I,

partly randomized, open-label study to evaluate the safety, tolerability, (PK) and PD of four dosages of E4 (2, 10, 20, or 40 mg), the lowest dose of 2 mg E4 was compared with 2 mg of estradiol valerate (E2V), for 28 days in healthy postmenopausal women.

After these two studies, a phase 2a proof of concept multiple-dose study, **PR3081**, was conducted. This was a feasibility study to evaluate the contraceptive effect of E4 (10 mg or 20 mg) alone or combined with either progesterone (P4) or desogestrel (DSG) (20 mg E4/150 mcg DSG and 20 mg E4/200 mg P4) in healthy women of reproductive age for 28 days.

ES-C01 was a phase 2a dose-finding study with active control group Yaz (20 mcg EE/3 mg DRSP). In this study the contraceptive efficacy of 5 or 10 mg E4 combined with either 3 mg DRSP or 150 mcg levonorgestrel (LNG), or 20 mg E4 combined with 150 mcg LNG, for three cycles of 24 days each followed by a 4-day treatment pause.

Study **ES-C02** was conducted as a phase 2b dose confirmation study on cycle control. This dose-finding study was performed to evaluate cycle control of 15 mg or 20 mg E4 combined with either 150 mcg LNG or 3 mg DRSP, compared to reference COC containing E2V and dienogest (DNG) Qlaira for six cycles. Treatments consisted of 15 mg E4/150 mcg LNG, 20 mg E4/150 mcg LNG; 15 mg E4/3 mg DRSP, 20 mg E4/3 mg DRSP; 1/2/3 mg E2V and 0/2/3 mg DNG (Qlaira) as control.

Further, to confirm the contraceptive mechanisms of action with the determined dose and regimen, study MIT-Es0001-C202 was performed. This was a dose-confirmative, two-arm study to evaluate the ovarian function inhibition of 15 mg E4/3 mg DRSP in comparison to 20 mcg EE/3 mg DRSP (Yaz), in a 24/4 day regimen for three consecutive cycles.

At last, **MIT-Es0001-C201** is a study that assessed the effect of E4/DRSP 15/3 mg on the endocrine function, metabolic control, and haemostasis during six treatment cycles.

No studies have been performed with DRSP alone within this MAA.

A tabular listing of these seven clinical PD pharmacology studies is provided in **Table 12** below.

Table 5. Description of key and supportive PD studies with E4 alone or E4/progestin for oral contraception

Study ID	No of study centres Location Study start	Study Phase Objective	Study design Diagnosis	Subjects (treated / completed)	Mean age (range)	Test product, dosage regimen, route of administration	Duration of treatment
ES-C02	10 FI Oct 2010	2b Efficacy / safety (dose-finding) -PD	R, OL, five-arm, MC Healthy WOCBP (18 to ≤35 years) requesting contraception	389/316	24.1 years (18-35)	E4/DRSP 15/3 mg: n=79* E4/DRSP 20/3 mg: n=75* E4/LNG 15/0.15 mg: n=80* E4/LNG 20/0.15 mg: n=77* E2V/DNG 1/2/3 0/2/3 mg: n=78	6 cycles
MIT-Es0001-C201	1 NL Sep 2016	2 Safety, PD	R, OL, three-arm, SC Healthy WOCBP (18 to ≤ 50 years) requesting contraception	100/88	26.2 years (18 – 47)	E4/DRSP 15/3 mg: n=38 EE/LNG 0.03/0.15 mg: n=30 EE/DRSP 0.02/3 mg: n=32	6 cycles
MIT-Es0001-C202	1 NL Feb 2017	2 Safety / efficacy	R, OL, two-arm, SC Healthy WOCBP (18 to ≤35 years) requesting contraception	82/71	25.6 years (19-35)	E4/DRSP 15/3 mg: 41 EE/DRSP 0.02/3 mg: 41	3 cycles
ES-C01	1 NL Nov 2009	2a Efficacy/safety (dose-finding) -PD	OL, R	109/85	22.9 years (18-33)	E4/DRSP 5/3 mg: n=17 E4/DRSP 10/3 mg: n=19 E4/LNG 5/0.15 mg: n=18 E4/LNG 10/0.15 mg: n=17 E4/LNG 20/0.15 mg: n=18 EE/DRSP 0.02/3 mg: n=20	3 cycles

Study ID	No of study centres Location Study start	Study Phase Objective	Study design Diagnosis	Subjects (treated / completed)	Mean age (range)	Test product, dosage regimen, route of administration	Duration of treatment
PR3081	1 NL Nov 2007	2a Safety – PK-PD	OL, R Healthy WOCBP (18 to ≤40 years)	52/49	25.8 years (18-40)	E4 10 mg: n=10 E4 20 mg: n=11 E4/DSG 20/0.15 mg: n=15 E4/P4 20/200 mg: n=16	1 cycle (28 days)
PR3050	1 NL Mar 2003	1 Safety – PK-PD	DB, R, placebo controlled, SD Healthy post-menopausal women	32/32	59.9 years (53-69)	Placebo: n=8 E4 0.1 mg: n=6 E4 1 mg: n=6 E4 10 mg: n=6 E4 100 mg: n=6	Single dose
PR3054	1 NL July 2005	1b Safety – PK-PD	OL, partly randomized, comparator controlled Healthy post-menopausal women (≤70 years)	49/49	59.6 years (47-70)	E2V 2 mg: n=10 E4 2 mg: n=10 E4 10 mg: n=10 E4 20 mg: n=10 E4 40 mg: n=9	1 cycle

Mechanism of action

Combined oral contraceptives (COCs) contain a progestin and an estrogen. Progestins inhibit ovulation primarily by a central feedback mechanism resulting in decreased Luteinizing Hormone (LH) secretion by the pituitary. Estrogen contributes to contraceptive efficacy, because of its inhibitory effect on Follicle Stimulating Hormone (FSH) secretion, but the major purpose for estrogen in the COC is to balance the effects of the progestin on the endometrium to provide an acceptable bleeding pattern during COC use.

The medicinal product is a combination of estetrol monohydrate 15 mg/drospirenone 3 mg (E4/DRSP 15/3 mg). E4 is a newly introduced estrogen and DRSP is a known progestin and widely used in the currently available COCs.

Estetrol (E4)

E4 is an estrogen which is only produced during human pregnancy by the human foetal liver and reaches the maternal circulation through the placenta. This hormone was first described by Diczfalusy *et al* in 1965 (Haagen et al., 1965). E4 binds specifically to estrogen receptors (ER) α and β, with a 4- to 5-fold preference for ERα. Human maternal plasma levels increase during pregnancy to achieve a plasma concentration ranging from 0.4 to 1.2 ng/mL towards the end of gestation, while fetal plasma levels have been reported to be over 10 times higher than maternal plasma levels at parturition (Visser et al., 2008; Coelingh Bennink et al., 2008a).

Drospirenone (DRSP)

DRSP is a synthetic progestin and an antagonist of mineralocorticoid and androgen receptors. It has no estrogenic, glucocorticoid and anti-glucocorticoid activity (Fuhrmann et al., 1996). Progestins, such as DRSP, diffuse freely into target cells in the female reproductive tract, mammary gland, hypothalamus, and the pituitary and bind to the PR. Once bound to the receptor, progestins slow the frequency of release of gonadotropin releasing hormone (GnRH) from the hypothalamus and blunt the pre-ovulatory LH surge. Endometrial transformation, inhibition of ovulation, and anti-mineralocorticoid, i.e. natriuretic effects and mild anti-androgenic effects were also reported in humans on DRSP (Elger et al., 2003). DRSP is currently widely used in the EU and US in the combination with EE (EE/DRSP 0.03/3 mg (Yasmin) and 0.02/3 mg (Yasminelle/Yaz)).

Primary and Secondary pharmacology

Primary pharmacology

PD of DRSP

The Applicant provided the following literature data:

DRSP is a well-characterized and widely used progestin described in detail in the scientific literature (Muhn et al., 1995; Krattenmacher, 2000; Blode et al., 2012; Martindale). DRSP is structurally related to spironolactone, the well-known aldosterone antagonist used as a potassium sparing diuretic (Krattenmacher, 2000).

In receptor-binding assays, DRSP showed an affinity for human PR comparable to that of progesterone itself (RBA 20% for DRSP and 30% for progesterone vs reference compound R5020) (Pollow et al., 1992). The Kd for DRSP was 0.109 nM and the binding capacity 465 fmol/mg protein. Krattenmacher (2000) reported an RBA of 19% for DRSP at human PR vs progesterone, in a review on the pharmacological and PK characteristics of DRSP

(Krattenmacher, 2000). In transactivation assays, agonistic potency of DRSP at human PR was higher than that of DNG, but lower than that of LNG, nomegestrol acetate and progesterone (van Diepen et al., 2011). High concentrations of DRSP (1 and 10 µM) inhibited growth factor-induced proliferation of normal human breast cells and E2-induced proliferation of ER- and PR-positive HCC1500 and T47-D breast cancer cells (Seeger et al., 2011). Effects of DRSP and progesterone were comparable, and more pronounced than effects of LNG or medroxyprogesterone acetate.

DRSP is a PR agonist and an antagonist of mineralocorticoid and androgen receptors. It has no estrogenic, glucocorticoid and anti-glucocorticoid activity (Fuhrmann et al., 1996). Progestins such as DRSP diffuse freely into target cells in the female reproductive tract, mammary gland, hypothalamus, and the pituitary and bind to the PR. Once bound to the receptor, progestins slow the frequency of release of gonadotropin releasing hormone (GnRH) from the hypothalamus and blunt the pre-ovulatory LH surge. Adequate ovarian suppression with DRSP alone was evident at dose levels of 2 and 3 mg, and at 3 mg all subjects had anovulatory cycles (Rosenbaum et al., 2000). Endometrial transformation, inhibition of ovulation, and anti-mineralocorticoid, i.e. natriuretic effects and mild anti-androgenic effects were recorded in humans for oral DRSP doses ranging from 0.5 to 4 mg per day (Elger et al., 2003). Combined with EE (EE/DRSP 0.03/3 mg), DRSP provides effective inhibition of ovulation and cycle control.

After oral administration, DRSP is rapidly absorbed with a bioavailability of 76% (Krattenmacher, 2000; Martindale, 2019). Peak levels occur one to two hours after an oral dose. It is about 97% bound to plasma proteins. Unlike 19-nortestosterone-derived progestogens widely used in combined hormonal contraceptives, DRSP does not bind to SHBG or CBG (Schindler et al. 2008). DRSP is extensively metabolized with a mean terminal half-life of about 30 to 40 hours (Martindale, 2019).

COCs containing DRSP are associated with good contraceptive reliability and cycle control (Krattenmacher, 2000) and have limited effects on weight gain, blood pressure, acne, and lipid levels. Additionally, EE/DRSP 0.2/3 mg (YAZ) has been shown to significantly improve symptoms of pre-menstrual dysphoric disorder, for which it is also indicated (Prescribing information YAZ, 2019).

DRSP causes a profound ovulation inhibition at the dosage of 3 mg (Krattenmacher, 2000). COCs containing DRSP are associated with good contraceptive reliability and cycle control. Overall, commercially available preparations containing DRSP are well tolerated.

DRSP was introduced for medical use in the year 2000. Currently, it is only used as a contraceptive. In view of the well-established use and proven clinical efficacy and safety of DRSP, no human biomaterial studies with DRSP alone or in combination with E4 and no clinical trials with DRSP alone have been conducted for this application.

PD of E4 alone

Initially, the safety, tolerability, PK and PD properties of E4 were analysed during two phase 1 single- and multiple-dose studies, PR3050 and PR3054. PK data have been assessed earlier in this report.

Study PR3050 evaluated the safety, tolerability, PK and PD of E4 in healthy postmenopausal volunteers. It showed no effect on LH levels after dosing with 0.1 and 1.0 mg E4. LH was slightly decreased after 10 mg in all subjects as compared to placebo. Levels were back to baseline after approximately 24 hours.

In the 100-mg group, an immediate decrease (lowest point 4-8 h post dose, mean decrease of 18 IU/L) was observed in all subjects as compared to placebo and returning to baseline at approximately 72 h post dose.

Inhibition of FSH levels over 48 hours could also be established in the 100 mg dose group (not measured in the other dosing groups), denoting a central inhibiting potency of the compound. The number and nature of AEs was similar in subjects on placebo and on 0.1, 1.0 and 10 mg.

Study PR3054 evaluated the safety, tolerability, PK and PD of four dosages of E4 (2, 10, 20, or 40 mg), the lowest dose of 2 mg E4 compared with 2 mg of estradiol valerate (E2V, used as active control), for 28 days in healthy postmenopausal women. There were no consistent changes in **E2** levels after administration of E4. A dose-dependent decrease was seen in **FSH** levels up to 87% in the E4 40 mg dose group.

Levels of **LH** decreased dose-dependently after an increase during the first days of E4 administration. LH levels in the E2V group showed a decrease that was comparable to the E4 10 mg dose group on Day 28.

Mean **prolactin** levels were higher on Day 28 compared to Day 1 in the E4 10 mg and 40 mg groups (relative change from baseline 32% and 46%, respectively), but had relatively changed with 8% in the E4 20 mg group.

There were no relevant changes in the total **testosterone** levels in both groups.

SHBG concentrations gradually and consistently increased with the dose of E4.

In this study, the most frequently occurring drug-related AEs were nervous system disorders (mainly headache), reproductive system and breast disorders (mainly nipple tenderness and vaginal discharge), and gastrointestinal disorders (mainly abdominal pain). No dose-dependent AEs were noted. No remarkable trends in laboratory parameters were observed. The vaginal cytology and the endometrial thickness were also studied, without any particular unexpected outcomes.

After the phase 1 single- and multiple-dose studies, PR3050 and PR3054, a phase 2a proof of concept multiple-dose study in women of reproductive age was conducted with E4 alone or E4 combined with progesterone or desogestrel (DSG). This study, PR3081, was performed to assess the feasibility of achieving ovulation inhibition and is discussed below:

Study PR3081 – a proof of concept study

A feasibility phase 2a study into the contraceptive effect of E4 alone or combined with either progesterone (P4) or desogestrel (DSG) by daily oral administration to healthy female volunteers of reproductive age for 28 days.

The main study objectives were to investigate ovarian suppression and ovulation inhibition, to evaluate the vaginal bleeding pattern and the PK of E4, but also the impact on the hypothalamic-pituitary-ovarian (HPO) function was assessed, as well as overall safety and tolerability in the studied population.

Hypothalamic-pituitary-ovarian function

The **LH** concentrations decreased compared to the treatment Day 3 level only in the E4 20 mg + DSG group over the treatment period. In the other groups the LH concentrations increased compared to the treatment Day 3 level. In the E4-only groups, LH concentrations increased more than in the E4 20 mg + P4 group.

Similar to the effects observed on LH, the **FSH** concentrations decreased compared to the treatment Day 3 level only in the E4/DSG 20/0.15 mg group over the treatment period. The other groups showed a small increase compared to the treatment Day 3 level.

The **E2** concentrations decreased compared to the treatment Day 3 level only in the E4 20 mg + DSG group. In the E4 10 mg and 20 mg only groups, E2 increased compared to the treatment Day 3 level, the increase being more pronounced in the E4 10 mg than in the 20 mg group. No conclusions could be drawn for the E4 20 mg plus P4 group due to the lack of Liquid Chromatography Mass Spectrometry (LC MS) data. The **progesterone**

concentrations remained low in the E4 20 mg + DSG group, reflecting anovulation. The progesterone levels increased from treatment Day 15 onwards in the E4-only groups in subjects who ovulated.

Ovulation inhibition

To confirm or exclude the suspicion of a possible ovulation, **progesterone levels** were determined at 3 (±1) days after the day that the ovulation was suspected to have occurred. If the progesterone level was < 16 nmol/L, the progesterone level was determined again 3 (±1) days later. A high ovulation rate was observed in the E4 10 mg treatment group (0.6). The ovulation rate was lower in the E4 20 mg treatment group (0.3). The E4/P4-combination treatment groups showed an ovulation rate of 0.13, whereas ovulations were absent in the E4/DSG group.

Hoogland score

The overall Hoogland score was higher in the E4 10 mg than in the E4 20 mg only treatment group, with scores ranging from 1 to 6 in both groups indicating a substantial pregnancy risk.

When combining E4 with DSG the ovarian activity was suppressed markedly with Hoogland scores of 1 and 2, indicating no pregnancy risk for the E4/DSG treatment group.

In addition to ovulation, the mean follicular diameter of the largest follicle in each ovary and the endometrial thickness was measured by TVUS. All subjects in the E4 10 mg treatment group had a maximum follicle size above 10 mm, whereas in the E4 20 mg treatment groups 60 to 80% of the subjects had a maximum follicle size below 10 mm. The maximum follicle size was lowest in the E4/DSG treatment group, with 80% of subjects having a maximum follicle size below 10 mm.

The vaginal bleeding patterns

Despite continuous treatment, vaginal bleeding-spotting did occur, and the mean number of vaginal bleeding-spotting days was markedly higher in the E4/progestin groups than in the E4-only groups, particularly due to the occurrence of spotting.

Safety profile

The safety profile comparable in the different treatment groups and there was one in-treatment pregnancy occurred in the 20 mg E4 group after a confirmed ovulation.

E4 with progestin for optimum dose finding

Two dose-finding studies, ES C01 and ES-C02, comparing the progestins levonorgestrel (LNG) and DRSP were conducted to select the optimum E4/progestin combination as judged from ovarian suppressive activity, vaginal bleeding pattern and safety profile.

Study ES C01 was a phase 2, open, parallel group, dose-finding study with active control group Yaz (EE 0.02 mg/DRSP 3 mg) to assess the contraceptive efficacy and the effect on liver function of 5 or 10 mg E4 combined with either 3 mg DRSP or 150 µg LNG, or 20 mg E4 combined with 150 µg LNG, by daily oral administration to healthy female volunteers for 3 cycles of 24 days each followed by a 4-day treatment pause. The primary objectives were investigation of ovulation inhibition and PD effect on liver function (SHBG, lipids, haemostasis, liver function, bone, glucose metabolism).

Ovulation inhibition

The mean maximum follicle size decreased with increasing dose of E4. In the EE/DRSP 0.02/3 mg group, mean maximum follicle tended to become even lower than achieved with E4/LNG 20/0.15 mg in Cycle 3. No differences were noted in mean maximum follicle size between subjects treated with E4 5 or 10 mg combined with either DRSP or LNG. Maximum follicular sizes were generally greater in Cycle 3 as compared to Cycle 1, except for the EE/DRSP group.

Hoogland score

No Hoogland scores higher than 4 were noticed.

Hypothalamic-pituitary-ovarian function

No consistent dose-related trends in mean **LH** and **FSH** have been found for subjects treated with E4 5 mg or 10 mg combined with either DRSP 3 mg or LNG 0.15 mg, but mean LH and FSH were lower in the E4/ LNG 20/0.15 mg group and the EE/DRSP 0.02/3 mg group compared to the other treatment groups. No notable differences in mean LH and FSH levels were observed with the type of progestin received.

Lower **E2** levels were observed with increasing doses of E4, regardless of whether subjects were treated with E4 plus DRSP or LNG. This dose-dependent trend was observed across all three treatment cycles. Over the entire treatment period, mean E2 levels were lower for subjects treated with EE plus DRSP than those treated with E4 plus DRSP. Across the treatment cycles, mean E2 levels were variable; however, values tended to be lowest in the EE group across the three treatment cycles. Mean E2 levels over the entire treatment period and across the cycles were slightly lower for subjects treated with LNG compared to subjects treated with DRSP.

Progesterone and **testosterone** levels were generally comparable across the entire treatment period for all subjects, with no dose-related trends with increasing dose of E4, and no difference between subjects treated with E4 plus DRSP or LNG and those treated with EE/DRSP. Furthermore, no notable differences in mean progesterone and testosterone levels were observed with the type of progestin received. Results for testosterone should be interpreted with caution, as a direct comparison between groups was not truly possible as most of the testosterone values were below the lower LOQ.

Generally, **growth endocrinology parameters** remained constant over the treatment cycles; however, IGF 1 decreased in subjects treated with EE plus DRSP but remained relatively stable in subjects treated with E4 plus DRSP or LNG. IGFBP1 and GH levels increased compared to baseline across the treatment cycles in all treatment groups, with the exception of IGFBP1, which did not increase in the 5 mg E4 plus LNG group. The steroid endocrinology parameters E1 and E1S decreased from baseline at treatment cycle 3 day 24 in the EE plus DRSP treatment group, the 10 mg E4 plus DRSP group and all E4 plus LNG treatment groups.

In relation to other parameters, such as the return to fertility, endometrial thickness, presence of cervical mucus and the vaginal bleeding pattern, all observations were in line with the expected profile.

The PD effects on liver function were assessed as a primary efficacy variable. A dose-dependent response was observed for the change from baseline at treatment cycle 3 day 24 for all **carrier protein** parameters (SHBG, CBG and ceruloplasmin). In general, a small increase in **lipid and lipoprotein values** occurred between baseline and treatment cycle 3 day 24 for the E4 plus DRSP treatment groups whereas a decrease in these parameters generally occurred for the E4 plus LNG groups. No clear dose-related trends were evident for lipids and lipoproteins (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides).

No dose-dependent trends were noted in relation to the dose of E4 for **haemostasis** parameters.

No clear trends were evident in relation to the dose for E4 or when comparing E4 plus DRSP versus EE plus DRSP for the change from baseline in **liver function parameters** (ASAT/SGOT, alkaline phosphatase, and γ-glutamyl transferase.

Regarding the **bone** parameters, a larger mean percentage decrease from baseline to treatment cycle 3 day 24 was recorded for bone parameters osteocalcin and C-terminal telopeptide of type I collagen with increased doses of E4. In addition, greater suppression in the EE plus DRSP treatment group compared with E4 plus DRSP was noted for osteocalcin and C-terminal telopeptide of type I collagen. No trends in relation to the type of progestin (LNG versus DRSP) were observed.

For **glucose metabolism parameters** (fasting serum glucose and HbA1c), no clear dose-related or drug-related trends were evident. **Other liver parameters** were also studied, such as angiotensinogen, for which a mean increase from baseline was noted with the highest dose of E4 (20 mg E4; 36.8%) in the LNG group whereas for the 5 mg and 10 mg E4 plus LNG groups, a small decrease in values from baseline was reported at treatment cycle 3 day 24. A greater mean percentage increase in angiotensinogen was recorded in the EE plus DRSP treatment group compared with the E4 plus DRSP groups. In the E4 plus DRSP groups angiotensinogen values increased but decreased in the E4 plus LNG groups. There was high variability in the mean percentage change from baseline for C-reactive protein, with the greatest increase recorded in the EE plus DRSP treatment group.

Safety profile

More than 85% of subjects per treatment group experienced at least 1 TE-AE. The most common drug-related TE-AEs were abdominal pain lower, nausea, headache, dysmenorrhea and acne. The incidence of drug-related headache was slightly higher in subjects treated with E4 compared to EE and the incidence of drug-related acne was higher in subjects treated with E4 plus LNG compared to E4 plus DRSP or EE plus DRSP.

Study ES-C02 – a dose-finding and selection study on cycle control

This is a randomized, open-label, multicentre, dose-finding study to evaluate cycle control of 15 mg or 20 mg E4 combined with either 150 µg LNG or 3 mg DRSP, compared to a combined oral contraceptive containing E2V and dienogest (DNG). This dose-selection study was performed to employ **cycle control** of E4 15 mg or 20 mg combined with LNG 0.15 mg or DRSP 3 mg.

The primary objective was to assess vaginal bleeding patterns (cycle control) of E4 15 mg and 20 mg combined with either LNG 0.15 mg or DRSP 3 mg during a 24:4 treatment regimen.

The primary bleeding parameters in this study were chosen to meet the primary objectives and are:

- unscheduled bleeding and spotting combined (referred to as bleeding/spotting) and
- absence of withdrawal bleeding.

Unscheduled bleeding/spotting

Unscheduled bleeding-spotting was a common finding, reported by >40% of subjects in any cycle, except the E4/DRSP 15/3 mg group in Cycle 6 (33.8%).

The incidence was generally lower in the E4/DRSP groups than in the other treatment groups.

By Cycle 6, the E4/DRSP 15/3 mg group had the lowest incidence of all groups (33.8% compared to 47.8% in the E2V/DNG group) resulting in a difference of 13.9% fewer subjects with unscheduled bleeding/spotting than in the E2V/DNG group (95% CI: -30.51, 2.68).

The incidence of unscheduled bleeding/spotting was 41.5% in the E4 20 mg/LNG group and 48.3% in the E4 15 mg/LNG group in treatment cycle 6 in the PP Population.

Absence of withdrawal bleeding

Absence of scheduled bleeding occurred in <20% of subjects in all E4 treatment groups throughout the study and in a much lower proportion than in the E2V/DNG group (27.1% of subjects in treatment cycle 6) in the PP Population. The percentage of subjects that did not have scheduled bleeding was very low in the E4/DRSP groups in the primary analysis cycles (Cycles 2, 3 and 6): no more than two subjects (<4%; only 1-2 subjects in any treatment cycle analysed) had an absence of scheduled bleeding in any treatment cycle throughout the study. In contrast, between 14.0% and 18.5% of subjects in the E4/LNG groups and 27.1% of subjects in the E2V/DNG group reported the absence of withdrawal bleeding in Cycle 6.

Secondary bleeding parameters

Other parameters were studied as well, such as bleeding/spotting cycle patterns by cycle day, occurrence of unscheduled bleeding by cycle, occurrence of unscheduled spotting by cycle, days of unscheduled bleeding/spotting, early withdrawal bleeding, continued withdrawal bleeding, days of withdrawal bleeding.

As a study conclusion, the E4/DRSP 15/3 mg group and the E4 20 mg/LNG group are the only groups that met both study criteria (at most 20% absence of withdrawal scheduled bleeding and at most 20% unscheduled bleeding in Cycle 6).

The E4/DRSP 15/3 mg group showed the lowest incidence of unscheduled intra-cyclic bleeding in Cycle 6 (16.9% of subjects), as well as the lowest incidence of absence of scheduled bleeding (3.5% at treatment cycle 6), and the lowest number of bleeding days and bleeding-spotting days within bleeding episodes, and an acceptable safety profile.

The E4/DRSP 15/3 mg regimen had the most favourable properties and was selected for further Phase 3 clinical development.

E4 with DRSP – dose confirmation

Finally, Study MIT-Es0001-C202 compared the effects of the final E4/DRSP 15/3 mg combination on ovarian function and vaginal bleeding pattern vs the established marketed comparator product EE/DRSP 0.02/3 mg. This study is assessed as a dose confirmative study:

Study MIT-Es0001-C202 - a dose confirmative study

This was a single-centre, randomized, open-label, two-arm study to evaluate the ovarian function inhibition of a monophasic combined contraceptive (COC) containing 15 mg E4 and 3 mg DRSP and a monophasic COC containing 20 mcg ethinylestradiol (EE)/3 mg DRSP (YAZ), administered orally once daily in a 24/4 day regimen for three consecutive cycles.

Study objectives

Primary objectives

- To evaluate the effects of the E4/DRSP 15/3 mg combination and the EE/DRSP 0.02/3 mg combination used as reference on ovarian function inhibition at treatment cycle 1 and treatment cycle 3.

Secondary objectives

- To evaluate levels of LH, FSH, E2, and progesterone during treatment cycle 1, (treatment cycle 2), and treatment cycle 3.
- To evaluate endometrial thickness.
- To evaluate return to fertility.
- To assess the safety and tolerability of E4/DRSP 15/3 mg and EE/DRSP 0.02/3 mg.

Exploratory objective

- To evaluate the effect of E4/DRSP 15/3 mg and EE/DRSP 0.02/3 mg on dysmenorrhea and breast tenderness/pain.

Study population – main inclusion criteria

Healthy female subjects ≥18 to ≤35 years with a BMI of 18-35 kg/m2 inclusive and who ovulated in the pre-treatment cycle between cycle day 9 (±1 day) and cycle day 27 (±1 day).

Criteria for evaluation

Primary endpoint

- Hoogland scores at treatment cycle 1 and treatment cycle 3 based on:
  - Follicular size assessed by TVUS
  - Endogenous hormone levels: serum E2 and serum progesterone.

Secondary endpoints

- Levels of LH, FSH, E2, and progesterone in serum on cycle day 3, 6, 9, 12, 15, 18, 21, 24, 27 (all days ±1 day) at treatment cycle 1 and treatment cycle 3 and on cycle day 3 (±1 day) of treatment cycle 2.
- Double layer endometrial thickness measured by TVUS on all visit days of all treatment cycles.
- Return to fertility measured by monitoring follicular growth using TVUS every three days from cycle day 3 of the post-treatment cycle until ovulation occurred or until cycle day 36 (all days ±1 day) and confirmed by serum progesterone.
- Safety and tolerability assessed by the monitoring of AEs, pregnancy reporting, vital signs, physical and gynaecological examination, clinical laboratory (including the cardiac profile parameters LDH1, LDH2, and troponin I and troponin T), 12-lead ECG, and echocardiogram.

Exploratory endpoints

- Subjective perception of dysmenorrhea and breast tenderness/pain as measured by a scoring scale (0 [no complaints] to 10 [hurts most]), from the first day of the pre-treatment cycle until the Follow-Up Visit.

Results and conclusions

Subject disposition

A total of 82 healthy female subjects were included in the study, 41 in each group and received one of two treatments administered as tablet for three consecutive treatment cycles of 28 days each as indicated in Table 26. They had a mean age of 25.6 years (range 19 - 35 years) and with a BMI between 18.6 and 34.9 kg/m2 and 71 subjects (86.6%) completed the clinical trial.

Table 6. Subject disposition

Group	Treatment	Treatment schedule/cycle	Number of subjects
Investigational group	E4/DRSP 15/3 mg	Days 1-24: 1 tablet E4/DRSP 15/3 mg/day Days 25-28: 1 placebo tablet/day	N = 41
Reference group	EE/DRSP 0.02/3 mg	Days 1-24: 1 tablet EE/DRSP 0.02/3 mg/day Days 25-28: 1 placebo tablet/day	N = 41

PD results

Hoogland scores

As shown in Figure 12, Hoogland scores for both treatments were similar in Cycle 1. In Cycle 3, Hoogland scores for EE/DRSP were similar to those in Cycle 1, while those for E4/DRSP appeared to be increased with more subjects having a score of 4. See Table 27 below and Figure 14:

Table 7. Summary of Hoogland scores (FAS)

		15 mg E4/3 mg DRSP (N=40)	20 mcg EE/3 mg DRSP (N=41)
Cycle Phase	**Hoogland Score**	**n (%)**	**n (%)**
Treatment Cycle 1	1: No Activity	34 (85.0)	34 (82.9)
	2: Potential Activity	3 (7.5)	4 (9.8)
	3: Non-Active FLS	1 (2.5)	-
	4: Active FLS	2 (5.0)	2 (4.9)
	5: LUF	-	-
	6: Ovulation	-	1 (2.4)[a]
	Scores 1 to 4[b]	40 (100.0)	40 (97.6)
	Scores 5 or 6	-	1 (2.4)
Treatment Cycle 3[c]	1: No Activity	25 (62.5)	31 (75.6)
	2: Potential Activity	4 (10.0)	3 (7.3)
	3: Non-Active FLS	1 (2.5)	-
	4: Active FLS	8 (20.0)	2 (4.9)
	5: LUF	-	-
	6: Ovulation	-	1 (2.4)[a]
	Scores 1 to 4[b]	38 (95.0)	36 (87.8)
	Scores 5 or 6	-	1 (2.4)

The overall ovarian function inhibition, as indicated by a Hoogland score ≤4, was similar for both treatments in Cycle 1 and Cycle 3. One subject receiving EE/DRSP had a score of 6 (ovulation) in both treatment cycles. During treatment Cycle 2, ovulation was suspected for one other subject receiving EE/DRSP.

Follicle size

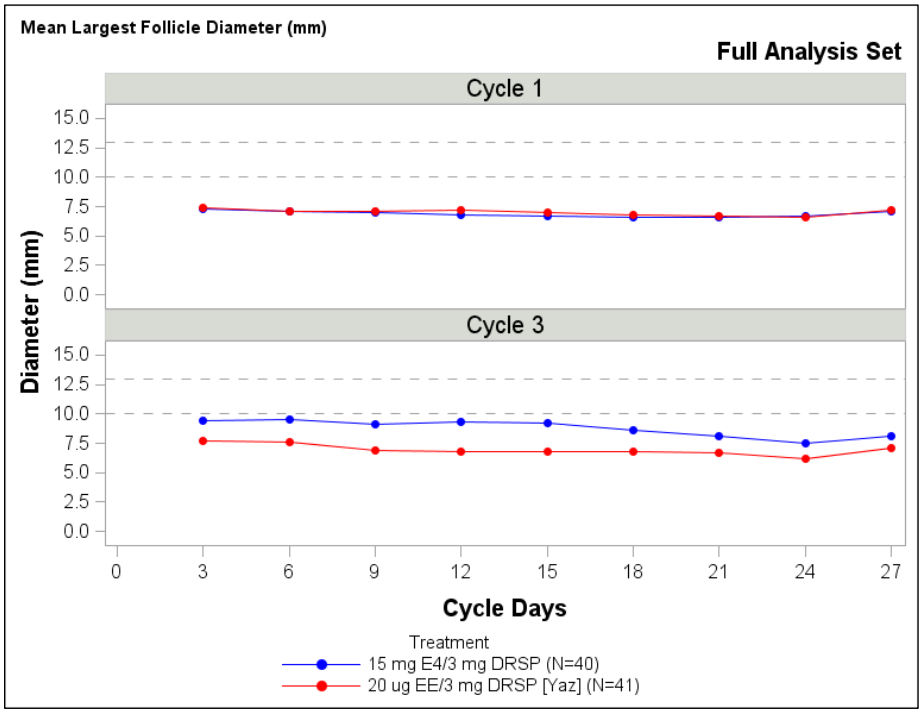
The frequency distribution of maximum follicle size per category is shown in Table 28.

Table 8. Frequency distribution of maximum follicle size per category (Full Analysis Set)

Cycle Phase	Statistic	Category	E4/DRSP 15/3 mg (N=40)	EE/DRSP 0.02/3 mg (N=41)
Pre-treatment cycle	n (%)	>13 and ≤30 mm	40 (100.0)	41 (100.0)
	mean (SD)		19.59 (3.198)	19.78 (2.566)
	min-max		14.3-28.9	14.1-26.5
Cycle 1	n (%)	≤10 mm	34 (85.0)	34 (82.9)
		>10 and ≤13 mm	3 (7.5)	4 (9.8)
		>13 and ≤30 mm	3 (7.5)	3 (7.3)
	mean (SD)		8.44 (2.538)	8.82 (3.983)
	min-max		5.8-17.4	5.8-28.7
Cycle 3[a]	n (%)	≤10 mm	26 (65.0)	31 (75.6)
		>10 and ≤13 mm	4 (10.0)	3 (7.3)
		>13 and ≤30 mm	8 (20.0)	2 (4.9)
		>30 mm	1 (2.5)	1 (2.4)
	mean (SD)		11.36 (6.133)	9.04 (5.731)
	min-max		5.9-31.5	4.9-33.4
Post-treatment cycle	n (%)	≤10 mm	-	1 (2.4)
		>13 and ≤30 mm	38 (95.0)	34 (82.9)
		>30 mm	-	2 (4.9)
	mean (SD)		19.84 (3.040)	21.07 (4.822)
	min-max		13.7-28.0	4.9-31.9

During both treatment cycles mean largest follicle diameters were stable over time in both treatment groups. During Cycle 3 the values of the mean largest follicle diameters were higher in the E4/DRSP group compared to the EE/DRSP group (Figure 14).

Figure 3. Mean diameter of the largest follicle – Day profiles (Full Analysis Set)

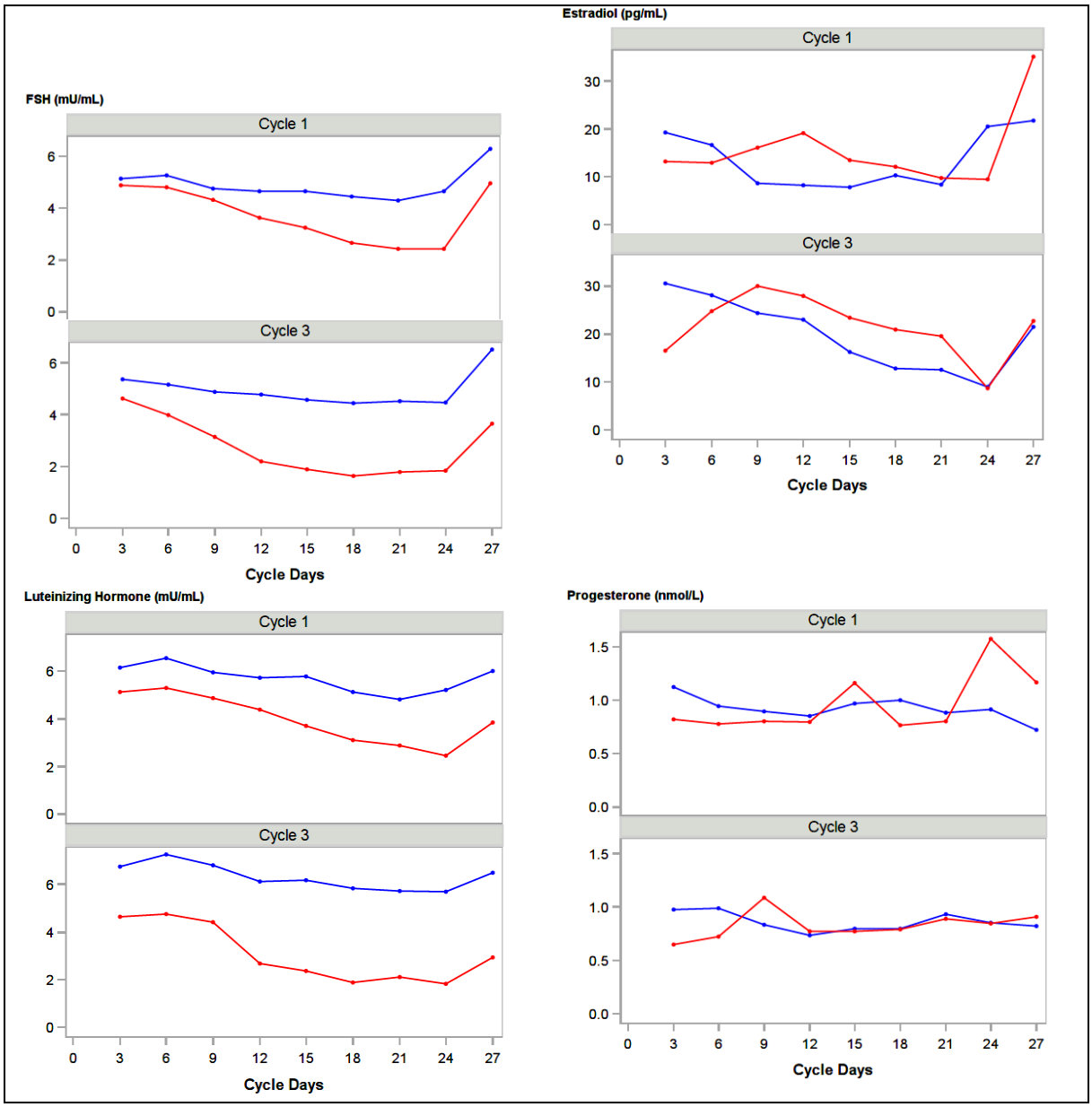


During the pre-treatment cycle all maximum follicle diameters were >13 and ≤30 mm. During Cycles 1 and 3 maximum follicle sizes decreased to ≤10 mm for most subjects. In Cycle 3, the percentage of subjects with a maximum follicle diameter >13 and <30 mm was higher in the E4/DRSP group than in the EE/DRSP group. For both treatments, during the post-treatment cycle the mean maximum follicle diameter returned to values similar to the pre-treatment cycle.

Endogenous Hormone Levels (HPO-axis)

As shown in Figure 15, the mean FSH and LH levels were higher with E4/DRSP than with EE/DRSP throughout treatment. Mean E2 levels were low, fluctuating between 10 and 20 pg/mL during active treatment, and were lower in the E4/DRSP group than in the EE/DRSP group. Mean progesterone levels were altogether low (below 1.0 nmol/mL) and showed little fluctuation over time in both groups.

Figure 4. Mean hormone concentrations over time (Full Analysis Set)



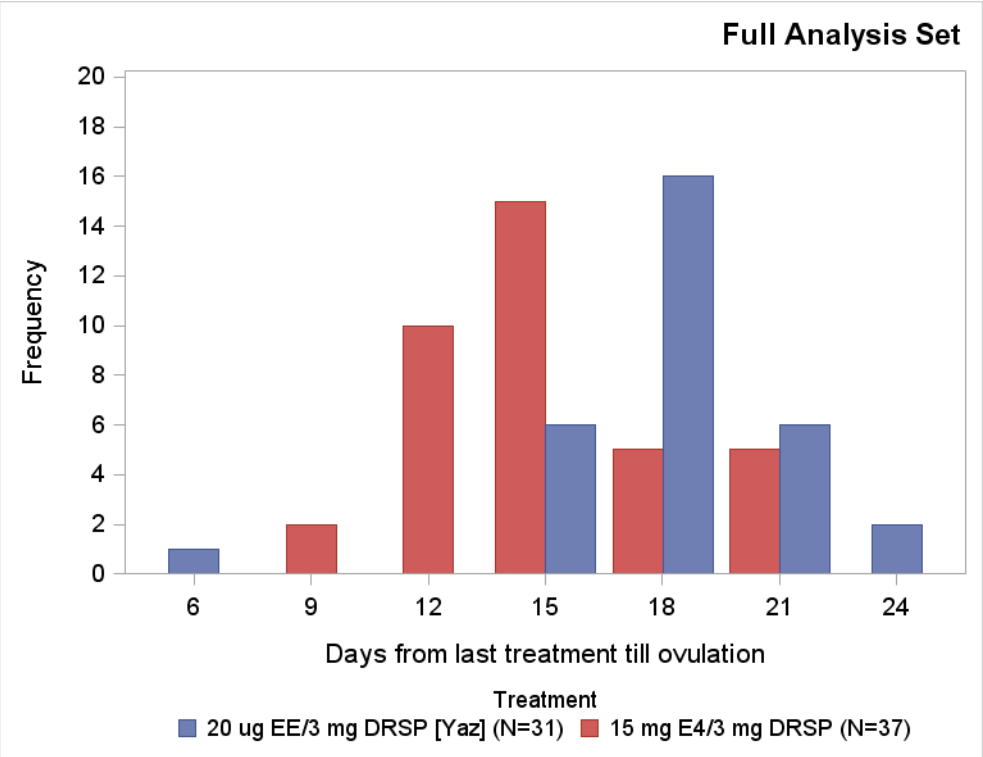
Endometrial thickness

Mean endometrial thickness increased during the pre-treatment and the post-treatment cycles with a slight decrease toward the end of the cycles. During treatment cycles, mean endometrial thickness was constant for both treatments, and below 5 mm.

Return to ovulation

The frequency distribution of days from last treatment until ovulation is shown in Figure 16.

Figure 5. Frequency of days from last treatment until ovulation (Full Analysis Set)



The earliest post-treatment ovulation was observed 6 days after intake of the last (placebo) tablet, in a subject that had been using EE/DRSP. This same subject had also ovulated during Cycles 1 and 3. The earliest ovulation in subjects that had been using E4/DRSP occurred 9 days after intake of the last (placebo) tablet. Most subjects that had been using E4/DRSP ovulated between 12 and 15 days after last tablet intake, while subjects having used EE/DRSP ovulation occurred later, with most subjects ovulating between 15 and 18 days after last tablet intake. For E4/DRSP, the mean duration from last tablet taken until ovulation occurred was 15.5 days, and for EE/DRSP the mean duration was 18.1 days.

During the post-treatment cycle, most subjects showed a steady growth of the largest follicle. The mean largest follicle diameter increased until Day 12 for the E4/DRSP group and until Day 15 for the EE/DRSP group. For four subjects, ovulation could not be confirmed during the post-treatment cycle. These subjects were withdrawn before ovulation occurred (1 subject in the E4/DRSP group, 2 subjects in the EE/DRSP group), or no ovulation could be confirmed before the end of the post-treatment cycle using TVUS and progesterone levels.

Safety

Both E4/DRSP and EE/DRSP treatments were generally safe and well tolerated. The incidence of breast pain was reported more often in the E4/DRSP group. No safety concerns were raised for EE/DRSP or E4/DRSP treatments.

Applicant's conclusions on PD results of study MIT-Es0001-C202

Ovarian function inhibition was adequate in both treatment groups. No ovulations were observed in the E4/DRSP group, while in the EE/DRSP treatment group, three ovulations were observed in two subjects throughout the treatment period. Hoogland scores, follicle diameter, and E2, progesterone, FSH, and LH levels were all reflective of strong ovarian suppression in both treatment groups. Hoogland scores were similar between both

treatment groups in Cycle 1, but slightly higher with E4/DRSP than with EE/DRSP in Cycle 3, due to slightly larger follicle diameters. E2 levels were slightly lower for E4/DRSP throughout treatment while progesterone levels were similarly low in both treatment groups, except for some peaks seen in the EE/DRSP treatment group due to the ovulations observed in this group. FSH and LH levels were slightly higher with E4/DRSP than with EE/DRSP. No difference between treatment groups was observed for endometrial thickness during the entire study. Resumption of ovulation was demonstrated for both treatments and was slightly faster after treatment with E4/DRSP than after treatment with EE/DRSP.

Secondary pharmacology

To study the effect of E4/DRSP on the endocrine function, metabolic control and haemostasis, Study MIT-Es0001-C201 was performed:

MIT-Es0001-C201 – testing endocrine function, metabolic control and haemostasis

This study was titled as a single centre, randomized, open-label, controlled, actively-controlled phase 2 three-arm study to evaluate the effect of a new combined oral contraceptive (COC) containing 15 mg E4 and 3 mg DRSP and of two reference COCs containing either 30 mcg EE and 150 mcg LNG or 20 mcg EE and 3 mg DRSP on endocrine function, metabolic control and haemostasis during six treatment cycles.

Study design

Healthy pre-menopausal women (age range 18 to 50 years) were enrolled as follows:

- E4/DRSP 15/3 mg (planned: N=40, randomized: N=39),
- EE/DRSP 0.02/3 mg (Yaz, planned and randomized: N=30) and
- EE/LNG 0.03/0.15 mg (Melleva, planned: N=30, randomized: N=32)

Two COCs were selected as reference treatment, one containing EE combined with LNG, which is recommended in the EMA guideline on clinical investigation of steroid contraceptives in women (EMA, 2005), and one containing EE combined with DRSP to allow a direct comparison between EE and E4. The EE/DRSP 0.02/3 mg COC allowed direct comparison of the impact of the estrogen component (since the DRSP content was the same) and the EE/LNG 0.03/0.150 mg comparator was a product containing EE/LNG, a combination considered to have the lowest thromboembolic risk of available COCs.

Study objectives

Primary objective

To evaluate the effects of 15 mg E4/3 mg DRSP, of 30 mcg EE/150 mcg LNG, and of 20 mcg EE/3 mg DRSP on haemostasis, endocrine function, and lipid and carbohydrate metabolism parameters during 6 treatment cycles.

Secondary objective

To assess the safety and tolerability of 15 mg E4/3 mg DRSP, of 30 mcg EE/150 mcg LNG, and of 20 mcg EE/3 mg DRSP during 6 treatment cycles.

Statistical methods

Sample size calculation

No formal sample size calculation was performed. Forty (40) subjects were planned to be randomized in the investigational group and 30 subjects were planned to be randomized per reference group.

Primary parameters

No formal statistical analysis was planned. Data are presented by descriptive summary statistics. Additional exploratory non-parametric analyses were performed to explore possible differences between treatments at Cycle 6 and changes from baseline.

Safety parameters

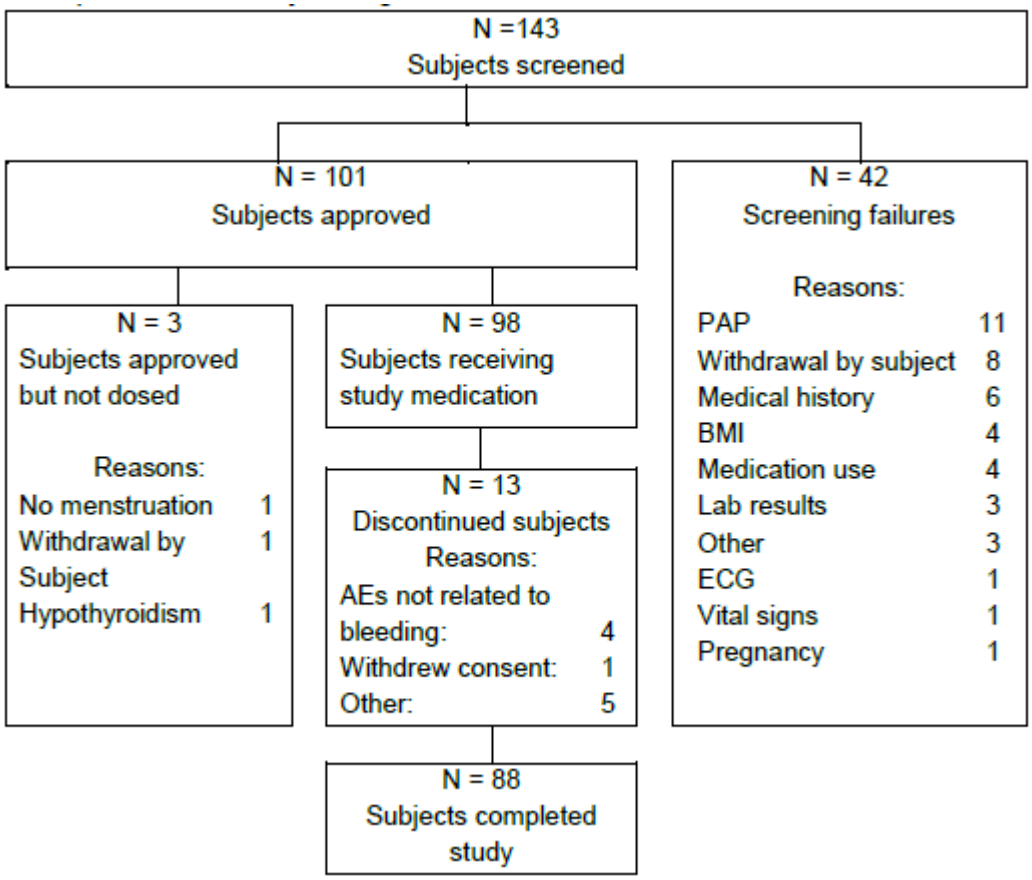
General safety and tolerability were evaluated based on the incidence and nature of AEs, results of clinical laboratory tests, vital signs, MDQ questionnaire, echocardiograms, and ECGs.

Results

Study disposition

A total of 143 subjects were screened, and 101 of these subjects were randomized.

Figure 6. Subject disposition



Demographics

A total of 98 female subjects between 18 and 47 years of age and with a body mass index (BMI) between 18.3 and 30.0 kg/m2 used the study medications. A total of 93 (95%) subjects were of white race, 3 (3%) subjects were of mixed race (1 subject was white + black and 2 subjects were white + Asian), 1 (1%) subject was black or African American, and 1 (1%) subject was Asian.

Pharmacodynamics

Haemostatic Parameters

No obvious treatment differences or changes over time were observed for fibrinogen, factor VIII, von Willebrand factor, plasminogen activator inhibitor-1 (PAI-1), soluble E-selectin, prothrombin fragments 1+2, prothrombin activity (factor II), antithrombin, protein C, free tissue factor pathway inhibitor *(TFPI), APC resistance (APTT based), D-dimer and Activated Coagulation time (-APC/+APC).*

Table 21: Percentages change from baseline in haemostatic parameters. Median and length of interquartile range. (PP Population)

Parameter	E4/DRSP 15/3 mg N=34	EE/LNG 0.03/0.15 mg N=27	EE/DRSP 0.02/3 mg N=30
Coagulation			
Activated Protein C Resistance - (ETP based)	30.0 [370] ***,1,2**	164.5 [126.0] *,1,3	218.5 [145.0] *,2,3
Activated Protein C Resistance - (APTT based)	0.0 [22.0]	5.0 [26.0] *	-1.0 [23.0]
Fibrinogen (mg/dL)	10.0 [26.0] *****	5.0 [34.0]	16.0 [31.5] *****
Factor VII Activity (%)	-3.0 [19.0] **2**	-5.0 [14.0] *****	20.0 [24.0]*
Factor VIII Activity (%)	5.0 [18.0]	3.0 [42.0]	9.0 [35.0]
von Willebrand Factor (%)	5.0 [22.0]	-2.0 [18.0] **3**	13.0 [24.0]*,3
Prothrombin Activity (%)	7.0 [12.0] *****	13.0 [13.0] *	7.0 [14.5] *
Prothrombin Fragments 1+2 (nmol/L)	23.0 [56.0] *,1,2	71.0 [55.0] *,1	64.0 [54.0] *,2
Coagulation Inhibitors			
Antithrombin (%)	-1.0 [7.0]	-5.0 [11.0] *****	-3.5 [13.5]
Protein S activity (%)	-4.0 [17.0] **2**	-5.0 [21.0] **3**	-30.5 [12.5] *,2,3
Protein S, Free (%)	5.0 [14.0] **2**	-3.0 [25.0] **3**	-22.5 [16.5] *,2,3

Parameter	E4/DRSP 15/3 mg N=34	EE/LNG 0.03/0.15 mg N=27	EE/DRSP 0.02/3 mg N=30
Protein C (Factor XIV Activity) (%)	2.0 [10.0] **2**	7.0 [22.0] *****	17.5 [21.5]***,2**
Free tissue factor pathway inhibitor (U/mL)	-8.5 [29.0]	-6.0 [39.0]	-20.0 [30.0] *****
Fibrinolysis			
Plasminogen (%)	12.0 [12.0] *** 1,2**	40.0 [18.0] ***,1**	35.5 [17.5] ***,2**
Tissue Plasminogen Activator Antigen (ng/mL)	-7.0 [32.0] **1,2**	-33.0 [30.0] ***,1**	-39.5 [36.0] ***,2**
Plasminogen Activator Inhibitor-1 (U/mL)	20.0 [78.0]	0.0 [50.0]	0.0 [63.0]
D-Dimer (mcg/mL FEU)	4.0 [32.0] *	7.0 [38.0]	0.0 [33.5]
Endothelial adhesion factor			
Soluble E-Selectin (ng/mL)	2.5 [24.0] **1,2**	-31.0 [15.0] *****	-21.0 [19.0] *****

*EMA recommended variables printed in italics; * Statistically significant (p<0.05) change from baseline; 1,2,3 Statistically significant (p<0.05) between treatments: 1 = E4/DRSP vs EE/LNG; 2 = E4/DRSP vs EE/DRSP; 3 = EE/LNG vs EE/DRSP*

EE/LNG

For women using EE/LNG, statistically significant changes from baseline to Cycle 6 were as follows: Several parameters of coagulation increased, including ETP-based activated Protein C (APC) resistance, APTT-based APC-resistance, prothrombin activity and prothrombin fragments 1+2 (F1+2).

Regarding inhibitors of coagulation, a decrease was observed for antithrombin and an increase for protein C.

Regarding fibrinolysis, an increase was observed in plasminogen and a decrease in tissue plasminogen activator (t-PA).

EE/DRSP 0.02/3 mg

Use of the EE/DRSP 0.02/3 mg combination was associated with larger changes than EE/LNG.

Notably, the change in coagulation parameter ETP-based APC resistance was larger than observed with EE/LNG, while also fibrinogen, Factor VII, Factor VIII and von Willebrand Factor were statistically significantly increased from baseline.

Inhibitors of coagulation generally showed statistically significant decreases from baseline as observed for Protein S activity, free Protein S, and free tissue factor pathway inhibitor (TFPI), while Protein C was increased.

Changed fibrinolysis was indicated by increased plasminogen and decreased t-PA not counterbalanced by decreased plasminogen activator inhibitor-1 (PAI-1), although D-dimer was unchanged.

E4/DRSP 15/3 mg

The E4/DRSP 15/3 mg combination was associated with the smallest changes.

The resistance to APC, a functional coagulation test measuring the generation of thrombin in the presence and absence of APC (ETP-based APC resistance), was considerably less with E4/DRSP than observed with EE/LNG and EE/DRSP, with respective changes from baseline of 30%, 165% and 219%. Similarly, the change in F1+2 (+23.0%) was smaller than observed with EE/LNG (+71.0%) and EE/DRSP (+64.0%).

No statistically significant changes from baseline were observed in coagulation inhibitors, while the changes in fibrinolytic parameters plasminogen (+12.0%), D-dimer (+4.0%), t-PA (-7.0%) and PAI-1 (+20.0%) are clinically irrelevant and not at all indicative of fibrinolytic activation to the extent observed for the two reference COCs.

E4/DRSP 15/3 mg does not affect soluble E-selectin, an endothelial adhesion molecule involved in inflammation and haemostasis, in contrast to EE/LNG and EE/DRSP.

Changes in SHBG and other binding globulins, angiotensinogen and C-reactive protein (CRP) were all smaller with E4/DRSP 15/3 mg as compared to EE/LNG 0.03/0.15 mg and EE/DRSP 0.02/3 mg, also reflecting the low (estrogenic) impact of E4/DRSP.

Applicant's conclusion on haemostatic profile of E4/DRSP

The E4/DRSP combination showed a more neutral haemostatic profile than EE/LNG and EE/DRSP. The results also confirm the findings from dose-finding study ES-C01, the 3-cycle study in which the effects on liver parameters was studied between women using EE/DRSP 0.02/3 mg, E4/DRSP 5/3 and 10/3 mg and E4/LNG 5/0.15, 10/0.15 and 20/0.15 mg. Large changes in ETP-based APC resistance, F1+2 and t-PA were noted in the EE/DRSP group that were absent from, or occurred to a much lower extent in the E4 groups (Kluft et al., 2017). Study PR3054 in postmenopausal women showed that treatment with E4 alone at daily oral dose of 2, 10, 20 or 40 mg for 28 days had minimal impact on ETP-based APC resistance, F1+2 and t-PA. The results obtained with the EE/LNG and EE/DRSP comparator are generally consistent with published data and indicate that E4/DRSP 15/3 mg is associated with minimal disturbance of haemostatic parameters, which is not only less than the haemostatic effects observed with EE/LNG 003/0.15 mg, but also less than observed with the COCs containing E2 (Ågren et al, 2011; Gaussem et al, 2012) and E2V (Junge et al., 2011; Raps et al., 2013), the latter of which has been associated with a VTE risk as low as EE/LNG, as reflected in an adjusted HR of 0.5 (95% CI 0.2-1.3) (Dinger et al., 2016).

In fact, the results obtained for E4/DRSP 15/3 mg are closest to those reported for the progestin-only formulation DRSP 4 mg, which has been reported to be associated with changes from baseline of +10.6% for ETP-based APC resistance, -5.1% for Factor VII, +4.7% for antithrombin, -2.8% for Protein C activity and -17.8% for D-dimer (Regidor et al., 2016). Progestin-only contraceptives have no increased risk of VTE (Blanco-Molina et al., 2012).

Based on these data, the risk of VTE with E4/DRSP 15/3 mg does not seem higher than with EE/LNG.

Lipid metabolism

The percentages changes from baseline to Cycle 6 in parameters of lipid metabolism are presented in Table 22, along with an indication of the statistical significance of the changes from baseline, and differences between groups.

Table 22: Percentages change from baseline in lipids and lipoproteins. Median [interquartile range] (PP Population)

Parameter	E4/DRSP 15/3 mg N=34	EE/LNG 0.03/0.15 mg N=27	EE/DRSP 0.02/3 mg N=30
Cholesterol (mg/dL)	4.0 [14.0]	1.0 [6.0]	6.5 [16.0] *
HDL Cholesterol (mg/dL)	4.0 [15.0] [1]	-16.0 [13.0] *[1,3]	8.5 [21.0] *[3]
Apolipoprotein A1 (mg/dL)	5.0 [15.0] *[1,2]	-3.0 [8.0] *[1,3]	19.5 [18.5] *[2,3]
LDL Cholesterol (mg/dL)	-2.0 [16.0]	7.0 [20.0]	-5.0 [19.0]
Apolipoprotein B (mg/dL)	4.0 [22.0] *[1,2]	23.0 [18.0] *[1,3]	11.5 [20.0] *[2,3]
HDL Cholesterol/LDL Cholesterol	0.0 [28.0] [1]	-17.0 [35.0] *[1,3]	17.0 [22.0] *[3]
Triglycerides (mg/dL)	24.0 [52.0] *[2]	28.0 [47.0] *[3]	65.5 [59.0] *[3]
Lipoprotein-a (nmol/L)	0.0 [7.0]	0.0 [30.0]	0.0 [23.0]

*: Statistically significant (p<0.05) change from baseline; 1,2,3: Statistically significant (p<0.05) between treatments: 1 = E4/DRSP vs EE/LNG; 2 = E4/DRSP vs EE/DRSP; 3 = EE/LNG vs EE/DRSP

E4/DRSP 15/3 mg did not induce relevant changes from baseline in lipid parameters. A 25% (~16.5 mg/dL) median increase in triglycerides was observed, which was similar to EE/LNG (+28.0%) but much less than observed with EE/DRSP (+65.5%).

The comparator EE/LNG induced a decrease in HDL-cholesterol and apolipoprotein A1, an increase in LDL and apolipoprotein B and a decrease in the HDL/LDL ratio.

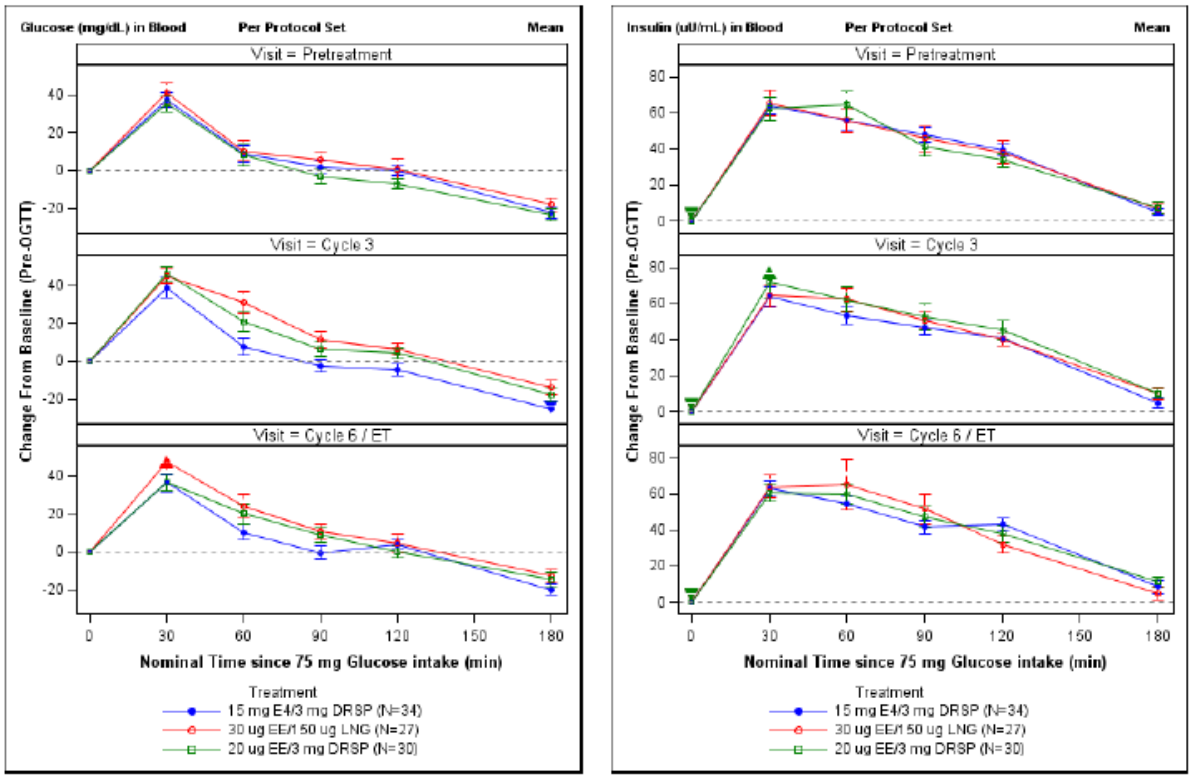
EE/DRSP treatment was associated with larger increases in HDL-cholesterol, apolipoprotein A1 and triglycerides.

These differences reflect the estrogenic/androgenic balance of the various treatments (Sitruk-Ware and Nath, 2011), with EE/LNG 0.03/0.15 mg showing an androgenic dominance, EE/DRSP 0.02/3 mg an estrogenic dominance and E4/DRSP 15/3 mg a balanced profile.

Carbohydrate metabolism

The effects of treatment on the glucose and insulin response in an oral glucose tolerance test is shown in Figure 16.

Figure 16: Glucose (left) and insulin (right) plasma concentration versus time plots during oGTT at Baseline, Cycle 3 and Cycle 6 (Means ± SE) (PP Population)



E4/DRSP 15/3 mg did not induce a change in glucose or insulin response, the areas under the respective concentration-time curves at Cycle 6 were 3.7% and 2.5% higher than at baseline.

The comparators treatments were associated with slightly greater changes, i.e., 4.4% and 8.9% (EE/LNG) and 8.1% and 10.1% (E4/DRSP).

Fasting levels of HbA1c and glucose were unchanged with all three treatments. Slightly increased fasting levels of insulin (+17%) and C peptide (+21%) were observed with E4/DRSP 15/3 mg at Cycle 6, which was less than noted with EE/LNG 0.03/0.15 mg (+16% and +31%, respectively) and EE/DRSP (+27% and +41%, respectively). It can be concluded E4/DRSP 15/3 mg has minimal impact on glycaemic control.

Endocrine Parameters - Adrenal and thyroid hormones

Effects on adrenal and thyroid hormones are shown in Table 23

Table 23: Percentages change from baseline in adrenal and thyroid hormones (Median [interquartile range]) (PP Population)

Parameter	E4/DRSP 15/3 mg N=34	EE/LNG 0.03/0.15 mg N=27	EE/DRSP 0.02/3 mg N=30
Aldosterone (pmol/L)	103.0 [207.0] *[1]	-40.0 [77.0] *[1,3]	179.5 [252.0] *[3]
Cortisol (µg/dL)	26.0 [49.0] *[1,2]	109.0 [71.0] *[1]	107.0 [81.0] *[2]
Triiodothyronine, free (pg/mL)	-4.5 [17.0] [1]	6.0 [18.0] *[1]	2.0 [18.0]
Thyroxine, free (ng/dL)	4.0 [15.0] *	6.0 [18.0] *	2.0 [8.0] *
Thyrotropin (mU/L)	6.0 [36.0]	12.0 [45.0]	7.0 [57.0]

The levels of aldosterone had increased during E4/DRSP and EE/DRSP treatment, which is considered to be related to the antimineralocorticoid activity of DRSP (Krattenmacher, 2000). E4/DRSP 15/3 mg slightly increased the levels of cortisol, but less than observed with both comparators. Thyroid hormones were minimally affected.

Androgens

Table 24 summarizes the changes in androgens. Androgen concentrations were reduced during treatment with the three COCs, a known phenomenon. Due to the strong induction of SHBG with EE/DRSP 0.02/3 mg, see Table 24 below, levels of free testosterone are lowest in that group.

Table 24: Percentages change from baseline in androgen parameters (Median [length of interquartile range]) (PP Population)

Parameter	E4/DRSP 15/3 mg N=34	EE/LNG 0.03/0.15 mg N=27	EE/DRSP 0.02/3 mg N=30
Testosterone (ng/dL)	-31.0 [12.0] *	-37.5 [35.0] *	-33.0 [26.0] *
Free testosterone (ng/dL)	-50.0 [27.0] *	-50.0 [27.0] *	-71.0 [23.0] *
Androstenedione (nmol/L)	-31.0 [24.0] *	-49.0 [32.0] *	-40.0 [28.0] *
Dehydroepiandrosterone sulfate (mcg/dL)	-10.5 [23.0] *,[2]	-16.0 [21.0] *,[3]	-27.0 [23.0] *,[1,3]
Dihydrotestosterone (nmol/L)	-13.0 [55.0]	-25.0 [70.0] *	-3.5 [57.0]

*:Statistically significant (p<0.05) change from baseline; 1,2,3: Statistically significant (p<0.05) between treatments: 1 = E4/DRSP vs EE/LNG; 2 = E4/DRSP vs EE/DRSP; 3 = EE/LNG vs EE/DRSP

FSH and LH

FSH levels were higher after treatment with E4/DRSP (4.55 mIU/mL [0.5, 9.6]) compared to treatment with EE/LNG (1.00 mIU/mL [0.1, 4.2]) and EE/DRSP (0.70 mIU/mL [0.1, 7.8]).

LH levels were higher after treatment with E4/DRSP (6.10 mIU/mL [0.2, 13.0]), compared to treatment with EE/LNG (0.70 mIU/mL [0.1, 6.8]) and EE/DRSP (0.60 mIU/mL [0.1, 8.4]).

Liver Protein Parameters

Table 25 summarizes the effects of the COCs on liver proteins.

Table 25: Percentages change from baseline in carrier proteins, angiotensinogen and C-Reactive Protein (Median [length of interquartile range]) (PP Population)

Parameter	E4/DRSP 15/3 mg N=34	EE/LNG 0.03/0.15 mg N=27	EE/DRSP 0.02/3 mg N=30
SHBG (nmol/L)	55.0 [51.0] *,2	74.0 [71.0] *,3	251.0 [98.0] *1,3
Cortisol Binding Globulin (µg/mL)	40.0 [30.0] *,1,2	152.0 [68.0] *,2	140.0 [90.0] *,1
Thyroxin Binding Globulin (mg/L)	17.0 [27.0] *,1,2	37.0 [30.0] *,1	70.0 [35.0] *2,3
Angiotensinogen (µg/mL)	75.0 [108.0] *,1,2	170.0 [228.0] *,1	206.5 [164.0] *,2
C-Reactive Protein (mg/dL)	0.0 [100.0]	30.0 [180.0]	30.0 [220.0] *

*:Statistically significant (p<0.05) change from baseline; 1,2,3:Statistically significant (p<0.05) between treatments: 1 = E4/DRSP vs EE/LNG; 2 = E4/DRSP vs EE/DRSP; 3 = EE/LNG vs E4/DRSP

SHBG was increased in all three treatment groups and most pronounced in users of EE/DRSP 0.02/3 mg (+251%). The increases observed in users of E4/DRSP 15/3 mg (+55%) and EE/LNG 0.03/0.15 mg (+74%) were smaller and comparable. These changes are reflective of the estrogenic/androgenic balance of the COCs.

Similarly, levels of Cortisol Binding Globulin and Thyroxin Binding Globulin were found to increase, especially in the EE-containing COC groups.

Differential treatment effects were also observed for the vasoconstrictive α2-globulin precursor angiotensinogen, which increased with both EE-based COCs and less so with E4/DRSP 15/3 mg.

The acute phase reactant CRP was not affected with E4/DRSP and EE/LNG.

Safety

A total of 69 subjects (70.4%) reported 219 treatment emergent adverse events (TEAEs). Of these 120 TEAEs were reported by 32 subjects (84.2%) in the E4/DRSP group, 36 TEAEs were reported by 18 subjects (62.1%) after treatment with EE/LNG, and 63 TEAEs were reported by 19 subjects (61.3%) in the EE/DRSP group.

A total of 2 TEAEs reported by 2 subjects (2.0%) were severe. The severe TEAE during EE/LNG treatment (hospitalization for papilloedema), and not related to the study drug. In the EE/DRSP group 1 subject (3.2%) reported 1 severe TEAE, (increased dysmenorrhea) which was judged as possibly related to the study drug.

A total of 42 TEAEs reported by 21 subjects (55.3%) in the E4/DRSP group were considered related to study drug as judged by the PI. In the EE/LNG group, a total of 11 TEAEs reported by 8 subjects (27.6%) were considered related. A total of 28 TEAEs reported by 10 subjects (32.3%) were considered related in the EE/DRSP group.

The most frequently reported related TEAEs by system organ class (SOC), i.e. TEAEs reported by at least 10% of subjects per treatment group:

The most frequently reported related TEAEs by preferred term (PT), i.e. TEAEs reported by at least 10% of subjects per treatment group are:

15 mg E4/3 mg DRSP

- Breast pain (7 subjects [18.4%] reporting 9 events)

30 mcg EE/150 mcg LNG

- Headache (4 subjects [13.8%] reporting 7 events)

20 mcg EE/3 mg DRSP

- Headache (4 subjects [12.9%] reporting 10 events)

The other measured safety parameters showed no relevant clinically relevant findings.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The Applicant evaluated the clinical pharmacology of estetrol alone or the combination of estetrol and drospirenone in 15 clinical and 19 *in vitro* studies according to the requirements of a full dossier. The clinical pharmacology data of drospirenone are based on a combination of clinical studies and literature data. The Applicant compared pharmacokinetic results with the final FTC E4/DRSP 15/3 mg tablet with literature studies with DRSP (3 mg) administered alone or as combination with EE or E2. A decrease ranging from 16 to 32% of DRSP exposure is observed with E4/DRSP compared to EE/DSRP, and a similar and even slightly more pronounced decrease of DRSP exposure compared to E2/DRSP. These differences have no clinical relevance as for the FTC E4/DRSP 15/3 a complete clinical dossier is submitted. In general, the pharmacokinetics of E4 and DRSP are well described.

PK properties

Aspects of the potential time-dependency of estetrol PK were not initially addressed/discussed by the Applicant. According to the Applicant, time-dependency data were available from two clinical studies, namely: MIT-Es0001-C102 and MIT-Es0001-C103. Both clinical studies have implied slight tendency towards the time-dependent PK. In the study MIT-Es0001-C102, AUC0-tau at steady-state was about 15% lower than AUC0-inf after the single-dose administration. In the second study, MIT-Es0001-C103, the same trend was observed with AUC0-tau values which were 6 - 18% lower compared to AUC0-inf after the single-dose

administration. The observed trend for time-dependency is however not expected to have a clinical relevance for estetrol itself when considering the relatively low magnitude of decrease in its exposure (i.e. less than 20%).

The concentration versus time profiles of estetrol - especially at multiples of the therapeutic dose - were characterized by the appearance of secondary peaks until 24 hours post-dosing. According to the Applicant, the clinical relevance of these secondary peaks is minor. The Applicant has sufficiently discussed and elucidated the possibility of biliary excretion pathway like reported for other oestrogens. It is agreed that the appearance of secondary peaks in the concentration-time profile of estetrol is most likely due to the process of enterohepatic circulation (EHC) of estetrol (both conjugated and unconjugated forms).

Estetrol molecule is chiral due to the presence of seven asymmetric carbons in its structure (C8 R, C9 S, C13 S, C14 S, C15 R, C16 R, C17 R). However, it is agreed with the Applicant that it seems unlikely that inter-conversion at specific chiral centres of estetrol in the D-ring would be of any clinical significance. Additionally, the potential for interconversion and genetic conversion was sufficiently discussed. It is agreed that any contribution of polymorphism can be considered of no clinical relevance for estetrol.

BCS classification cannot be granted at the moment because high permeability was not confirmed for estetrol.Permeability has not been investigated for drospirenone.

Special populations

E4 and DRSP are similar with respect to PK exposure for White and Black or African American subjects. Also, in the provided literature, it was confirmed that ethnic origin had no clinically relevant influence on PK of DRSP.

Based on results of the analysis of the pharmacokinetic parameters and weight in phase 1 studies (Study Es0001-C101, Study MIT-Es0001-C103, Study MIT-Es0001-C110, Study MIT-Es-0001-C106), BMI does not appear to significantly influence Cmax or AUCinf /AUC0 24 of E4 following single or multiple dose administration of E4/DRSP 15/3 mg.

Interactions

The interaction risks were evaluated by the Applicant based on the estimated Ki values. A justification was presented for the selection of all probe substrates and positive control inhibitors which are not listed/proposed in the EMA's DDI guideline.

No positive signals of CYP induction were observed in accordance with the EMA DDI guideline.

Based on the presented *in vitro* data it can be concluded that estetrol does not act as a substrate of SLC transporters OATP1B1 and OATP1B3.

SmPC comments

The Applicant has used standard SmPC 4.5 text from other oral contraceptive products containing drospirenone. Literature references regarding all DDI interaction studies which are listed for drospirenone in the 4.5 SmPC were provided by the Applicant.

Estetrol does not appear to be metabolised via CYP enzymes but via UGT (i.e. UGT2B7). Importantly, the interaction potential with estetrol (as a victim drug) and other medicinal products which act as enzyme inducers was not studied in vivo. Therefore, the interaction risk with enzyme inducers (which can affect not only CYP but also UGT enzymes) cannot be excluded at present. Thus, the SmPC warning concerning interaction risk with enzyme inducing drugs is applicable not only for drospirenone but for estetrol as well.

Primary pharmacodynamics

E4/DRSP 15/3 mg is a combined oral contraceptive containing the progestin drospirenone (DRSP) and the estrogen estetrol (E4). E4 is a natural estrogen identical to the human foetal estetrol, only produced during human pregnancy by the human foetal liver. E4 is an estrogen, that is not previously used in any medical product, while DRSP is a known progestin, that is used in combination with ethinylestradiol as a COC (Yasmin, Yasminelle, Yaz), and in combination with estradiol as an HRT (Angeliq). The contraceptive efficacy of a combined hormonal contraceptive is mainly based on inhibition of ovulation. Next to inhibition, also an adequate bleeding pattern (cycle control) of the COC is of importance, i.e. a low percentage of breakthrough bleeding will improve compliance. Both degree of ovulation inhibition and cycle control are therefore objectives in dose selection of both components.

Drospirenone (DRSP) alone

No PD studies have been performed with DRSP alone, but the PD data provided are based on public literature. Its pharmacological profile is well-characterized, and it is a widely used progestin in COCs. Its pharmacological profile is more related to that of natural progesterone with an affinity for the human PR comparable to that of progesterone itself. DRSP also has anti-androgenic and mild anti-mineralocorticoid properties, but no estrogenic, glucocorticoid or anti-glucocorticoid properties.

The clinical pharmacology programme of E4/DRSP 15/3 mg consisted of seven PK/PD studies.

Estetrol (E4)

The first two dose descending phase 1 studies, PR3050 and PR3054, with E4 alone (0.1, 1, 10 and 100 mg and 2, 10, 20, or 40 mg) were performed in postmenopausal women and could therefore not contribute to dose finding in ovulation inhibition, but showed an anti-gonadotropic activity characterized by a dose-dependent decrease in both serum FSH and LH levels with the highest doses used.

E4 in combination with progestins

A subsequent feasibility study (PR3081) into the contraceptive effect of 10 mg and 20 mg E4 alone compared to a combination of 20 mg E4/desogestrel (DSG) and 20 mg E4/progesterone (P4) was performed. A slight increase in LH and FSH concentrations was seen with 10 and 20 mg E4 only. In the 10 mg E4-only group, the estradiol and progesterone levels increased from treatment Day 15 onwards, suggesting ovulations. The 20 mg E4/DSG combination showed a slight decrease in LH, FSH, estradiol and progesterone and showed adequate inhibition of ovulation according to Hoogland scores, while 20 mg E4/P4 combination had comparable effects on LH, FSH and estradiol, as seen with 20 mg E4 only, but inadequate inhibition of ovulation.

The safety and contraceptive properties of varying doses of E4 in combination with several different progestins was studied in healthy women of reproductive age enrolled in three Phase 2 clinical studies, ES-C01, ES-C02 and MIT-Es0001-C202. Study ES-C01 evaluated ovarian suppression over 3 cycles of 5, 10, or 20 mg E4 with 3 mg DRSP or 150 mcg LNG compared with 20 mcg EE/3 mg DRSP (Yaz), as active control, administered in a 24/4-day regimen. No ovulations were observed in any of the treatment groups but mean maximum follicle size decreased with increasing dose of E4. Further, in the Hoogland scores, lowest ovarian activity was noted in the highest E4 dose treatment groups.

Study ES-C02, a large phase 2b dose-finding study, evaluated cycle control of 15 mg or 20 mg E4 combined with either 150 mcg LNG or 3 mg DRSP, compared to E2V and DNG (Qlaira), as control, over 6 months. The aim of this study was to find a dosing regimen with at most 20% absence of withdrawal scheduled bleeding and at most 20% unscheduled bleeding in Cycle 6. The E4/DRSP 15/3 mg group and the E4 20 mg/LNG group were the only

groups meeting both criteria. As of these two combinations, E4/DRSP 15/3 mg showed the lowest incidence of unscheduled intra-cyclic bleeding in Cycle 6, as well as the lowest incidence of absence of scheduled bleeding, and the lowest number of bleeding days and bleeding-spotting days within bleeding episodes, and an acceptable safety profile.

The latter study, MIT-Es0001-C202, was performed to confirm the ovulation inhibitory properties of the selected combination E4/DRSP 15/3 mg, using the established marketed COC EE/DRSP 0.02/3 mg (Yaz) as a comparator. Ovarian function was adequately suppressed in both the intended therapeutic combination E4/DRSP 15/3 mg and the comparator treatment EE/DRSP 0.02/3 mg. Overall ovarian function inhibition, indicated by a Hoogland score ≤4, was similar for both treatments E4/DRSP and EE/DRSP in Cycles 1 and 3. Follicle diameters in Cycle 1 were similar in both treatment groups and was slightly larger with E4/DRSP than with EE/DRSP during Cycle 3. Return to fertility was demonstrated for both COCs and was slightly faster after treatment with E4/DRSP than after treatment with EE/DRSP. The combination of E4/DRSP 15/3 mg was therefore selected for further Phase 3 clinical development.

Secondary pharmacodynamics

Exploratory evaluation in study ES-C01 of effects on liver function (SHBG, lipids, haemostasis, liver function, bone, glucose metabolism) showed a generally lower effect with E4 combinations than with EE combinations.

Endocrine function, metabolic control and haemostasis was evaluated in the MIT-Es0001-C201 study, in which E4/DRSP 15/3 mg in a 24/4 day regimen was compared over 6 treatment cycles with two marketed COCs, an 20 mcg EE/3 mg DRSP pill (Yaz) and an 30 mcg EE/150 mcg levonorgestrel (LNG) pill (Melleva).

For evaluation of the effects on haemostasis, a large number of haemostatic parameters, including those recommended in the EMA guideline on hormonal contraception, but also other parameters that are indicated to play a role in the haemostatic balance, have been evaluated. The results indicate that effects on haemostasis were smallest with E4/DRSP, followed by the combination of EE/LNG, while most pronounced effects were noted with EE/DRSP, as shown by greater changes in the pro-coagulant, anticoagulant, and fibrinolytic system. However, as none of these parameters is considered a validated surrogate of the clinical event of VTE, no definite conclusions on clinical implications can be drawn (see further discussion in clinical safety section).

The effects of E4/DRSP on the lipid parameters tested are small. The effects of EE/LNG show a more androgenic effect, while the effects of EE/DRSP are more anti-androgenic, which is expected based on the more androgenic profile of levonorgestrel. Evaluation of effects on the glucose and insulin response in an oral glucose tolerance test indicated that differences on carbohydrate metabolism between COCs appear to be minimal. The observed differences in effects on aldosterone of E4/DRSP and EE/DRSP versus EE/LNG confirm the effect of DRSP, which progestogen also acts like an aldosterone receptor-antagonist.

In accordance with the guideline on clinical investigation of steroid contraceptives in women (EMEA/CPMP/EWP/519/98 Rev 1), pharmacological action including the effect on ovarian function, endometrial mucosa and cervical secretion has been assessed in the earlier mentioned studies. E4, as monotherapy, suppresses ovarian activity and inhibits ovulation dose-dependently. However, complete ovarian suppression and adequate hypothalamic-pituitary-ovarian (HPO) function is only obtained when E4 is combined with a progestin, as seen in studies PR3050, PR3054 and PR3081. Further, the effects on ovarian function (by plasma concentrations of ovarian steroids and gonadotrophins and ultrasound of ovaries) in women with normal ovulatory function has been described, as reflected by Hoogland scores, follicle diameter, and E2, progesterone, FSH, and LH levels, showed adequate suppression, in studies ES-C01, and ES-C02 and MIT-Es0001-C202. In latter study MIT-Es0001-C202, the intended therapeutic combination E4/DRSP 15/3 mg was as effective as EE/DRSP 0.02/3 mg (Yaz) in suppressing ovarian function, with a similar overall inhibition as indicated by a

Hoogland score ≤4. Also, the time to onset of action, in relation to start of treatment and dose of steroids and the time to return of normal ovarian function after discontinuation of treatment has been studied and was confirmed to be adequate in a sufficient number of subjects from studies ES-C01 (n=109), ES-C02 (n=36), Study MIT-Es0001-C202 (n=82), and also in the two large phase 3 clinical trials (n=1,577 and n=2,148). Furthermore, other pharmacological effects on the reproductive system and process, including endometrial effects and effects on cervical mucus have been described.

2.4.5. Conclusions on clinical pharmacology

The Applicant has conducted several clinical studies addressing the PK of estetrol alone, as well as the clinical studies addressing the PK of estetrol with co-administration of drospirenone. In general, sufficient PK information of estetrol was provided/described by the Applicant.

The clinical results of the abovementioned clinical pharmacology programme generally appear to be sufficient for the proposed dose range and regimen (E4/DRSP 15/3 mg). An appropriate well-tolerated contraceptive treatment effect has been observed with E4/DRSP 15/3 mg, which supports initiation of the phase 3 program. Clarifications of minor concerns were requested to improve understanding of some observed results. The Applicant has responded adequately, and no concerns remain related to pharmacodynamic data for E4/DRSP.

2.5. Clinical efficacy

The clinical dose finding studies and pivotal efficacy and safety studies are tabulated below.

Study ID	Phase Type	Title	Location
Phase 2 trials			
ES-C02	Efficacy/safety (dose-finding) -PD	A randomized, open-label, multicenter study to assess the cycle control of 15 mg or 20 mg estetrol combined with either 150 µg levonorgestrel or 3 mg drospirenone, compared to a combined oral contraceptive containing estradiol valerate and dienogest	Module 5.3.5.1
MIT-Es0001-C201	Safety/PD	A single center, randomized, open-label, controlled, three-arm study to evaluate the effect of a new combined oral contraceptive (COC) containing 15 mg estetrol (E4) and 3 mg drospirenone (DRSP) and of two reference COCs containing either 30 mcg ethinylestradiol (EE) and 150 mcg levonorgestrel (LNG) or 20 mcg EE and 3 mg DRSP on endocrine function, metabolic control and hemostasis during 6 treatment cycles	Module 5.3.4.1
MIT-Es0001-C202	Efficacy/safety-PD	A single-center, randomized, open-label, two-arm study to evaluate the ovarian function of a monophasic combined oral contraceptive (COC) containing 15 mg estetrol (E4) and 3 mg drospirenone (DRSP) and a monophasic COC containing 20 mcg ethinylestradiol (EE)/3 mg DRSP (Yaz®), administered orally once daily in a 24/4 day regimen for three consecutive cycles	Module 5.3.4.1
Phase 3 trials			

MIT-Es0001-C301	Efficacy/safety	A multicenter, open-label, single-arm study to evaluate the contraceptive efficacy and safety of a combined oral contraceptive containing 15 mg estetrol and 3 mg drospirenone (E4 FREEDOM: **F**emale **R**esponse concerning **E**fficacy and safety of **E**stetrol/**D**rospirenone as **O**ral contraceptive in a **M**ulticentric study)	Module 5.3.5.2
MIT-Es0001-C302	Efficacy/safety	A multicenter, open-label, single-arm study to evaluate the contraceptive efficacy ands of a combined oral contraceptive containing 15 mg estetrol and 3 mg drospirenone (E4 FREEDOM: **F**emale **R**esponse concerning **E**fficacy and safety of **E**stetrol/**D**rospirenone as **O**ral contraceptive in a **M**ulticentric study)	Module 5.3.5.2

COC = combined oral contraceptive, DRSP = drospirenone, E4 = estetrol, EE = ethinylestradiol, LNG = levonorgestrel, PD = pharmacodynamics

2.5.1. Dose response studies

Proof of concept and dose finding

Combined hormonal contraceptives (CHCs) act by ovulation inhibition, while the remaining ovarian activity determines the contraceptive robustness, i.e., the vulnerability to non-compliance, or to interacting conditions and drugs. Because control of vaginal bleeding is the major determinant of the tolerability of a CHC, this is an important element of dose selection. In a CHC, the progestogen is the main component responsible for ovulation suppression, supported by some anti-ovulatory effect of the oestrogen. The main purpose of the oestrogen component, however, is to exert effects on the endometrium and thereby contributing to a predictable bleeding pattern.

The three studies described above (PR3081, ES-C01, ESC02) were dedicated to establish the proof of concept of selected doses of estetrol (E4) alone and in combination with progestogens in order to achieve a suitable combination for reliable ovulation inhibition and a predictable bleeding pattern for cycle control.

The study PR 3081 showed that E4 had very weak effects on follicular development when given alone in doses up to 20mg/day and even in combination with progesterone. Only when combined with an already established anti-ovulatory dose of desogestrel (DSG), ovulation inhibition could be demonstrated.

Study ES-C01 demonstrated that 5, 10 and 20 mg of E4, in combination with 3 mg DRSP or 0.15 mg levonorgestrel (LNG), did inhibit ovulation, presumably mainly a progestogenic effect. The bleeding pattern analyses suggested that a daily dose of 10 mg E4 or more seemed to provide a predictable and thus acceptable bleeding pattern.

Study ES-C02, focussing on the bleeding pattern, confirmed that 15 mg E4 combined with 3 mg DRSP appeared associated with fewer women reporting bleeding/spotting during days of pill taking, as well as fewer women without a withdrawal bleed, than the other tested combinations, including one marketed COC (Qlaira). This finding, together with results supporting reliable ovulation inhibition, justifies the selection the combination of 15 mg E4 with 3 mg DRSP for further development.

Once the dose of E4 and the chosen combination had been selected, study MIT-Es0001-C202 was dedicated to further evaluate and confirm the ovarian function of a monophasic oral CHC containing 15 mg E4 and 3 mg drospirenone (DRSP) in comparison with an established oral CHC.

To confirm the contraceptive mechanisms of action with the E4/DRSP 15/3 mg 24/4 regimen, Study MIT-Es0001-C202 was performed, including Yaz (EE/DRSP 0.02/3 mg) as comparator. This dose confirmation study suggest that the E4/DRSP 15/3 mg 24/4 regimen may provide as acceptable contraceptive efficacy as the already marketed product EE/DRSP 0,02/3 mg (YAZ).

The number and age span of women included in the phase 2 studies, the methods of analysis (measuring the hormones FSH, LH, estradiol and progesterone), the use of frequent transvaginal ultrasound and combining the results into the Hoogland score, are all considered adequate methods for the evaluation of effects on the ovarian function in the establishment of a contraceptive product, forming the basis for the phase 3 clinical program.

2.5.2. Main studies

The application for E4/DRSP is supported by two Phase 3, multi-centre, open-label, single-arm studies; Study MIT-Es0001-C301 (conducted in Europe/Russia) and Study MIT-Es0001-C302 (conducted in the US/Canada).

Study MIT-Es0001-C301 and Study MIT-Es0001-C302

Methods

Both pivotal studies had a multi-centre, open-label, single-arm design. Since they share most design features, they are described together below.

Study Participants

The studies included heterosexually active females at risk for pregnancy and requesting contraception, and who were willing to use the investigational product as the primary method of contraception for 13 consecutive cycles. The women were aged 18 to 50 years (inclusive) in Study C301 and 16-50 years in Study C302. The women should have good physical and mental health on the basis of medical, surgical and gynaecological history, physical examination, gynaecological examination, clinical laboratory, and vital signs, and a Body mass index (BMI) ≤ 35.0 kg/m^2. The inclusion criteria are considered adequate to include heterosexually active women of fertile age.

The exclusion criteria reflected the general contraindications for combined hormonal contraceptives, e.g. with respect to the risks for venous thromboembolism, hypertension, diabetes, hepatic abnormalities, etc. Hyperkalaemia is included, which is relevant considering the antimineralocorticoid effects of DRSP.

The listed prior and concomitant therapies that were not allowed were also acceptable. Use of any contraceptive method other than the investigational product was unauthorized in the study, including emergency contraception. At-risk cycles were defined as cycles in which no other methods of birth control (including condoms and emergency contraception) were used as confirmed in the subject diary.

Treatments

Eligible subjects were treated with 15 mg E4/3 mg DRSP for a maximum of 13 consecutive cycles. The treatment was to be taken once daily at approximately the same time of the day in a 24/4-day regimen, i.e., 24 active, pink tablets followed by 4 placebo, white tablets (4-day hormone-free interval). Specific instructions were provided for starting the first pack of tablets, depending on whether the woman had used any previous hormonal contraceptive method or not and if so, the type of method. Specific instructions were also provided in case of missed tablet(s) or in conditions potentially reducing the contraceptive efficacy.

Subject diaries were given to the participating subjects at Visit 2 (subject enrolment) and the subjects were instructed on how to complete it. Information recorded in the subject diary related to the date of the intake of the first tablet at each cycle, tablet intake on a daily basis, absence or occurrence of vaginal bleeding/spotting event(s) on a daily basis (classified as 0 = Absence of vaginal bleeding or spotting, 1 = Spotting and 2 = Bleeding), use of contraceptive method other than the investigational product (e.g., condom) during the cycle, occurrence of heterosexual intercourse during the cycle and results of the UPT(s) performed at home (at Cycle 1 before the first pill intake and at subsequent cycles in case of absence of menstruation).

Participating subjects were asked to record their bleeding/spotting episodes daily in the subject diary, to allow evaluation of the bleeding pattern and the cycle control. Treatment compliance was assessed using data from the subject diary across the entire study and by cycle, treatment compliance from diary was compared on site with the drug accountability (returned tablet) and any discrepancy was to be documented in the subject's source document.

The subject diary was also used to determine whether a cycle was at risk for the Pearl Index calculation, i.e. a cycle in which no other contraceptive method other than the investigational product was used and sexual intercourse occurred. Use of condoms was allowed during the course of the study only to avoid transmission of sexually transmitted infections or in case of missed tablet(s) or unauthorized concomitant therapy(ies). Condom and any other contraceptive methods use had to be recorded in the subject diary.

Serum pregnancy tests were performed during the study at the Screening Visit (Visit 1) and Visit 7 (Cycle 14).

Urine pregnancy tests (UPT) were performed at home by the subject just before intake of the first investigational product and in cases of a missed menstrual period. In case of a positive UPT result, the subject was instructed to contact the study staff immediately and not to take the investigational product. An appointment was scheduled for pregnancy follow-up as soon as possible. For subjects included in the Endometrial Safety Substudy, an additional UPT was performed at the study site before performing the endometrial biopsy (Visit 7a).

Objectives

The primary objective of both studies was to evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index in subjects aged 18 to 35 years (16 to 35 years in Study C302), inclusive, at the time of screening.

The secondary objectives were to evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the method failure Pearl Index and life-table analysis in subjects aged 18 (or 16) to 35 years, inclusive, at the time of screening and to evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index, the method failure Pearl Index and life-table analysis in the overall (up to 50 years) study population.

Other secondary objectives were to evaluate cycle control and bleeding pattern associated with 15 mg E4/3 mg DRSP, to evaluate general safety of 15 mg E4/3 mg DRSP and to evaluate the impact of 15 mg E4/3 mg DRSP on physical, psychological, and social functioning and well-being.

Study C301 also had an objective to evaluate the endometrial safety using histological assessment of endometrial biopsy samples in a subset of subjects aged 18 to 50 years, inclusive, at the time of screening (Endometrial Safety Substudy).

Study C302 included a Population PK Substudy, with the aim to assess the effect of various individual characteristics/covariates (e.g., body weight, race, smoking, and fed/fasted condition) on the pharmacokinetics of 15 mg E4/3 mg DRSP.

Outcomes/endpoints

The primary efficacy variable was the number of on-treatment pregnancies assessed by the Pearl Index in the intention-to-treat (ITT) population of women aged 18 to 35 years (16 to 35 years in Study C302), inclusive, at the time of screening with at-risk cycles, defined as no use of other methods of birth control (including condoms) as confirmed in the subject diary, and confirmation that sexual intercourse occurred during the cycle in the diary. The focus on the 18 (or 16) to 35-year age range for the primary efficacy outcome is endorsed.

The secondary efficacy variables were the following:

- The number of on-treatment pregnancies assessed by the method failure Pearl Index and the cumulative pregnancy rate in subjects aged 18 to 35 years, inclusive, at the time of screening.
- The number of on-treatment pregnancies assessed by the Pearl Index, the method failure Pearl Index and the cumulative pregnancy rate in the overall study population.

Other secondary variables were the following:

- Cycle control and bleeding patterns based on vaginal bleeding information recorded daily by the subjects in the diaries.
- Safety data in the overall study population obtained from routine laboratory parameters, vital signs, and physical, gynaecological and breast examinations, evaluated as the number, frequency, type and intensity of TEAEs and SAEs.
- Change from baseline to end of treatment in the various items of well-established questionnaires to evaluate physical, psychological, and social functioning and well-being.
- Change in endometrial histology from baseline to end of treatment in subjects treated for at least 10 complete cycles (study C301 only).
- Plasma E4 and DRSP concentration data from a subset of approximately 500 subjects for the development of a population PK model (Population PK Substudy) (study C302 only).

The study objectives and outcomes are adequate for studies evaluating a new contraceptive. The number of subjects and the duration of treatment are in accordance with the requirements of the EMA guideline on steroid contraceptives (EMEA/CPMP/EWP/519/98 Rev1), i.e. at least 400 women completing one year of treatment.

Sample size

Sample size was based on needing a sufficient number of cycles such that the difference between the Pearl Index and the upper limit of the 2-sided 95% CIs for the Pearl Index did not exceed 1. Assuming that the true Pearl Index was 1.0 and that a Poisson model was used to derive the CIs, then at least 12,337 at-risk cycles were required for a power of 90% in the 18 to 35-year old population. If a not at-risk cycle rate of 10% and a dropout rate of approximately 30% (assuming that there was an average of 4 cycles for subjects that discontinued) were assumed, approximately 1,350 subjects aged 18 to 35 years needed to be enrolled. Additionally, it was planned to enrol a maximum of 200 subjects aged 36 to 50 years. Therefore, in total, 1,550 subjects were planned to be enrolled in the study.

No formal sample size was estimated for the Endometrial Safety Substudy. Approximately 100 subjects with both Screening Visit and Visit 7a biopsies were planned to be included in the Endometrial Safety Substudy. Assuming a 40% dropout rate for a 13-cycle treatment, this would have yielded approximately 167 subjects who had a screening biopsy performed at selected sites.

The sample size was based on the precision in the Pearl Index estimate. This is in accordance with the guideline on clinical investigation of steroid contraceptives in women (EMEA/CPMP/EWP/519/98 Rev 1).

Randomisation and blinding (masking)

The studies had a non-comparative, open-label single arm design. Hence, there were no objectives related to superiority or non-inferiority and randomisation and blinding were not necessary.

The use of a single arm, non-comparative study design can be accepted for the evaluation of a new hormonal contraceptive, in accordance with the EMA guideline on steroid contraceptives. The lack of an active comparator for the studies evaluating the contraceptive efficacy of a new contraceptive method is acceptable according to this guideline, as long as the number of cycles studied are sufficient to obtain the desired precision of the estimate of contraceptive efficacy and unless the expected PI is high (PI>1). Comparative data are however required for the studies evaluating ovarian function and metabolic effects. In the studies evaluating ovarian function and haemostatic parameters, relevant active comparators were included. For bleeding control data, the guideline mentions that the information should to a considerable extent come from studies including an active comparator. The two pivotal studies did not include an active comparator for comparison of bleeding patterns, which is a deficiency. However, earlier studies (e.g. ES-C02 which included Qlaira, estradiol valerate/dienogest) have included comparators that can contribute to assessment of the bleeding pattern.

Statistical methods

The sample size in the two pivotal studies were based on the precision in the Pearl Index estimate which is in accordance with the guideline on clinical investigation of steroid contraceptives in women (EMEA/CPMP/EWP/519/98 Rev 1), and hence acceptable. The statistical methods are largely acceptable for a single arm, non-comparative study.

Contraceptive efficacy data were displayed for subjects aged 18(16) to 35 years and for all subjects in both pivotal studies. The contraceptive efficacy in subjects aged >35 years has also been calculated, on the pooled population from Phase 3 + Phase 2 studies. Results were presented in the Integrated Summary of Efficacy report.

Missing data in the diary were interpreted as "No" for pill intake and sexual intercourse and as "Yes" for use of other contraceptive methods. Overall, the number of cycles with missing diary data for sexual intercourse and

use of other contraceptive methods was rather low in relation to the total number of cycles. Also, for bleeding the missing information interpolated with adjacent data was low (generally <3%).

Overall, the pivotal studies have been designed in accordance with the requirements in the EMA guideline on clinical investigation of steroid contraceptives in women (EMEA/CPMP/EWP/519/98 Rev 1) and in agreement with scientific advice provided by the CHMP. In the early advice from 2012, it was commented that since DRSP is tied to a higher relative risk of VTE, the company could consider using another progestin, however, DRSP was kept as the progestagen following results of Phase 2 studies. From this advice, it is also understood that the intention of the Applicant was to include Qlaira (estradiol/dienogest) as an active comparator in the pivotal studies (or one of them), although the CHMP mentioned that an active comparator is generally not requested for efficacy purposes. An active comparator was finally not included in any of the pivotal studies. Advice related to haemostasis, ovarian function data, QT interval assessment have largely been followed.

Concerning GCP aspects, no obvious concerns have been identified based on the review of the studies. Nevertheless, since the Sponsor has not previously been inspected for a CAP MA, and since this product represents some degree of novelty (new estrogen not previously used in any other product) a verification of GCP compliance of trials supporting the application was requested by the CHMP and the GCP inspection was performed, as described in Section 2.4.1.

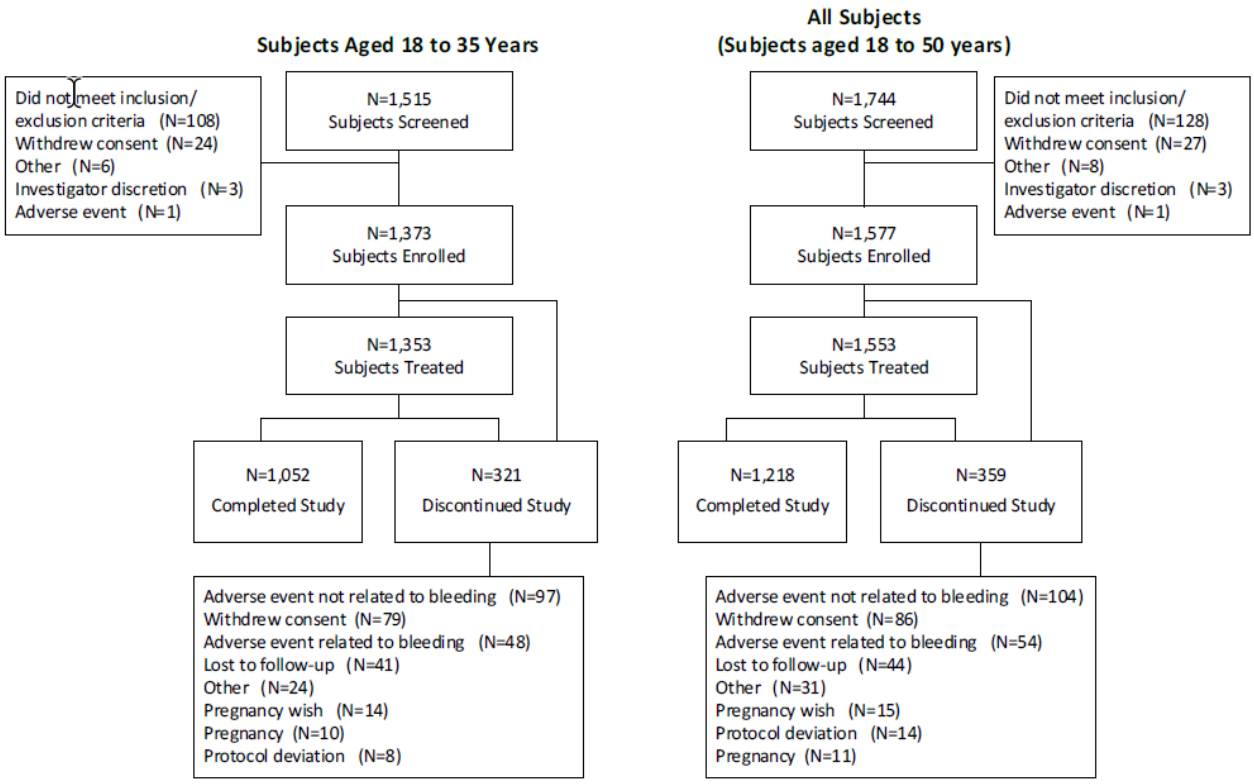
Results

The results are presented separately for each pivotal study.

Study MIT-Es0001-C301

Participant flow

Figure 7. Subject Disposition



The rate of discontinuation was moderate, 22% up to Cycle 13.

The most common reasons for discontinuing the study among all subjects were AEs not related to bleeding (6.0%), followed by consent withdrawal (4.9%) and AEs related to bleeding (3.1%). Pregnancy wish was the reason for discontinuation in 15 subjects (0.9%), and pregnancy in 11 subjects (0.6%). Of the 11 pregnancies, five were on-treatment pregnancies whereas the other were pre- or post-treatment pregnancies.

Recruitment

The study was performed in 69 enrolling sites in Europe (Belgium [8 sites], Czech Republic [12 sites], Finland [8 sites], Germany [7 sites], Hungary [11 sites], Norway [4 sites], Poland [6 sites], and Sweden [3 sites]) and Russia (10 sites). The Endometrial Safety Substudy was conducted at 14 sites in Finland, Germany, and Poland.

The date of first screening was 28 June 2016 and the date of last patient completed was 26 April 2018.

Conduct of the study

Protocol amendments

The study was initiated according to the Protocol Amendment version 1.2, dated 26 April 2016. An urgent safety memo with clarification of pill initiation instructions for subjects switching from an implant or IUD was issued on 04 August 2016. Two subsequent amendments to the protocol were created, as follows:

- Protocol Amendment version 2.0, dated 01 September 2016 (concerned requirement to use condoms for the first 7 days after switching from an intrauterine or dermally implantable contraceptive)
- Protocol Amendment version 2.1, dated 06 February 2017 (concerned clarifications e.g. relating to discontinuations in the study, pregnancy follow-up applied only to all enrolled subjects who started study product)

The clinical study report was prepared from the last Protocol Amendment version 2.1.

Protocol Deviations

Important protocol deviations were reported in 612 subjects (39.4%).

The most common category of important protocol deviations was study drug (e.g., the subject did not return study drug blisters, or did not follow the instructions for missing pills, etc), which affected 299 subjects (19.3%). Other categories of important protocol deviations were other deviations (e.g. related to insurance policies, physician's error with the IWRS, etc), which affected 187 subjects (12.0%); laboratory/endpoint data (e.g., laboratory samples taken without fasting, questionnaire completed at wrong timing, etc), which affected 155 subjects (10.0%); visit window, which affected 54 subjects (3.5%); safety assessment (e.g., pregnancy test performed at wrong timing, wrong handling of laboratory samples, etc), which affected 53 subjects (3.4%); IC (e.g., missing administrative information in the form, missing additional consenting to general practitioner notification and long-term storage of samples, etc), which affected 24 subjects (1.5%); exclusion criteria (mainly hypertension), which affected 18 subjects (1.2%); prohibited concomitant medication, which affected 5 subjects (0.3%); and inclusion criteria (Pap smear test performed late in 1 subject, and the other subject was enrolled before the endometrial biopsy report was sent to the site and resulted to be abnormal), which affected 2 subjects (0.1%).

Compliance

Treatment compliance for the investigational drug was defined as the actual number of tablets taken (based on the data collected in the subject diary) divided by the expected number of tablets taken. Treatment compliance was calculated as a percentage and derived for each cycle that the subject started. If the number of active (pink) and inactive (white) pills was blank in the diary, then it was assumed that no pills were taken on that day.

The majority of the subjects (> 87%) in each cycle did not miss any pills, and the proportion of subjects who did not miss any pills was > 90% in all cycles starting from Cycle 8. Cycle 3 had the lowest percentage of subjects with no pills missed (87% of subjects), and Cycle 12 had the highest percentage (93% of subjects).

The percentage of subjects who missed 1 pill ranged from 4.3% of subjects in Cycle 12 to 7.8% of subjects in Cycle 3. The percentage of subjects who missed 2 pills ranged from 1.2% of subjects in Cycle 12 to 3.1% of subjects in Cycle 3. The percentage of subjects who missed > 2 pills ranged from 0.9% of subjects in Cycle 13 to 2.5% of subjects in Cycle 6.

The mean total number of pills taken per cycle ranged from 27.7 to 27.9 pills, with a median of 28 pills at each cycle. Mean compliance over the study was > 99%, ranging from 99.3 to 100% per cycle, with a median

compliance of 100% overall and for each cycle. The mean % compliance was above 100% for several cycles and ranged up to 143% (cycle 7; range of number of tablets taken was 1 to 40). Clarification has been provided regarding the 'over-compliance'. In the majority of cycles being over-compliant, 29 or 30 pills were taken, presumably merely by the subject´s mistake. The exact reasons do not seem to be known. The number of cycles with ≥ 31 tablets taken were fewer and in most cases likely related to gastrointestinal disturbances.

Baseline data

Table 9. Subject Characteristics (ITT Population)

Property	Statistic	MIT-Es0001-C301 (Europe, Russia)	
		18 to 35 years	All
Number of subjects	N	1,353	1,553
Age (Years)	Mean (SD)	25.0 (4.46)	27.1 (6.86)
	Median (Min, Max)	24.0 (18, 35)	25.0 (18, 49)
	≥16 – ≤25 (n, %)	793 (58.6)	793 (51.1)
	>25 - ≤35 (n, %)	560 (41.4)	560 (36.1)
	>35 - ≤50 (n,%)		200 (12.9)
Body weight (kg)	Mean (SD)	63.7 (10.65)	63.8 (10.53)
	Median (Min, Max)	61.6 (35.0, 111.5)	62.0 (35.0, 111.5)
BMI (kg/m^2)	Mean (SD)	22.9 (3.46)	23.0 (3.47)
	Median (Min, Max)	22.3 (15.0, 35.0)	22.4 (15.0, 35.0)
	<18.5	1,278 (94.5)	1,464 (94.3)
	≥18.5 - <25		
	≥25 - <30		
	≥30	75 (5.5)	89 (5.7)
Race*	White	1,334 (98.6)	1,532 (98.6)
	Black or African American	8 (0.6)	8 (0.5)
	Asian	9 (0.7)	10 (0.7)
	Other**	2 (0.1)	3 (0.2)
Ethnicity	Hispanic or Latino	11 (0.8)	13 (0.8)
Highest education	Less than Upper Secondary School	113 (8.4)	130 (8.4)
	Completed Upper Secondary School	518 (38.3)	584 (37.6)
	Completed Vocational School	130 (9.6)	150 (9.7)
	Completed College	413 (30.5)	481 (31.0)
	Completed Graduate School	179 (13.2)	208 (13.4)
Previous contraceptive use	Switchers	833 (61.6)	947 (61.0)
	Starters	520 (38.4)	606 (39.0)
	New Users	331 (24.5)	370 (23.8)
Smoking status	Current smoker	246 (18.2)	246 (15.8)
	Non smoker	1,107 (81.8)	1,307 (84.2)

Property	Statistic	MIT-Es0001-C301 (Europe, Russia)	
		18 to 35 years	All
	Former smoker	54 (4.0)	71 (4.6)
	Never smoker	1,053 (77.8)	1,236 (79.6)

BMI = body mass index, ITT = intention-to-treat, Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation

***** Subjects may be included under more than one race category. For the subjects that were enrolled in more than one of the clinical trials, their demography and baseline characteristics is presented twice in the pooled database and will be considered as separate subjects.

** Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and Others

The majority of the women included in Study C301 were aged 35 years or below (12.9% were >35 years), White (98.6%), non-smokers (84%) with a BMI <30 kg/ m^2 (94%).

About two thirds (61%) were 'switchers' (i.e. subjects who had used hormonal contraceptives within the 3 months prior to the date of first dose of investigational product.), while 39% were 'starters' (subjects who had not used hormonal contraceptive(s) within the 3 months prior to the date of first dose of investigational product). Approximately 25% of subjects were true new users (subjects who had never been using hormonal contraception; i.e. a subset of the starter subgroup).

Of the 1577 subjects enrolled, 282 subjects were enrolled in 10 sites in Russia, thus, about 82% of the study population were from Europe.

Numbers analysed

Table 10. Study MIT-Es0001-C301. Number of subjects by population

	Analysis sets		
	All subjects	18 – ≤35 years	>35 years
Population			
Screened (N)	1,744	1,515	229
Enrolled (N)	1,577	1,373	204
Treated (ITT and Safety Populations) (N [%])[a]	1,553 (98.5)	1,353 (98.5)	200 (98.0)
PP (N [%])[a]	1,535 (97.3)	1,337 (97.4)	198 (97.1)

[a] percentage of enrolled subjects
ITT = intention-to-treat, N = number of subjects, PP = per protocol

Screened: included all subjects who signed an informed consent form.
Enrolled: included all enrolled subjects.
ITT, Safety Population: included all enrolled subjects who receive at least 1 dose of investigational product
PP: included all subjects in the ITT Population who had at least 1 evaluable cycle for the bleeding analysis

The ITT population comprised 98.5% of the enrolled population and the PP population comprised 97.3%.

Outcomes and estimation

Pregnancies

Two pre-treatment pregnancies, five on-treatment pregnancies and four post-treatment pregnancies were reported in the ITT Population. Of the five on-treatment pregnancies, two were considered user failures.

Two subjects started study treatment with 15 mg E4/3 mg DRSP and it was later known that they were already pregnant before treatment initiation and, therefore, discontinued the study. In addition to the 2 pre-treatment pregnancies, 4 further subjects had a positive pregnancy test result after being enrolled and did not start the investigational product intake.

During the study, 5 on-treatment pregnancies were reported, of which 2 pregnancies were considered user failure, i.e., pregnancies where the subject did not take the investigational product correctly as per the protocol during the cycle in which the conception occurred. One pregnancy resulted in a spontaneous abortion, which was reported as an SAE. All on-treatment pregnancies occurred in subjects aged 18 to 35 years at screening.

Post-treatment pregnancies were reported in 4 subjects.

Pearl Index

Primary efficacy variable: Pearl Index in subjects aged 18 to 35 years with at-risk cycles

The summary and analysis of Pearl Index in subjects aged 18 to 35 years with at-risk cycles is provided below.

Table 11. Study MIT-Es0001-C301. Summary and analysis of Pearl Index in subjects aged 18 to 35 years with at-risk cycles (ITT Population)

Cohort Variable Statistic	E4/DRSP 15/3 mg (N=1,553)
Subjects aged 18 to 35 Years at Screening with at least 1 cycle included in the denominator, n	1,313
Number of at-risk cycles	13,692
Number of on-treatment pregnancies	5
Pearl Index	0.47
95% CI[a] for Pearl Index	(0.15, 1.11)
Difference between upper limit of 95% CI and Pearl Index	0.64

CI= confidence intervals, DRSP = drospirenone, E4 = estetrol, ITT= intention-to-treat, N = number of subjects

[a] Notes: Confidence intervals (CIs) are calculated using a Poisson distribution.

At-risk cycles are defined as cycles with no other methods of birth control (including condoms) and confirmed sexual intercourse.

On-treatment pregnancy: a pregnancy with an estimated date of conception after the date of the first dose of investigational product to 2 days after the last dose of investigational product (regardless of whether the last dose was an active or inactive tablet) inclusive.

There were five on-treatment pregnancies. Thus, for the defined primary efficacy variable, the Pearl Index in subjects aged 18 to 35 years with at-risk cycles, the PI for E4/DRSP 15/3 mg was **0.47** (**95% CI: 0.15, 1.11**). The requirement for precision of the PI was thereby met in accordance with the EMA Guideline on Steroid

Contraceptives, since the difference between the upper limit of the corresponding 2-sided 95% CI for the Pearl Index and the point estimate was < 1.

The modified at-risk Pearl Index (EU definition), for which only cycles with use of other methods of birth control are excluded from the denominator but cycles without confirmed sexual intercourse are included, was **0.44 (95% CI: 0.14, 1.03**) in subjects aged 18 to 35 years (See Table below).

Secondary efficacy variables: Pearl Index in all subjects / PI calculated with alternative methods

Table 12. Study MIT-Es0001-C301. Summary and analysis of Pearl Index for all subjects and Pearl Indices calculated with different methods in subjects with at-risk cycles (ITT Population)

Cohort Variable Statistic	E4/DRSP 15/3 mg (N=1,553)								
	Overall at-risk PI in overall population[A]	"Typical use" PI [B]		Modified at-risk PI [C]		Method Failure PI[D]		Method Failure PI including compliant at-risk cycles[E]	
n	1,510	1,353	1,553	1,343	1,542	1,313	1,510	1,303	1,499
Age group (Years)	18-50	18-35	18-50	18-35	18-50	18-35	18-50	18-35	18-50
Number of at-risk cycles	15,849	15,343	17,684	14,759	17,037	13,692	15,849	13,053	15,131
Number of on-treatment pregnancies	5	5	5	5	5	3	3	3	3
PI	0.41	0.42	0.37	0.44	0.38	0.29	0.25	0.30	0.26
95% CI for PI	(0.13, 0.96)	(0.14, 0.99)	(0.12, 0.86)	(0.14, 1.03)	(0.12, 0.89)	(0.06, 0.83)	(0.05, 0.72)	(0.06, 0.87)	(0.05, 0.75)
Difference between upper limit of 95% CI and PI	0.55	0.57	0.49	0.59	0.51	0.54	0.47	0.5	0.49

[A] Pearl Index: At-risk cycles are defined as cycles with no other methods of birth control (including condoms) and confirmed sexual intercourse.
[B] "Typical use" Pearl Index: All cycles are included in the denominator regardless of other methods of birth control, occurrence of sexual intercourse or compliance with the protocol.
[C] Modified at-risk Pearl Index: At-risk cycles are those where no other methods of birth control are used (modified risk). Cycles without confirmed sexual intercourse are not excluded.
[D] Method Failure Pearl Index: uses the same method used for the Pearl Index, but excludes those pregnancies due to user failures from the numerator, i.e. subject did not take the study medication correctly during the cycle in which the estimated conception occurred or used drugs that have the potential to trigger interactions with COC.
[E] Only compliant modified at-risk cycles are included in the denominator of the Pearl Index calculation. Compliant modified at-risk cycle = a cycle where no other methods of birth control (including condoms) was used, the subject did not have a user failure pregnancy and the subject had no adverse event of vomiting and/or diarrhea.
CI = confidence interval, DRSP = drospirenone, E4 = estetrol, ITT = intention-to-treat, n = number of subjects with at least 1 cycle included, PI = Pearl Index

Notes: Confidence intervals (CIs) are calculated using a Poisson distribution. Any cycles after the cycle of conception in the case of pregnancy were excluded.

Also, in the whole group (up to 50 years of age) and with alternative calculation methods, the Pearl Indices ranged from 0.25 to 0.44 and the difference between the point estimates and the upper limits of the corresponding 2-sided 95% CIs was below 1 for all Pearl Indices. The PI for Method failure was 0.29 (95% CI 0.06, 0.83) for the age group 18-35 years and 0.25 (95% CI 0.05, 0.72) for the whole study population.

Life table analyses

Life-table analyses (based on Kaplan-Meier estimates) were consistent with the Pearl Index results.

Cumulative on-treatment pregnancy rate: After 13 cycles, the cumulative on-treatment pregnancy rate was 0.45% (95% CI: 0.19, 1.09) for subjects aged 18 to 35 years and 0.39% (95% CI: 0.16, 0.94) for subjects aged 18 to 50 years, i.e., the probability of contraceptive protection after up to 1 year of treatment was estimated to be 99.6%.

Cumulative on-treatment method-failure pregnancy rate: After 13 cycles, the cumulative on-treatment method-failure pregnancy rate was 0.28% (95% CI: 0.09%, 0.86%) for subjects aged 18 to 35 years and 0.24% (95% CI: 0.08%, 0.74%) for subjects aged 18 to 50 years i.e., the probability of contraceptive protection during up to 1 year of treatment was approximately 99.7%.

Vaginal bleeding pattern

The women enrolled in the clinical trials were to record their vaginal bleeding experience for the entire treatment duration in the subject diary. Each day they had to mark a box for either "no bleeding," "spotting" (vaginal blood loss that did not require new use of sanitary protection, including pantyliners), or "bleeding" (vaginal blood loss requiring the use of sanitary protection with a tampon, pad or pantyliner).

The definitions for bleeding, spotting, episodes and the proposed terminology for characterizing bleeding episodes as 'unscheduled' or 'scheduled' were adopted from Mishell et al. (2007). The recommendations for cycle analysis were also followed, except for the definitions of scheduled and unscheduled bleeding.

Mishell et al. propose to deviate from the 'classical' cycle analysis by applying stricter definitions for scheduled bleeding, i.e., episodes that begin during a hormone-free interval and continue through Days 1–4 of the subsequent active cycle; this continuation into the next cycle is thus considered part of a 'scheduled' bleeding ('modified cycle analysis'). This definition has the original 21/7 contraceptive regimen in mind, as other 28-day cyclic regimens had not yet been introduced at the time. Thus defined, a regular 21/7 regimen has an 11-day expected bleeding interval, during which bleeding is considered 'scheduled'.

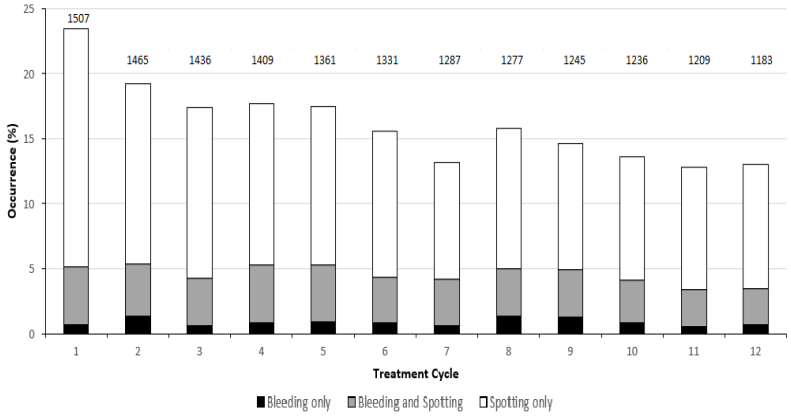
However, with the hormone-free interval being shortened to 4 days, as in the current E4/DRSP 15/3 mg contraceptive, this expected bleeding period would thus defined be shortened to 8 days, which puts this regimen at an a priori higher risk of unscheduled bleeding. Similarly, with a 24-day rather than 21-day active tablet intake period, the expected non-bleeding period is lengthened by 3 days and there is also a higher a priori risk of an early start of the scheduled bleeding with the 24/4 regimen. In other words, the exact same bleeding pattern would have higher unscheduled bleeding and lower scheduled bleeding incidences for 24/4 as compared to 21/7 regimens and would preclude meaningful (historical) comparisons to be made (see below).

Unscheduled bleeding-spotting

After an initial incidence of 23.5% in Cycle 1, the overall incidence of unscheduled bleeding and/or spotting was below 20%, reaching incidences of 13% to 16% upon longer duration of use. The vast majority of bleeding and/or spotting episodes concerned spotting-only, implying that in each cycle, 95%

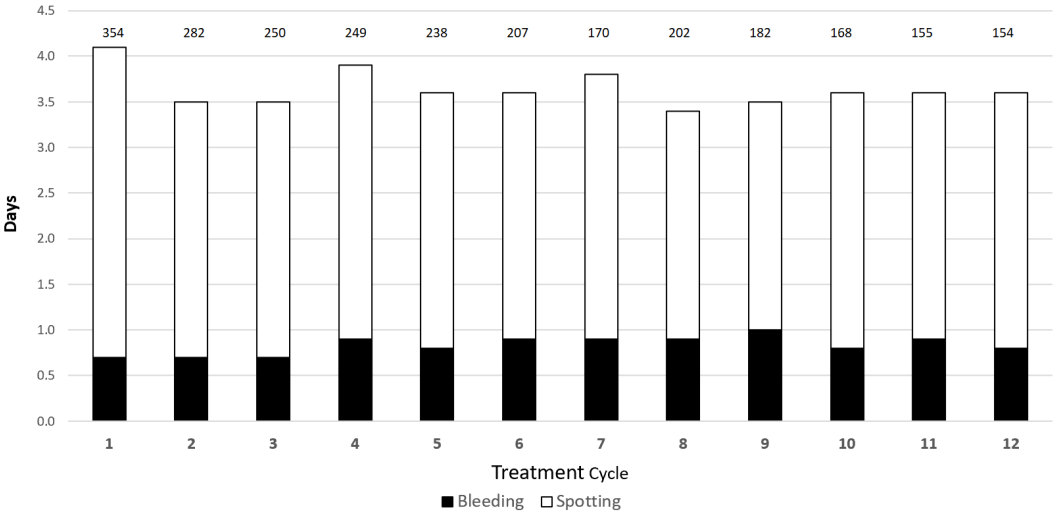
or more of the subjects did not experience unscheduled bleeding requiring the use of sanitary protection. About 85% of subjects did not experience any unscheduled bleeding or spotting at all per cycle (Figure 19).

Figure 8. Study MIT Es0001-C301. Incidence of unscheduled bleeding-spotting per treatment cycle (ITT Population)



When restricted to those subjects who actually experienced unscheduled bleeding-spotting, the mean number of bleeding and/or spotting days over Cycles 2-12 ranged between 3.4 and 3.9 days per cycle (Figure 20). The contribution of bleeding days was minimal (≤1 day). The median duration of unscheduled bleeding-spotting was 3.0 days in all.

Figure 9. Study MIT-Es0001-C301. Mean number of unscheduled bleeding-spotting days per treatment cycle in subjects experiencing unscheduled bleeding-spotting (ITT Population)



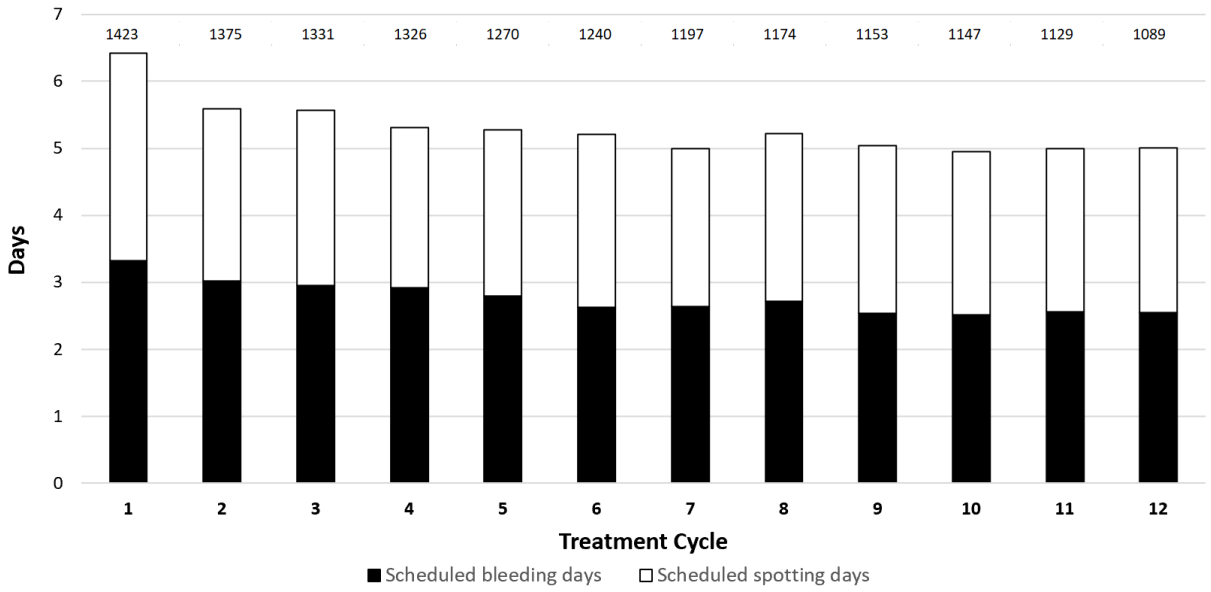
Scheduled (withdrawal) bleeding

The predictability of vaginal bleeding can be expressed by the occurrence of scheduled bleeding, or by its undesirable complement absence of scheduled bleeding.

Absence of scheduled bleeding occurred in 5.6% to 8.1% of subjects per cycle, implying that 91.9% to 94.4% of the women did have their scheduled withdrawal bleeding. There were on average 5.0 to 5.6 scheduled bleeding-spotting days in a cycle, consisting of equal numbers of bleeding and spotting days (Figure 21). The median number of bleeding-spotting days in scheduled episodes was 4.0 to 5.0 days.

Over Cycles 2-12 almost 90% of scheduled bleedings started during the period Day 25 through Day 1 of the next cycle. The most frequent starting day of scheduled bleeding was Day 27 (27.8%), followed by Day 28 (20.2%), Day 26 (16.2%), Day 1 of the next cycle (12.0%) and Day 25 (10.8%). Consequently, close to 10% of scheduled bleedings started before Day 25 (EWB), while in view of the average duration of 5.0 to 5.6 days per withdrawal bleeding episode, a substantial proportion of scheduled bleeding extended beyond Day 3 of the next cycle (CWB).

Figure 10. Study MIT-Es0001-C301. Mean number of scheduled bleeding-spotting days per treatment cycle in subjects experiencing scheduled bleeding (ITT Population)



The use of E4/DRSP 15/3 mg is associated with a reasonably predictable bleeding pattern with less than 10% of women experiencing no withdrawal bleed. As there is no comparator, it can only be assumed that the bleeding pattern in women using E4/DRSP 15/3 mg is comparable with that in women using other low dose CHCs. The average number of days with bleeding/spotting was close to what is reported by young women during natural cycles.

Discontinuation due to bleeding pattern-related TEAEs was 3.4%, reflecting good tolerability in the majority of women.

Subjects' Well-being

Quality of Life

The Q-LES-Q-SF is a self-report measure designed to assess the degree of enjoyment and satisfaction in daily functioning. For the different items, the subject gives a score ranging from 1 (very poor) to 5 (very good). The total score of the Q-LES-Q-SF was derived by summing the first 14 items of the questionnaire to obtain the raw total score. The last 2 items ("satisfaction with medicine" and "overall life satisfaction and contentment over the past week") are not included in the total score but are standalone items.

At baseline, subjects showed good satisfaction (mean score around 4) with the medicine and overall life satisfaction and contentment over the past week in the Q-LES-Q-SF, including all subjects, switchers and starters. The mean score of the percentage maximum of the Q-LES-Q-SF was also high at baseline for all subjects (73.4%), and it was slightly higher in switchers (74.9%) than in starters (70.9%).

In all subjects, no meaningful change from baseline (73.4%) at end of treatment (73.8%) was observed in the mean score of the percentage maximum of the Q-LES-Q-SF. Similarly, no change from baseline at end of treatment was observed in the subjects' satisfaction with the medication or overall life satisfaction and contentment during the previous week of the Q-LES-Q-SF, with mean scores of 4.0 (meaning good) for both categories at baseline and end of treatment.

When divided into starters and switchers, the results were overall similar with no meaningful changes from baseline to end of treatment.

Menstrual Distress Questionnaire

The MDQ is a standard method for measuring cyclical perimenstrual symptoms, and it includes scores for pain, water retention, autonomic reactions, negative affect, impaired concentration, behaviour change, arousal and control. Phases evaluated were menstrual (most recent flow), premenstrual (4 days before) and intermenstrual (remainder of cycle).

Overall, baseline *pain* mean score was highest in the menstrual phase and lowest in the intermenstrual phase, and in the menstrual phase, it was higher in starters (4.3) compared to all subjects (4.0) and switchers (3.8).

In all subjects, minimal changes in pain mean score were observed from baseline at end of treatment in the intermenstrual and premenstrual phases, but a slight mean decrease (-0.4) was observed for pain in the menstrual phase. In switchers, minimal changes in pain mean score were observed from baseline to end of treatment in any of the phases. In starters, a decrease in pain mean score was observed from baseline to end of treatment in all phases, which was more prominent in the menstrual phase (-1.0 in the menstrual phase compared to -0.2 in the intermenstrual phase, and -0.4 in the premenstrual phase).

Overall, baseline *negative affect* mean scores were higher in the premenstrual and menstrual phases than in the intermenstrual phases. A decrease in the negative affect mean score from baseline at end of treatment was observed in all subjects and in starters in the premenstrual and menstrual phases, which was more prominent in starters (-1.0 in both phases) and milder in all subjects (-0.3 in the premenstrual phase and -0.4 in the menstrual phases). Minimal changes in the negative affect mean score were observed from baseline at end of treatment in switchers.

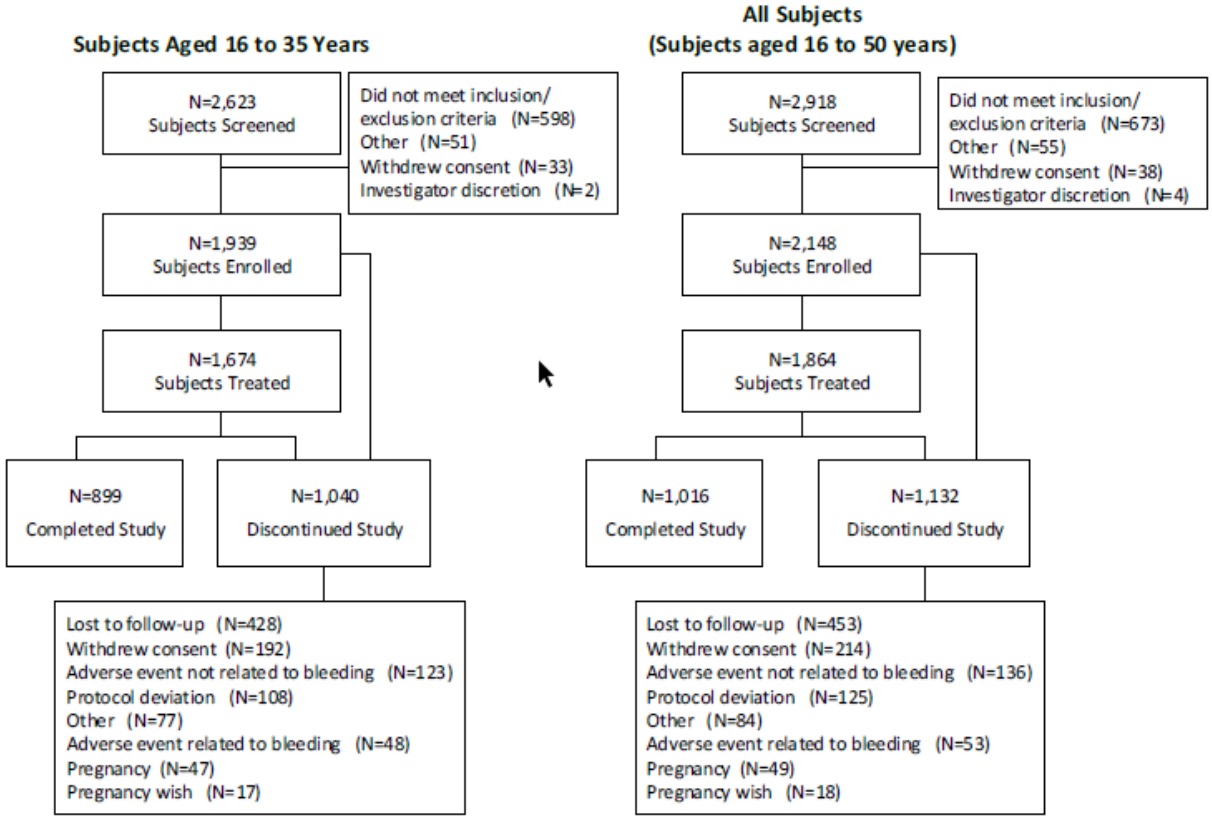
Minimal changes in scores for *water retention, autonomic reactions, impaired concentration*, *behaviour change, arousal* and *control* were observed from baseline at end of treatment.

It is concluded that for the endpoints addressing subjects' well-being and Quality of Life, the mean changes observed from baseline to end of treatment were overall small. Conclusions about these endpoints should be made with caution, due to the open-label, non-comparative study design. The results however do not indicate obvious adverse effects of the treatment on the subjects´ well-being.

Study MIT-Es0001-C302

Participant flow

Figure 11. Subject Disposition (Screened Population)[1]



Reasons for discontinuation are based on the End of Study form.

[1] Correction in the number of subjects with reasons for screen failure in the 16 to 35 years group made after CSR approval date: subjects who did not meet inclusion/exclusion criteria: it read 600, whereas there were 598 subjects; subjects who withdrew consent: it read 31, whereas there were 33 subjects; the other reasons had the correct number of subjects. This correction has no impact in the interpretation of results.

The cumulative discontinuation rate was high in this study; 45.5% in the overall population and 46.3% in subjects aged 16 to 35 years. The most common reasons for study discontinuation were lost to follow-up (15.5%), consent withdrawal (7.3%), AEs not related to bleeding (4.7%) and protocol deviations (4.3%). Adverse events related to bleeding were the reason for study discontinuation in 1.8%. Pregnancy (1.7%) and desire of pregnancy (0.6%) were other reasons for discontinuation.

Recruitment

The study was performed in 77 sites in North America: 70 sites in the United States of America (USA) and 7 sites in Canada.

The date of first screening was the 30 August 2016 and the date of last subject completed the 16 November 2018.

Conduct of the study

Protocol amendments

The study was initiated according to the Protocol Final Version 1.1, dated 7 June 2016. A relevant safety communication was issued on 23 August 2016 to clarify pill initiation instructions for subjects switching from an implant or intrauterine contraceptive. Two subsequent amendments to the protocol were created, as follows:

- Protocol Amendment 1.0, dated 14 December 2016 (e.g. "Fed/fasted condition" added as a PK covariate, revised instructions related to starting the first pack of tablets based on menstrual cycle length, requirement to use condoms for the first 7 days after switching from an intrauterine or subdermally implantable contraceptive, requirement to return all blister packs to site personnel at the next visit , instructions for the subject to consider emergency contraception as per current practice if they had unprotected intercourse during a missed pill interval, instructions for the subject to take another tablet from the extra packet in the case of vomiting/diarrhea, clarification that if an enrolled subject became pregnant and claimed she never started the investigational product, the pregnancy did not have to be followed if she could prove she never started the investigational product).
- Protocol Amendment 1.1, dated 10 July 2017 (increased in the number of sites from approximately 70 to 80, introduction of text stating that the subjects would be treated "up to" 13 consecutive cycles).

The clinical study report was prepared from the last Protocol Amendment 1.1, dated 10 July 2017.

Protocol deviations

Important protocol deviations were reported in 1,026 subjects (55.0%). The most common type of important protocol deviations was related to study drug (e.g., the subject did not return study drug blisters, did not follow the instructions for missing pills, was not compliant with the instructions of use, etc), which were reported in 477 subjects (25.6%).

Study drug-related protocol deviations were also the most common type leading to discontinuation.

Other types of important protocol deviations reported in > 5% of subjects were:

- laboratory/endpoint data (e.g., laboratory samples taken without fasting, subject did not return the diaries for some cycles or did not return questionnaires, etc), reported in 430 subjects (23.1%);
- safety assessment (e.g., urine pregnancy test not performed despite the subject not having menses, physical or gynecological examinations not performed, etc), reported in 208 subjects (11.2%);
- visit window, reported in 188 subjects (10.1%);
- IC (e.g., subject did not re-consent an updated IC, re-consent process not correctly documented, etc), reported in 95 subjects (5.1%);
- prohibited co-medication (e.g., fluconazole), reported in 94 subjects (5.0%).

Important deviations related to subject's selection criteria affected 33 subjects (1.8%) for exclusion criteria and 22 subjects (1.2%) for inclusion criteria.

Compliance

The majority of subjects (> 78%) in each cycle did not miss any pills, and the proportion of subjects who did not miss any pills was > 85% in all cycles starting from Cycle 7. Cycle 2 had the lowest percentage of

subjects with no pills missed (78.3% of subjects), and Cycle 13 had the highest percentage (89% of subjects).

Missed pills were more commonly reported in early Cycles 1 to 3 and less frequently reported in later cycles of use. The percentage of subjects who missed one pill ranged from 6.3% of subjects in Cycle 12 to 11.3% of subjects in Cycle 1. The percentage of subjects who missed two pills ranged from 2.7% of subjects in Cycle 9 to 4.5% of subjects in Cycle 2. The percentage of subjects who missed more than two pills ranged from 2.3% of subjects in Cycle 13 to 6.9% of subjects in Cycle 2.

Mean compliance over the study based on the subjects' diaries was 98.7%, ranging from 98.6 to 99.8% per cycle, with a median compliance of 100% overall and for each cycle. The range in compliance was up to 120%. Clarification has been provided regarding the 'over-compliance'. In the majority of cycles being over-compliant, 29 or 30 pills were taken, presumably merely by the subject´s mistake. The exact reasons do not seem to be known. The number of cycles with ≥ 31 tablets taken were fewer and in most cases likely related to gastrointestinal disturbances.

Baseline data

Table 13. Subject Characteristics (ITT Population)

Property	Statistic	MIT-Es0001-C302 (US, Canada)	
		16 to 35 years	All
Number of subjects	N	1,674	1,864
Age (Years)	Mean (SD)	25.8 (4.75)	27.3 (6.48)
	Median (Min, Max)	25.0 (16, 35)	26.0 (16, 50)
	≥16 – ≤25 (n, %)	839 (50.1)	839 (45.0)
	>25 - ≤35 (n, %)	835 (49.9)	835 (44.8)
	>35 - ≤50 (n,%)		190 (10.2)
Body weight (kg)	Mean (SD)	69.0 (14.22)	69.4 (14.17)
	Median (Min, Max)	67.1 (36.7, 148.8)	67.6 (36.7,148.8)
BMI (kg/m²)	Mean (SD)	25.8 (4.73)	25.9 (4.71)
	Median (Min, Max)	25.13 (14.3, 48.4)	25.31 (14.3, 48.4)
	<18.5	1,298 (77.5)	1,432 (76.8)
	≥18.5 - <25		
	≥25 - <30		
	≥30	376 (22.5)	432 (23.2)
Race*	White	1,174 (70.1)	1,300 (69.7)
	Black or African American	326 (19.5)	369 (19.8)
	Asian	81 (4.8)	87 (4.7)
	Other**	93 (5.6)	108 (5.8)
Ethnicity	Hispanic or Latino	429 (25.6)	488 (26.2)

Property	Statistic	MIT-Es0001-C302 (US, Canada)	
		16 to 35 years	All
Highest education	Less than Upper Secondary School	89 (5.3)	95 (5.1)
	Completed Upper Secondary School	771 (46.1)	827 (44.4)
	Completed Vocational School	151 (9.0)	173 (9.3)
	Completed College	530 (31.7)	611 (32.8)
	Completed Graduate School	133 (7.9)	158 (8.5)
Previous contraceptive use	Switchers	701 (41.9)	785 (42.1)
	Starters	973 (58.1)	1,079 (57.9)
	New Users	290 (17.3)	304 (16.3)
Smoking status	Current smoker	222 (13.3)	222 (11.9)
	Non smoker	1,452 (86.7)	1,642 (88.1)
	Former smoker	189 (11.3)	221 (11.9)
	Never smoker	1,263 (75.4)	1,421 (76.2)

BMI = body mass index, ITT = intention-to-treat, Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation

***** Subjects may be included under more than one race category. For the subjects that were enrolled in more than one of the clinical trials, their demography and baseline characteristics is presented twice in the pooled database and will be considered as separate subjects.

** Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and Others

The majority of the women included in Study C302 were aged 35 years or below (10.2% were >35 years). There were 13 subjects aged below 18 years enrolled and treated in study MIT-Es0001-C302. Eight of these completed one year of treatment whereas five discontinued prematurely.

Approximately 70% were White, around 20% were Black or African American and slightly below 5% were Asian. There were about 25% who were Hispanic or Latino. The median BMI was 25.3 kg/m^2 for the whole population and 23% had a BMI ≥30 kg/m^2. The majority of subjects (76%) had never smoked and < 15% were current smokers.

More than half of the subjects (58%) were 'starters' with approximately 17% of subjects classified as true new users; approximately 42% of subjects were switchers from a previous hormonal contraceptive method.

There were no remarkable findings with respect to medical history, or prior and concomitant medications, reflecting a relatively young and healthy population.

Numbers analysed

Table 14. Study MIT-Es0001-C302. Number of subjects by population

	Analysis sets		
	All subjects	**16 – ≤35 years**	**>35 years**
Population			
Screened (N)	2,918	2,623	295
Enrolled (N)	2,148	1,939	209
Treated (ITT and Safety Populations) (N [%])[a]	1,864 (86.8)	1,674 (86.3)	190 (90.9)
PP (N [%])[a]	1,727 (80.4)	1,544 (79.6)	183 (87.6)
PK (N [%])[a]	455 (21.2)	408 (21.0)	47 (22.5)

[a] percentage of enrolled subjects
ITT = intention-to-treat, N = number of subjects, PK = pharmacokinetics, PP = per protocol

Screened: included all subjects who signed an informed consent form.
Enrolled: included all enrolled subjects.
ITT, Safety Populations: included all enrolled subjects who receive at least 1 dose of investigational product
PP: included all subjects in the ITT Population who had at least 1 evaluable cycle for the bleeding analysis
PK: included all subjects enrolled in the PK Sub-study who provided concentration data for at least 1 sample

The ITT population comprised 86.8% of the enrolled population and the PP population comprised 80.4%).

Outcomes and estimation

Pregnancies
Four pre-treatment pregnancies, 28 on-treatment pregnancies and nine post-treatment pregnancies were reported in the ITT Population. Of the 28 on-treatment pregnancies, 26 occurred in subjects aged 16 to 35 years at screening. Twelve pregnancies were considered user failures and 16 Method Failures. Among women aged 36 to 50 years, two on treatment pregnancies were reported, neither of which were considered user failure.

Seven subjects had spontaneous abortions and one subject had an ectopic pregnancy that were reported as serious TEAEs (see Safety section).

In addition, two subjects had false positive pregnancy tests. One
subject had a chemical pregnancy. Three subjects had a positive pregnancy test at screening, which was the result of recent abortions. The subjects were confirmed as not pregnant before enrolment.

The total number of pregnancies was high in this study, with 28 on-treatment pregnancies. Five pregnant women (all who conceived on-treatment) were lost to follow-up.

In study C302, a rather large part of pregnancies was terminated. There were also several cases of spontaneous abortions (one case also in study C301) and one (on-treatment pregnancy) case of ectopic pregnancy. This is further discussed in the safety section, but it was confirmed that these corrections did not impact the calculations of the Pearl Indices.

It seems like in those cases where the pregnancies resulted in live births, there were no complications, although some were late pre-term births. There was one female infant born at 39 weeks with a benign cardiac murmur. No concern is raised based on this case.

Pearl Index

Primary efficacy variable: Pearl Index in Subjects Aged 16 to 35 Years with At-Risk Cycles

The summary and analysis of Pearl Index in subjects aged 16 to 35 years with at-risk cycles is provided below.

Table 15. Study MIT-Es0001-C302. Summary and analysis of Pearl Index in subjects aged 16 to 35 years with at-risk cycles (ITT Population)

Cohort Variable Statistic	E4/DRSP 15/3 mg (N=1,864)
Subjects aged 16 to 35 Years at Screening with at least 1 cycle included in the denominator, n	1,524
Number of at-risk cycles	12,763
Number of on-treatment pregnancies	26
Pearl Index	2.65
95% CI[a] for Pearl Index	(1.73, 3.88)

DRSP = drospirenone, E4 = estetrol; ITT = intention-to-treat, N= number of subject in the ITT Population

[a] Confidence intervals (CIs) are calculated using a Poisson distribution.

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as:

Pearl Index = (1300*number of on-treatment pregnancies)/number of women 28-day equivalent cycles treatment.

Only at-risk cycles were included in the denominator of the Pearl Index calculation, unless a conception occurred during a cycle.

At-risk cycle = a cycle in which no other methods of birth control (including condoms and emergency contraception) were used by the subject as confirmed in the subject diary, and the subject confirmed that sexual intercourse occurred during the cycle in the subject diary. Any cycles after the cycle of conception in the case of pregnancy were excluded.

On-treatment pregnancy: a pregnancy with an estimated date of conception after the date of the first dose of investigational product to 7 days after the last dose of investigational product (regardless of whether the last dose was an active or inactive tablet) inclusive.

There were 26 on-treatment pregnancies, resulting in a Pearl Index of **2.65** (**95% CI: 1.73, 3.88**) for E4/DRSP 15/3 mg in subjects aged 16 to 35 years with at-risk cycles, the defined primary efficacy variable. Thus, the requirement for precision of the PI was not met in accordance with the EMA Guideline on Steroid Contraceptives, since the difference between the upper limit of the corresponding 2-sided 95% CI for the Pearl Index and the point estimate was > 1.

The modified at-risk Pearl Index (EU definition), for which only cycles with use of other methods of birth control are excluded from the denominator but cycles without confirmed sexual intercourse are included, was **2.42** (**95% CI: 1.58, 3.54**) in subjects aged 18 to 35 years (Table 20).

Table 16. Study MIT-Es0001-C302. Summary and analysis of Pearl Indices calculated with different methods in subjects with at-risk cycles (ITT Population)

	Overall at-risk PI in the overall population[A]	"Typical use" PI[B]		Modified at-risk PI[C]		Method Failure PI[D]		Method Failure PI including compliant at-risk cycles[E]	
Cohort Variable Statistic	E4/DRSP 15/3 mg (N=1,864)								
n	1,705	1,673	1,863	1,592	1,777	1,524	1,705	1,469	1,645
Age group (Years)	16-50	16-35	16-50	16-35	16-50	16-35	16-50	16-35	16-50
Number of at-risk cycles	14,437	15,467	17,393	13,979	15,797	12,763	14,437	11,743	13,328
Number of on-treatment pregnancies	28	26	28	26	28	14	16	14	16
PI	2.52	2.19	2.09	2.42	2.30	1.43	1.44	1.55	1.56
95% CI for PI	(1.68, 3.64)	(1.43, 3.20)	(1,39, 3.03)	(1.58, 3.54)	(1.53, 3.33)	(0.78, 2.39)	(0.82, 2.34)	(0.85, 2.60)	(0.89, 2.53)

[A] Pearl Index: At-risk cycles are defined as cycles with no other methods of birth control (including condoms) and confirmed sexual intercourse.
[B] "Typical use" Pearl Index: All cycles are included in the denominator regardless of other methods of birth control, occurrence of sexual intercourse or compliance with the protocol.
[C] Modified at-risk Pearl Index: At-risk cycles are those where no other methods of birth control are used (modified risk). Cycles without confirmed sexual intercourse are not excluded.
[D] Method Failure Pearl Index: uses the same method used for the Pearl Index but excludes those pregnancies due to user failures from the numerator, i.e. subject did not take the study medication correctly during the cycle in which the estimated conception occurred or used drugs that have the potential to trigger interactions with COC.
[E] Only compliant modified at-risk cycles are included in the denominator of the Pearl Index calculation. Compliant modified at-risk cycle = a cycle where no other methods of birth control (including condoms) were used, the subject does not have a user failure pregnancy and the subject had no adverse event of vomiting and/or diarrhoea.

CI = confidence interval, DRSP = drospirenone, E4 = estetrol, ITT = intention-to-treat, n = number of subjects with at least 1 cycle included, PI = Pearl Index

Notes: Confidence intervals (CIs) are calculated using a Poisson distribution. Any cycles after the cycle of conception in the case of pregnancy were exclude

In the whole group (up to 50 years of age) and with alternative calculation methods, the Pearl Indices ranged from **2.09 to 2.52** and the difference between the point estimates and the upper limit of the corresponding 2-sided 95% CIs was in most cases above 1.

The PI for Method failure was **1.43** (95% CI 0.78, 2.39) for the age group 16-35 years and **1.44** (95% CI 0.82, 2.34) for the whole study population, both with acceptable precision according to the EMA guideline.

Applicants discussion on Pearl Indices obtained in the US/CA

In the US/Canada study, 26 on-treatment pregnancies were observed in women aged 16 to 35 years with 12,763 cycles of at-risk (FDA) exposure, giving rise to a Pearl Index (95% CI) of 2.65 (1.73, 3.88). With the upper limit of the 95% CI well below 5, E4/DRSP 15/3 mg fulfils the FDA criterion of an effective COC (Guidance for Industry. Establishing effectiveness and safety for hormonal drug products intended to prevent pregnancy. July 2019). Making comparisons across various COCs is hampered by the observation that Pearl Indices reported in clinical trials of new COCs submitted to the FDA for approval have increased over the last 15 years, most likely due to more frequent pregnancy testing with more sensitive tests and less adherent study populations (Trussel and Portman, 2013). The point estimate of 2.65 is therefore higher than reported for Yaz back in 2007 (1.41), but slightly lower than the ones provided in 2017 for the EE-containing COCs LoLoestrin (2.92) and Quartette (3.19). The Pearl Index (95% CI) is lower than recently reported for the DRSP 4 mg progestin-only pill Slynd (4.0).

The typical use Pearl Index (95% CI) was 2.19 (1.43, 3.20) and hence similar to the Pearl Index. Twelve of the 26 on treatment pregnancies occurred during documented imperfect use of E4/DRSP 15/3 mg, resulting in a Perfect Use Pearl Index of 1.43 (0.78, 2.39). Two additional pregnancies were observed in women aged 36 to 50, giving rise to very similar Pearl Indices for the overall population 16 to 50 years.

In the Europe/Russia study (MIT-Es0001-C301) Pearl Indices were lower than the US/Canada results. In the Europe/Russia study, 5 on treatment pregnancies were observed in 14,759 cycles of modified risk (EMA) exposure. The Pearl Index achieved in women aged 18 to 35 years amounted to 0.44, with a 95% confidence interval of 0.14, 1.03. The difference between the upper limit of the 95% confidence interval and the point estimate is less than 1, indicating the precision is well within the range required by EMA (EMA, 2005). The point estimate of 0.44 is similar to those observed in European trials for Zoely (0.38), Yasmin (0.57) and Yaz (0.80), as indicated in the respective Summary of Product Characteristics.

The typical use Pearl Index (95% CI) was 0.42 (0.14, 0.99) and hence similar to the primary one. Two of the 5 pregnancies occurred during imperfect use of E4/DRSP 15/3 mg, resulting in a Perfect Use Pearl Index (95% CI) of 0.28 (0.06, 0.81). No pregnancies were observed in women aged 36 to 50, so Pearl Indices for the overall population 18 to 50 years were lower.

Life-table rates

Life-table analyses (Based on Kaplan-Meier estimates) were consistent with the Pearl Index results.

- After 13 cycles, the cumulative on-treatment pregnancy rate was 2.06% (95% CI: 1.40%, 3.04%) for subjects aged 16 to 35 years and 2.00% (95% CI: 1.38%, 2.91%) for subjects aged 16 to 50 years, i.e., the probability of contraceptive protection during up to 1 year of treatment was approximately 98%.
- After 13 cycles, the cumulative on-treatment method-failure pregnancy rate was 1.18% (95% CI: 0.69%, 2.01%) for subjects aged 16 to 35 years and 1.22% (95% CI: 0.74%, 1.99%) for subjects aged 16 to 50 years, i.e., the probability of contraceptive protection during up to 1 year of treatment was approximately 99%.

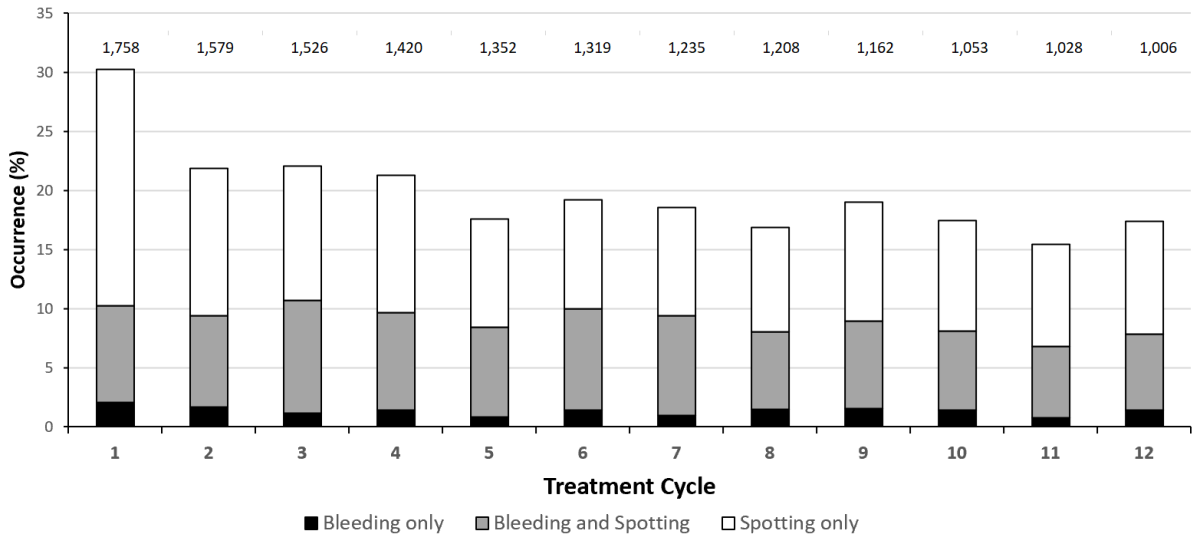
Vaginal bleeding pattern

Methods for bleeding data collection, definitions for scheduled and unscheduled bleeding/spotting and method of analysis were the same as in study MIT Es0001-C301.

Unscheduled bleeding-spotting

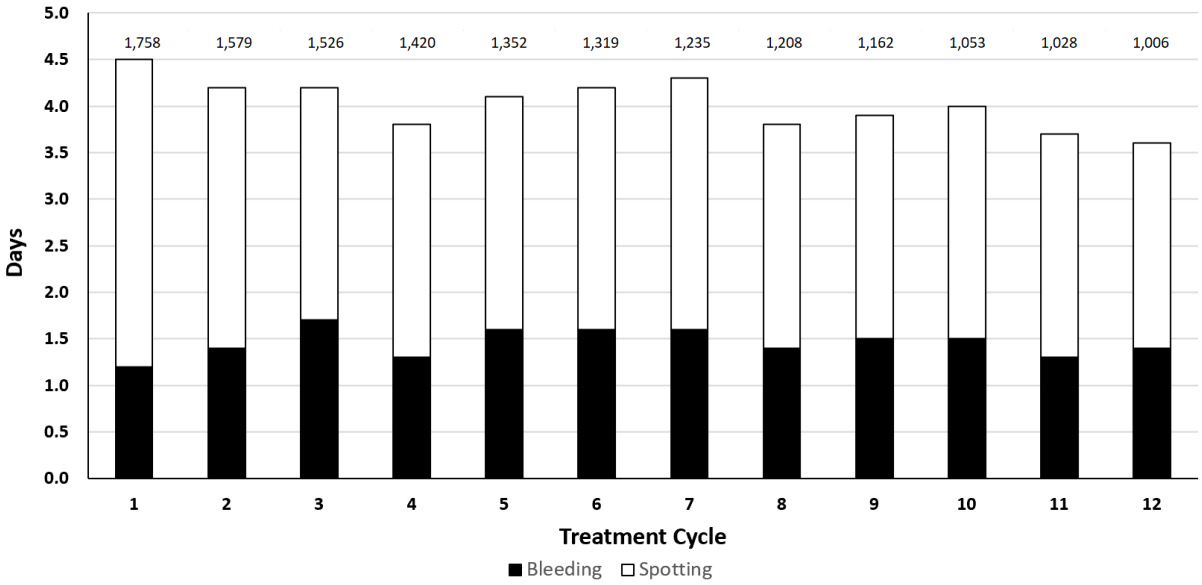
After an initial incidence of 30.3% in Cycle 1, the overall incidence of unscheduled bleeding and/or spotting was just above 20% during Cycles 2 to 4, reaching incidences of 15% to 20% upon longer duration of use (Figure 23). The majority of bleeding and/or spotting episodes concerned spotting-only, implying that in each cycle approximately 90% of the subjects did not experience unscheduled bleeding requiring the use of sanitary protection. About 80% of subjects did not experience any unscheduled bleeding or spotting at all per cycle.

Figure 12. Study MIT Es0001-C302. Incidence of unscheduled bleeding-spotting per treatment cycle (ITT Population)



When restricted to those subjects who actually experienced unscheduled bleeding-spotting, the mean number of bleeding and/or spotting days over Cycles 2-12 ranged between 3.7 and 4.1 days per cycle (Figure 24); the contribution of bleeding days was on average around 1.5 days per cycle. The median duration of unscheduled bleeding-spotting was 3.0 days in all.

Figure 13. Study MIT-Es0001-C302. Mean number of unscheduled bleeding-spotting days per treatment cycle in subjects experiencing unscheduled bleeding-spotting (ITT Population)



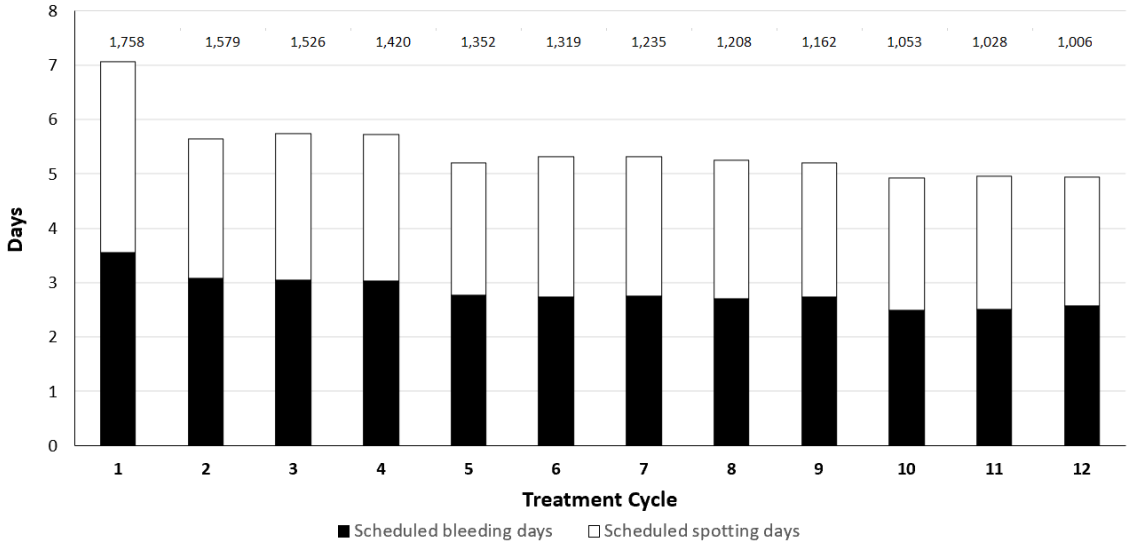
In study MIT-Es0001-C302, the rate of women recording unscheduled bleeding/spotting was close to or slightly below 20% except during the first treatment cycle. The number of bleeding/spotting days recorded among those women was just above or around 4 throughout the treatment year.

Scheduled (withdrawal) bleeding

Absence of scheduled bleeding occurred in 13.0% to 17.1% of subjects per cycle, implying that 82.9% to 87.0% of the women did have their scheduled withdrawal bleeding. There were on average 4.9 to 5.7 scheduled bleeding-spotting days in a cycle, consisting of equal numbers of bleeding and spotting days). The median number of bleeding-spotting days in scheduled episodes was 4.0 to 5.0 days.

Over Cycles 2 through 12, almost 80% of scheduled bleedings started during the period Day 25 through Day 1 of the next cycle. The most frequent starting day of scheduled bleeding was Day 27 (20.8%), followed by Day 26 (16.3%), Day 28 (15.2%), Day 25 (14.2%) and Day 1 of the next cycle (12.1%). 13.6% to 19.1% of scheduled bleedings started before Day 25, while in view of the average duration of 5.0-5.6 days per withdrawal bleeding episode, a substantial proportion of scheduled bleeding extended beyond Day 3 of the next cycle.

Figure 14. Study MIT-Es0001-C302. Mean number of scheduled bleeding-spotting days per treatment cycle in subjects experiencing scheduled bleeding (ITT Population)



In comparison with data from study MIT-Es0001-C301, performed in Europa/Russia, data from the USA and Canada included more women with unscheduled bleeding. Although data from the USA and Canada, in comparison with data from Europe/Russia, showed a slightly less predictable bleeding pattern during use of E4/DRSP 15/3 mg, the difference does not appear to be great.

As there is no comparator arm in the study, it can only be assumed that the bleeding pattern in women using E4/DRSP 15/3 mg is comparable with that in women using other low dose CHCs. The average number of days with bleeding/spotting was close to what is reported by young women during natural cycles. Discontinuation due to bleeding pattern-related TEAEs was 2.6%, reflecting good tolerability in the majority of women.

Subjects' Well-being

Quality of Life

The Q-LES-Q-SF was used also in this study. At the baseline evaluation, subjects showed good satisfaction (mean score > 4) with overall life satisfaction and contentment over the past week, including all subjects, switchers and starters. The mean score of the percentage maximum of the Q-LES-Q-SF was also high at baseline for all subjects (75.8%), switchers (76.4%) and starters (75.3%).

In all subjects, no meaningful change from baseline (75.8%) to end of treatment (75.4%) was observed in the mean score of the percentage maximum of the Q-LES-Q-SF. Similarly, no change from baseline to end of treatment was observed in the subjects' satisfaction with the medicine or overall life satisfaction and contentment during the previous week of the Q-LES-Q-SF, with mean scores > 4 (meaning good) for both categories at baseline and end of treatment. Similar results to those described for all subjects were observed in switchers and starters, with no meaningful change from baseline to end of treatment in the score of the Q-LES-Q-SF categories.

Menstrual Distress Questionnaire

In all subjects, baseline mean *pain* score was highest in the menstrual phase (6.0) and lowest in the intermenstrual phase (3.3). Some improvement in mean pain score was observed from baseline to end of treatment in the menstrual phase (-0.6) and in the intermenstrual phase (-0.3), with minimal change in the premenstrual phase (-0.1).

Baseline mean pain scores in switchers and starters were similar to those observed in all subjects. In switchers, a minor improvement in mean pain score was observed from baseline to end of treatment in the intermenstrual and menstrual phases (-0.3). In starters, remarkable improvement in mean pain score was observed from baseline to end of treatment in the menstrual phase (-0.9), as well as a noticeable improvement in the intermenstrual phase (-0.3).

For all other MDQ items (*water retention, autonomic reactions, negative affect, impaired concentration, behaviour change, arousal and control*), only minimal changes were observed from baseline to end of treatment in all phases in all subjects (starters and switchers).

For the endpoints addressing subjects' well-being and Quality of Life, the mean changes observed from baseline to end of treatment were overall small. Similar to what was concluded in Study C301, the results do not indicate obvious adverse effects of the treatment on the subjects´ well-being, even if conclusions should be made with caution, due to the open-label, non-comparative study design.

Ancillary analyses

Not applicable, given the product characteristics.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 3. Summary of Efficacy for trial MIT-Es0001-C301

Title: A Multicentre, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone (E4 FREEDOM: Female Response concerning Efficacy and safety of Estetrol/Drospirenone as Oral contraceptive in a Multicentre study)		
Study	MIT-Es0001-C301	
Design	This study was a multicentre, open-label, single-arm study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	A maximum of 13 consecutive cycles Not applicable Not applicable
Hypothesis	Equivalence (using a historical control)	

Treatments groups	Subjects aged 18 to 35 years		15 mg E4/3 mg DRSP for a maximum of 13 consecutive cycles, 1,373 subjects enrolled
	Subjects aged 18 to 50 years		15 mg E4/3 mg DRSP for a maximum of 13 consecutive cycles, 1,577 subjects enrolled
Endpoints and definitions	Primary endpoint	PI at-risk cycles - FDA	Pearl Index-FDA in subjects 18-35 and 18-50 years of age, including all on-treatment pregnancies in the numerator and at-risk cycles in the denominator. At-risk cycles, i.e., only those cycles with confirmed vaginal intercourse and without use of other methods of birth control.
	Secondary endpoint	PI modified at-risk cycles - EMA	Pearl Index-EMA in subjects 18-35 and 18-50 years of age, including all on-treatment pregnancies in the numerator and modified at-risk cycles in the denominator. Modified at-risk cycles, i.e., only cycles without use of other methods of birth control, regardless the occurrence of vaginal intercourse.
	Secondary endpoint	"typical-use" PI	PI including all cycles in subjects 18-35 and 18-50 years of age, including all on-treatment pregnancies and all cycles. All cycles, regardless the use of other methods of birth control, vaginal intercourse, or protocol compliance
	Secondary endpoint	"perfect-use" PI - FDA	Method failure PI at-risk cycles in subjects 18-35 and 18-50 years of age, including only those on-treatment pregnancies that occurred in the absence of user errors, i.e., excluding pregnancies that occurred in cycles with incorrect tablet intake (4 or more missed, of 2 or more missed in a row), intake of potentially interacting drugs, or occurrence of vomiting/diarrhoea. At-risk cycles, i.e., only those cycles with confirmed vaginal intercourse and without use of other methods of birth control.

	Secondary endpoint	"perfect-use" PI - EMA	Method failure PI at-risk cycles in subjects 18-35 and 18-50 years of age, including only those on-treatment pregnancies that occurred in the absence of user errors, i.e., excluding pregnancies that occurred in cycles with incorrect tablet intake (4 or more missed, of 2 or more missed in a row), intake of potentially interacting drugs, or occurrence of vomiting/diarrhoea. Modified at-risk cycles, i.e., only cycles without use of other methods of birth control, regardless the occurrence of vaginal intercourse.
Database lock	Study Period: 22 months Date of First Screening: 28 June 2016 Date of Last Completed: 26 April 2018		

Results and Analysis

Analysis description	**Primary and secondary analysis**		
Analysis population and time point description	Intent to treat population: healthy female subjects at risk for pregnancy, between 18 and 50 years old, and requesting contraception were enrolled.		
Effect estimate per comparison	Treatment group	Subjects aged 18 to 35 years	Subjects aged 18 to 50 years
	Number of subject	1,373	1,577
	PI at-risk cycles – FDA Estimate (95% CI)	0.47 (0.15, 1.11)	0.41 (0.13, 0.96)
	PI modified at-risk cycles – EMA Estimate (95% CI)	0.44 (0.14, 1.03)	0.38 (0.12-0.89)
	"typical-use" PI Estimate (95% CI)	0.42 (0.14, 0.99)	0.37 (0.12, 0.86)
	"perfect-use" PI – FDA Estimate (95% CI)	0.29 (0.06, 0.83)	0.25 (0.05, 0.72
	"perfect-use" PI – EMA Estimate (95% CI)	0.26 (0.05-0.77)	0.23 (0.05-0.67)

Table 4. Summary of efficacy for trial MIT-Es0001-C302

Title: A Multicentre, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone (E4 FREEDOM: Female Response concerning Efficacy and safety of Estetrol/Drospirenone as Oral contraceptive in a Multicentric study)			
Study	MIT-Es0001-C302		
Design	This study was a multicentre, open-label, single-arm study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		A maximum of 13 consecutive cycles Not applicable Not applicable
Hypothesis	Equivalence (using a historical control)		
Treatments groups	Subjects aged 16 to 35 years		E4/DRSP 15/3 mg for a maximum of 13 consecutive cycles, 1,939 subjects enrolled
	Subjects aged 16 to 50 years		E4/DRSP 15/3 mg for a maximum of 13 consecutive cycles, 2,148 subjects enrolled
Endpoints and definitions	Primary endpoint	PI at-risk cycles - FDA	Pearl Index-FDA in subjects 16-35 and 16-50 years of age, including all on-treatment pregnancies in the numerator and at-risk cycles in the denominator. At-risk cycles, i.e., only those cycles with confirmed vaginal intercourse and without use of other methods of birth control.
	Secondary endpoint	PI modified at-risk cycles - EMA	Pearl Index-EMA in subjects 16-35 and 16-50 years of age, including all on-treatment pregnancies in the numerator and modified at-risk cycles in the denominator. Modified at-risk cycles, i.e., only cycles without use of other methods of birth control, regardless the occurrence of vaginal intercourse.

	Secondary endpoint	"typical-use" PI	PI including all cycles in subjects 16-35 and 16-50 years of age, including all on-treatment pregnancies and all cycles. All cycles, regardless the use of other methods of birth control, vaginal intercourse, or protocol compliance
	Secondary endpoint	"perfect-use" PI - FDA	Method failure PI at-risk cycles in subjects 16-35 and 16-50 years of age, including only those on-treatment pregnancies that occurred in the absence of user errors, i.e., excluding pregnancies that occurred in cycles with incorrect tablet intake (4 or more missed, of 2 or more missed in a row), intake of potentially interacting drugs, or occurrence of vomiting/diarrhoea. At-risk cycles, i.e., only those cycles with confirmed vaginal intercourse and without use of other methods of birth control.
	Secondary endpoint	"perfect-use" PI - EMA	Method failure PI at-risk cycles in subjects 16-35 and 16-50 years of age, including only those on-treatment pregnancies that occurred in the absence of user errors, i.e., excluding pregnancies that occurred in cycles with incorrect tablet intake (4 or more missed, of 2 or more missed in a row), intake of potentially interacting drugs, or occurrence of vomiting/diarrhoea. Modified at-risk cycles, i.e., only cycles without use of other methods of birth control, regardless the occurrence of vaginal intercourse.
Database lock	Study Period: 27 months Date of First Screening: 30 August 2016 Date of Last Completed: 16 November 2018		

Results and Analysis

Analysis description	**Primary and secondary analysis**		
Analysis population and time point description	Intent to treat population: healthy female subjects at risk for pregnancy, between 18 and 50 years old, and requesting contraception were enrolled.		
Effect estimate per comparison	Treatment group	Subjects aged 18 to 35 years	Subjects aged 18 to 50 years
	Number of subject	1,939	2,148

	PI at-risk cycles – FDA Estimate (95% CI)	2.65 (1.73-3.88)	2.52 (1.68-3.64)
	PI modified at-risk cycles – EMA Estimate (95% CI)	2.42 (1.58-3.54)	2.30 (1.53-3.33)
	"typical-use" PI Estimate (95% CI)	2.19 (1.43-3.20)	2.09 (1.39-3.03)
	"perfect-use" PI – FDA Estimate (95% CI)	1.43 (0.78-2.39)	1.44 (0.82-2.34)
	"perfect-use" PI – EMA Estimate (95% CI)	1.30 (0.71-2.18)	1.32 (0.75-2.14)

Analysis performed across trials (pooled analyses and meta-analysis)

An integrated analysis was performed based on the pooling of pregnancy data, bleeding data and MDQ and Q-LES-Q-SF data from the two pivotal Phase 3 trials MIT-Es0001-C301 and MIT-Es0001-C302.

The pooled ITT Population included 3,417 subjects, with 3,027 aged 16 to 35 years, receiving at least 1 dose of 15 mg E4/3 mg DRSP.

The pooled PP population included 3,262 subjects, 2,881 of them aged 16 to 35 years and 381 aged 36-50 years.

In the pooled overall (16-50 years) ITT population, 50% were enrolled in the US, with all other countries each constituting less than 10% of the pooled population (from 0.3% for Sweden up to 9.8% for the Czech Republic.

Pearl Index

The primary efficacy variable was the number of on-treatment pregnancies assessed by the Pearl Index in the ITT Population of women aged 16 to 35 years, inclusive, at the time of screening with at-risk cycles (cycles in which no other methods of birth control [including condoms and emergency contraception] and during which the subjects confirmed that sexual intercourse had occurred).

The table below summarizes the analysis of the Pearl Index in subjects aged 16 to 35 years with at-risk cycles.

Table 17. Primary efficacy variable: Summary and analysis of Pearl Index in subjects aged 16 to 35 years with at-risk cycles (ITT Population)

Cohort Variable Statistic	E4/DRSP 15/3 mg (N=3,417)
Subjects aged 16 to 35 Years at Screening with at least 1 cycle included in the denominator, n	2,837
Number of at-risk cycles	26,455
Number of on-treatment pregnancies	31
Pearl Index	1.523
95% CI for Pearl Index	(1.035, 2.162)

DRSP = drospirenone, E4 = estetrol, N = number of subjects in the ITT Population
Note: Confidence intervals (CIs) are calculated using a Poisson distribution.

The primary outcome was based on 31 on-treatment pregnancies among 2,837 subjects aged 16 to 35 years who provided 26455 at-risk cycles, resulting in a Pearl Index of **1.52 (95% CI: 1.035, 2.162**).

The difference between the upper limit of the corresponding 2-sided 95% CI and the Pearl Index (point estimate) is 0.64 and fulfils the criterion on the precision of the estimate as claimed in the EMA Guideline on Clinical Investigation of Steroid Contraceptives (EMA, 2005) that this difference does not exceed 1.

Secondary efficacy variables, e.g. the Method Failure Pearl Index, "typical-use Pearl Index" are depicted in Table 43 below.

The Method Failure Pearl Index was similar for women aged 16 to 35 years (0.84, 95% CI: 0.487, 1.338) and for women aged 16 to 50 years (0.82, 95% CI: 0.49, 1.27).

Table 18. Summary and analysis of the Pearl Index for the overall population and Pearl Indices calculated with different methods in subjects with at-risk cycles (ITT Population)

	E4/DRSP 15/3 mg (N = 3,417)					
	Cohort				Variable	Statistics
	Age Group	n	Number of at-risk cycles	Number of on-treatment pregnancies	PI	95% CI
PI in all subjects[A]	16-50	3,215	30,286	33	1.416	(0.975, 1.989)
PI including all cycles in the denominator ("typical-use" PI)[B]	16-35	3,026	30,810	31	1.308	(0.889, 1.857)
	16-50	3,416	35,077	33	1.223	(0.842, 1.718)
PI with modified at-risk cycles[C]	16-35	2,935	28,738	31	1.402	(0.953, 1.990)
	16-50	3,319	32,834	33	1.307	(0.899, 1.835)
Method Failure Pearl Index[D]	16-35	2,837	26,455	17	0.835	(0.487, 1.338)
	16-50	3,215	30,286	19	0.816	(0.491, 1.274)
Method Failure PI excluding at-risk cycles with non-compliance[E]	16-35	2,857	28,738	17	0.769	(0.448, 1.231)
	16-50	3,234	32,834	19	0.752	(0.453, 1.175)

[A] Pearl Index: At-risk cycles are defined as cycles with no other methods of birth control (including condoms) and confirmed sexual intercourse.
[B] "Typical use" Pearl Index: All cycles are included in the denominator regardless of other methods of birth control, occurrence of sexual intercourse or compliance with the protocol.
[C] Modified at-risk Pearl Index: At-risk cycles are those where no other methods of birth control are used (modified risk). Cycles without confirmed sexual intercourse are not excluded.
[D] Method Failure Pearl Index: uses the same method used for the Pearl Index but excludes those pregnancies due to user failures from the numerator, i.e. subject did not take the study medication correctly during the cycle in which the estimated conception occurred or used drugs that have the potential to trigger interactions with COC.
[E] Only compliant modified at-risk cycles are included in the denominator of the Pearl Index calculation. Compliant modified at-risk cycle = a cycle where no other methods of birth control (including condoms) was used, the subject did not have a user failure pregnancy and the subject had no adverse event of vomiting and/or diarrhea.
CI = confidence interval, DRSP = drospirenone, E4 = estetrol, ITT = intention-to-treat N = number of subjects in the ITT Population, n = number of subjects with at least 1 at-risk cycle included in the denominator, PI = Pearl Index

Notes: Confidence intervals (CIs) are calculated using a Poisson distribution. On-treatment pregnancy: a pregnancy with an estimated date of conception after the date of the first dose of study medication to 2 (EU definition (C301)) or 7 days (North American definition (C302)) after the last dose of study medication (regardless of whether the last dose is an active or inactive tablet) inclusive.

Life Table Rates

Cumulative pregnancy rates were determined by the life-table method. Kaplan-Meier estimates of cumulative event rates for pregnancies and method-failure pregnancies are summarized for the ITT Population below.

In subjects aged 16 to 35 years, 31 on-treatment pregnancies were reported, of which 19 pregnancies were considered user failure. Among women aged 36 to 50 years, 2 on-treatment pregnancies were reported, neither of which were considered user failure.

After 13 cycles, the cumulative on-treatment pregnancy rate was 1.28% (95% CI: 0.83%, 1.73%) for subjects aged 16 to 35 years and 1.20% (95% CI: 0.79%, 1.62%) for subjects aged 16 to 50 years, i.e., the probability of contraceptive protection up to 1 year of treatment was approximately 98.8%.

After 13 cycles, the cumulative on-treatment Method-failure pregnancy rate was 0.73% (95% CI: 0.38%, 1.08%) for subjects aged 16 to 35 years and 0.72% (95% CI: 0.40%, 1.05%) for subjects aged 16 to 50 years, i.e., the probability of contraceptive protection during up to 1 year of treatment was approximately 99%.

The Applicant has presented pooled Pearl index results for the two pivotal studies. The studies are both large and the European study provided a Pearl index with an acceptable precision without a need for pooling.

Clinical studies in special populations

Sub-group analyses have been performed based on integrated data for the two studies as well as for each study separately. The sub-groups investigated are considered relevant, e.g. based on BMI, previous contraceptive use, smoking status, age and region. For several subgroups both the number of pregnancies and numbers of evaluable cycles were too low to achieve meaningful results. This often resulted in estimated PI:s with very wide confidence intervals.

BMI

For BMI, for those 16 to 35 years old in the integrated analysis, a trend was observed for an increase of the Pearl Index with increasing BMI. The PI:s in the subgroups with BMI ≥ 25 - <30 and BMI > 30 were 2.2 and 2.3, respectively, while the PI estimate in the group with BMI of ≥ 18.5 to < 25 kg/m^2 was about half; 1.05. In those with BMI < 18.5 kg/m^2, only two on-treatment pregnancies were reported, resulting in a PI of 2.70 (95% CI: 0.33, 9.74). Thus, the 95% CI:s were wide for the groups with either low or high BMI.

For the individual studies, it is noted that for Study C301 (Europe and Russia), no on-treatment pregnancies were reported in subjects aged 18 to 35 years with a BMI ≥ 30 mg/kg^2 and the number of subjects with at least one at-risk cycle was much lower in the subgroup with a BMI ≥ 30 mg/kg^2 (73 subjects) compared to that with a BMI < 30 mg/kg^2 (1,240 subjects).

In Study C302 (US and Canada), the PI in subjects aged 16 to 35 years was higher in those with BMI ≥ 30 mg/kg^2 (PI 2.94) compared with those with a BMI < 30 mg/kg^2 (PI 2.57), although the group with high BMI was much smaller (337 subjects vs. 1,187 subjects). Thus, the 95% CI for the BMI ≥ 30 group was wide (1.08, 6.41). When the whole age group (16-50 years) was considered, the PIs in both BMI groups were around 2.50, but with wider 95% CIs for the BMI ≥ 30 group.

Race

When race was considered in the integrated analysis, the Pearl Index was 0.90 (95% CI: 0.51, 1.46) in white subjects aged 16 to 35 years (>23 000 at-risk cycles). The PI for black or African American subjects of the same

age range (1,956 at-risk cycles) was 7.98 (95% CI: 4.12, 13.93). A similar pattern was observed for subjects aged 16 to 50 years in both race subgroups. The Method Failure Pearl Index was about half as high as the Pearl Index for both white and black/African Americans subgroups aged 16 to 35 and 16 to 50 years indicating a high rate of user failures. For Asians and other races, the numbers of cycles and pregnancies were low, precluding firm conclusions due to wide confidence intervals.

For the separate studies, the Study C301 data yielded a Pearl Index of 0.29 (95% CI: 0.06, 0.84) in white subjects aged 18 to 35 years while two on-treatment pregnancies reported in black or African American subjects resulted in an extreme Pearl Index of 57.78 (95% CI: 7.00, 208.71) for both age groups. There were only 45 at-risk cycles (6 subjects) in the black/African-American group, hence, meaningful comparisons could not be made.

In Study C301, there were more African American women included and the PI was 6.80 (95% CI: 3.26, 12.51) while in white women it was 1.77 (95% CI: 0.94, 3.02), both in the age group 16-35 years. In the small group of Asian subjects of the same age range, the PI was 4.28 (95% CI: 0.52, 15.45). For other races, observations should be made with caution due to small numbers.

Previous contraceptive use

Concerning previous contraceptive use, in the integrated analysis for subjects aged 16 to 35 years, starters had a somewhat higher Pearl Index than switchers (1.88 vs. 1.24). This may be due to better compliance in tablet intake for switchers due to the previous experience with CHCs. This theory was supported by results for the Method Failure Pearl Index, which was reduced in starters compared to switchers indicating a higher rate of user failures in starters. This was mainly seen in the 16-35-year-old group in the US/Canadian study C302.

Smoking status

For smoking status, in the integrated analysis, the Pearl Index was 2.25 (95% CI: 0.90, 4.63) in 436 smokers aged 16 to 35 years, which was higher than the value determined for the subgroup of non-smokers; 1.39 (95% CI: 0.89, 2.07). Similar patterns with higher PI estimates in smokers vs. non-smokers were observed in the individual studies, with wide confidence intervals in the smoker subgroups due to fewer cycles.

Age
For age, in the integrated analysis, the Pearl Index was lower in the eldest group of subjects compared to the other age subgroups. In both subgroups of subjects below 35 years, Pearl Index and Method Failure Pearl Index were in the same range as the Pearl Index in the overall study population of subjects aged 16 to 35 years and 16 to 50 years, respectively (about 1.5 and 0.8). The lower Pearl Index in the subgroup of subjects aged > 35 to ≤ 50 years could be due to lower fertility and a better compliance to tablet intake with age, however, it should be noted that the age subgroups were of different sample sizes. The same pattern with higher PIs in the younger subgroups was observed in the individual studies.

Concerning elderly subjects, this is not applicable for this product, being a contraceptive. Hence, the table usually requested on number of subjects in different age categories (>65 years) is not applicable.

Region
For region, in the integrated analysis, subjects from the US aged 16 to 50 years had a Pearl Index of 2.75 and the corresponding Method Failure Pearl Index was 1.6. These values were higher than the Pearl Index in the overall study population of subjects aged 16 to 50 years, respectively (about 1.4 and 0.82). Both the Pearl Index and the Method Failure Pearl Index value for US subjects were about six times higher than the values found for the European only study population.

Overall, black and Asian women had higher Pearl Index compared to white women and that a higher Pearl Index was observed in starters compared to switchers. Concerning BMI, a trend was observed for an increase of the Pearl Index with increasing BMI. Smokers also tended to have higher PI vs. non-smokers. No major causes for

concern are observed based on the data, however, firm conclusions are difficult to make due to small sample sizes for some subgroups.

Supportive studies

No supportive studies have been conducted.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application for E4/DRSP is supported by two Phase 3, multi-centre, open-label, single-arm studies; Study MIT-Es0001-C301 (conducted in Europe/Russia) and Study MIT-Es0001-C302 (conducted in the US/Canada).

The studies included heterosexually active females at risk for pregnancy and requesting contraception, and who were willing to use the investigational product as the primary method of contraception for 13 consecutive cycles. The women were aged 18 to 50 years (inclusive) in Study C301 and 16-50 years in Study C302. The women should have good physical and mental health on the basis of medical, surgical and gynaecological history, physical examination, gynaecological examination, clinical laboratory, and vital signs, and a Body mass index (BMI) ≤ 35.0 kg/m^2.

The exclusion criteria reflected the general contraindications for combined hormonal contraceptives, e.g. with respect to the risks for venous thromboembolism, hypertension, diabetes, hepatic abnormalities, etc. Hyperkalaemia is included, which is relevant considering the antimineralocorticoid effects of DRSP.

The in- and exclusion criteria were in line with those applied in other hormonal contraception studies and generally acceptable to identify the population using contraceptives, although it has not clearly been mentioned in the inclusion criteria whether women had established ovulatory cycles.

The listed prior and concomitant therapies that were not allowed were acceptable. Use of any contraceptive method other than the investigational product was unauthorized in the study including emergency contraception. It was specified that at-risk cycles were defined as cycles in which no other methods of birth control (including condoms and emergency contraception) were used as confirmed in the subject diary.

Eligible subjects were treated with 15 mg E4/3 mg DRSP for a maximum of 13 consecutive cycles. The treatment was to be taken once daily at approximately the same time of the day in a 24/4-day regimen, i.e., 24 active, pink tablets followed by 4 placebo, white tablets (4-day hormone-free interval). Specific instructions were provided for starting the first pack of tablets, depending on whether the woman had used any previous hormonal contraceptive method or not and if so, the type of method. Specific instructions were also provided in case of missed tablet(s) or in conditions potentially reducing the contraceptive efficacy.

Subject diaries were given to the participating subjects at Visit 2 (subject enrolment) and the subjects were instructed on how to complete it. Information recorded in the subject diary related to the date of the intake of the first tablet at each cycle, tablet intake on a daily basis, absence or occurrence of vaginal bleeding/spotting event(s) on a daily basis (classified as 0 = Absence of vaginal bleeding or spotting, 1 = Spotting and 2 = Bleeding), use of contraceptive method other than the investigational product (e.g., condom) during the cycle, occurrence of heterosexual intercourse during the cycle and results of the UPT(s) performed at home (at Cycle 1 before the first pill intake and at subsequent cycles in case of absence of menstruation).

Participating subjects were asked to record their bleeding/spotting episodes daily in the subject diary, to allow evaluation of the bleeding pattern and the cycle control. Treatment compliance was assessed using data from the subject diary across the entire study and by cycle, treatment compliance from diary was compared on site with the drug accountability (returned tablet) and any discrepancy was to be documented in the subject's source document.

The subject diary was also used to determine whether or not a cycle was at risk for the Pearl Index calculation, i.e. a cycle in which no other contraceptive method other than the investigational product was used and sexual intercourse occurred. Use of condoms was allowed during the course of the study only to avoid transmission of sexually transmitted infections or in case of missed tablet(s) or unauthorized concomitant therapy(ies). Condom and any other contraceptive methods use had to be recorded in the subject diary.

Serum pregnancy tests were performed during the study at the Screening Visit (Visit 1) and Visit 7 (Cycle 14).

Urine pregnancy tests (UPT) were performed at home by the subject just before intake of the first investigational product and in cases of a missed menstrual period. In case of a positive UPT result, the subject was instructed to contact the study staff immediately and not to take the investigational product. An appointment was scheduled for pregnancy follow-up as soon as possible. For subjects included in the Endometrial Safety Substudy, an additional UPT was performed at the study site before performing the endometrial biopsy (Visit 7a).

Both pivotal trials were non-comparative; hence, all women received the same treatment, i.e. one active tablet containing 15 mg E4/3 mg DRSP per day for 24 days, followed by four days with intake of placebo tablets. The treatment duration was for 13 consecutive cycles.

The primary objective of both studies was to evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index in subjects aged 18 to 35 years (16 to 35 years in Study C302), inclusive, at the time of screening.

The corresponding primary efficacy variable was the number of on-treatment pregnancies assessed by the Pearl Index in the intention-to-treat (ITT) population of women aged 18 to 35 years (16 to 35 years in Study C302), inclusive, at the time of screening with at-risk cycles, defined as no use of other methods of birth control (including condoms) as confirmed in the subject diary, and confirmation that sexual intercourse occurred during the cycle in the diary. The focus on the 18 (or 16) to 35 years age range for the primary efficacy outcome is endorsed.

This is the overall (method + user failure) Pearl Index determined (according to the FDA definition) and can be considered the strictest determined Pearl Index.

The Pearl Index is calculated as follows:

$$\text{Pearl Index} = 100 * \frac{\text{number of on-treatment pregnancies} * 13}{\text{number of women} * \text{28-day equivalent cycles of treatment}}$$

The secondary objectives were to evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the method failure Pearl Index and life-table analysis in subjects aged 18 (or 16) to 35 years, inclusive, at the time of screening and to evaluate the contraceptive efficacy of 15 mg E4/3 mg DRSP using the Pearl Index, the method failure Pearl Index and life-table analysis in the overall (up to 50 years) study population.

Other secondary objectives were to evaluate cycle control and bleeding pattern associated with 15 mg E4/3 mg DRSP, to evaluate general safety of 15 mg E4/3 mg DRSP and to evaluate the impact of 15 mg E4/3 mg DRSP on physical, psychological, and social functioning and well-being.

Study C301 also had an objective to evaluate the endometrial safety using histological assessment of endometrial biopsy samples in a subset of subjects aged 18 to 50 years, inclusive, at the time of screening (Endometrial Safety Substudy). Study C302 included a Population PK Substudy, with the aim to assess the effect of various individual characteristics/covariates (e.g., body weight, race, smoking, and fed/fasted condition) on the pharmacokinetics of 15 mg E4/3 mg DRSP.

The study objectives and outcomes are adequate for studies evaluating a new contraceptive. The number of subjects and the duration of treatment are in accordance with the requirements of the EMA guideline on steroid contraceptives (EMEA/CPMP/EWP/519/98 Rev1), i.e. at least 400 women completing one year of treatment. The studies had a non-comparative, open-label single arm design. Hence, there were no objectives related to superiority or non-inferiority and randomisation and blinding were not necessary. The use of a single arm, non-comparative study design can be accepted for the evaluation of a new hormonal contraceptive, in accordance with the EMA guideline on steroid contraceptives. The lack of an active comparator for the studies evaluating the contraceptive efficacy of a new contraceptive method is acceptable according to this guideline, as long as the number of cycles studied are sufficient to obtain the desired precision of the estimate of contraceptive efficacy and unless the expected PI is high (PI>1). Comparative data are however required for the studies evaluating ovarian function and metabolic effects. In the studies evaluating ovarian function and haemostatic parameters, relevant active comparators were included. For bleeding control data, the guideline mentions that the information should to a considerable extent come from studies including an active comparator. The two pivotal studies did not include an active comparator for comparison of bleeding patterns, which is a deficiency. However, earlier studies (e.g. ES-C02 which included Qlaira, estradiol valerate/dienogest) have included comparators that can contribute to assessment of the bleeding pattern.

The sample size in the two pivotal studies was based on the precision in the Pearl Index estimate which is in accordance with the guideline on clinical investigation of steroid contraceptives in women (EMEA/CPMP/EWP/519/98 Rev 1), and hence acceptable. The statistical methods are largely acceptable for a single arm, non-comparative study.

Contraceptive efficacy data were displayed for subjects aged 18(16) to 35 years and for all subjects in both pivotal studies. The application included a presentation of the complementary subgroup (subjects above 35 years) as well. In subjects above 35 years, the PI was low (0.679) with a rather wide 95% CI, as expected, due to the small size of this subgroup. Missing data in the diary were interpreted as "No" for pill intake and sexual intercourse and as "Yes" for use of other contraceptive methods. It was clarified how many cycles that were classified as "at risk" or "not at risk" based on missing data for each of those reasons and overall, the number of cycles with missing diary data was rather low in relation to the total number of cycles. Furthermore, missing bleeding information were interpolated with adjacent data. Also for bleeding, the missing information interpolated with adjacent data was low (generally <3%).

Overall, the pivotal studies have been designed in accordance with the requirements in the EMA guideline on clinical investigation of steroid contraceptives in women (EMEA/CPMP/EWP/519/98 Rev 1) and in agreement with scientific advice provided by the CHMP. In an early advice from 2012, it was commented that since DRSP is tied to a higher relative risk of VTE, the company could consider using another progestin, however, DRSP was kept as the progestagen following results of Phase 2 studies. From this advice, it is also understood that the intention of the Applicant was to include Qlaira (estradiol/dienogest) as an active comparator in the pivotal studies (or one of them), although the CHMP mentioned that an active comparator is generally not requested for

efficacy purposes. An active comparator was finally not included in any of the pivotal studies. Advice related to haemostasis, ovarian function data, QT interval assessment have largely been followed.

Concerning GCP aspects, no obvious concerns have been identified based on the review of the studies. Nevertheless, since the Sponsor to the EMA's knowledge had not previously been inspected for a CAP MA, and since this product represents some degree of novelty (new estrogen not previously used in any other product) a verification of GCP compliance of trials supporting the application was requested via an inspection (see above).

Efficacy data and additional analyses

Study C301 was performed in 69 enrolling sites in Europe (59 sites) and Russia (10 sites). The study population in terms of distribution among EU countries appears to be representative for the EU setting and only a small population (18%) was recruited from Russia.

The rate of discontinuation was moderate, 22% up to Cycle 13. The most common reasons for discontinuing the study among all subjects were AEs not related to bleeding (6.0%), followed by consent withdrawal (4.9%) and AEs related to bleeding (3.1%). Pregnancy wish was the reason for discontinuation in 15 subjects (0.9%), and pregnancy in 11 subjects (0.6%). Among 5% of subjects discontinued the study due to consent withdrawal and 2% due to other concerns. More details were requested on these cases. The Applicant provided available details on why these patients withdrew consent. No safety concerns have been revealed from these data.

Study C302 was performed in 77 sites in North America; 70 sites in the US and 7 sites in Canada. The cumulative discontinuation rate was higher in this study compared with C301; 45.5% in the overall population (46.3% in subjects aged 16 to 35 years). The most common reasons for study discontinuation were lost to follow-up (15.5%), consent withdrawal (7.3%), AEs not related to bleeding (4.7%), protocol deviations (4.3%) and adverse events related to bleeding (1.8%). Pregnancy (1.7%) and desire of pregnancy (0.6%) were other reasons for discontinuation. Also for this study, details on subjects who did not complete the study were requested. The Applicant provided available details on why these patients withdrew consent. Similar to Study C301, no safety concerns were revealed from these data.

In **C301**, important protocol deviations were reported in 39%, the most common category was related to study drug (e.g., the subject did not return study drug blisters, or did not follow the instructions for missing pills, etc), in about 19%. Other reasons were related to errors with the IWRS, laboratory/endpoint data, visit window, and pregnancy test performed at wrong timing, wrong handling of laboratory samples. Additional details were provided on the protocol deviations categorized by age and starters/switchers, or other factors and it was discussed whether they could have impacted the interpretation of the data. Regarding deviations in study drug intake, a disbalance has been found between starters and switchers, since protocol deviations occurred more frequent and were more common among starters (65.9%) than among switchers (52.5%). From the phase 3 clinical trials, switchers showed also a lower PI 1.24 (95% CI 0.68, 2.08) compared to starters with a PI of 1.88 (95% CI 1.09, 3.00), which might be a consequence of the protocol deviations. However, the proportion of switchers and starters are generally equal among the groups and therefore it is not considered that this has impacted the overall study outcomes/primary endpoints. No relevant differences were found for the other factors.

Concerning compliance, the majority of the subjects (> 87%) in each cycle did not miss any pill. The percentage of subjects who missed 1 pill ranged from 4% to 8% across cycles, the percentage who missed 2 pills ranged from 1% to 3%. The percentage of subjects who missed > 2 pills was rather low, ranging up to 2.5%. Mean compliance over the study was > 99%, ranging from 99.3 to 100% per cycle, with a median compliance of 100%

overall and for each cycle. Clarification was provided regarding the "over-compliance" (reported estimates of compliance >100%). In the majority of cycles being over-compliant, 29 or 30 pills were taken (i.e. only one or two additional pills), presumably merely by the subject ´ s mistake. The exact reasons do not seem to be known. The number of cycles with ≥ 31 tablets taken were fewer and in most cases likely related to gastrointestinal disturbances.

In **C302**, important protocol deviations were reported in 55% of subjects, thus, higher compared with study C301. The most common type of important protocol deviations was related to study drug (e.g., no return of study drug blisters, instructions for missing pills not followed, non- compliance with instructions of use), reported in 26%. Study drug-related protocol deviations were also the most common type leading to discontinuation. Other common deviations concerned laboratory/endpoint data (e.g., subject did not return the diaries for some cycles or did not return questionnaires) reported in 23%, safety assessments in 11%, visit window in 10%.

Concerning compliance, the majority of subjects (> 78%) in each cycle did not miss any pill. Missed pills were more commonly reported in early Cycles 1 to 3 than in later cycles of use. The percentage of subjects who missed more than two pills ranged from 2% to 7% across cycles. Mean compliance over the study based on the subjects' diaries was 98.7%, ranging from 98.6 to 99.8% per cycle, with a median compliance of 100% overall and for each cycle.

In Study **C301**, the ITT population comprised 1553 subjects (98.5% of the enrolled population) and the PP population comprised 1535 subjects (97.3%). The majority of the women included were aged 35 years or below (13% were >35 years), White (98.6%), non-smokers (84%) with a BMI <30 kg/ m^2 (94%). About two thirds (61%) were 'switchers' (i.e. subjects who had used hormonal contraceptives within the 3 months prior to the date of first dose of investigational product.), while 39% were 'starters' (subjects who had not used hormonal contraceptive(s) within the 3 months prior to the date of first dose of investigational product). Approximately 25% of subjects were true new users (subjects who had never been using hormonal contraception; i.e. a subset of the starter subgroup). About 82% of the study population were from Europe and the remainder from Russia.

In Study **C302**, the ITT population comprised 1864 subjects (86.8% of the enrolled population) and the PP population comprised 1727 subjects (80.4%). The majority of the women included were aged 35 years or below (10% were >35 years). There were only 13 subjects aged below 18 years that were enrolled and treated in this study. Eight of these completed one year of treatment whereas five discontinued prematurely. Overall, it can be concluded that the number of women below 18 years exposed to E4/DRSP is low and any conclusions on efficacy or safety would have to be extrapolated from data on older women.

Approximately 70% were White, around 20% were Black or African American and slightly below 5% were Asian. There were about 25% who were Hispanic or Latino. The median BMI was 25.3 kg/m^2 for the whole population and 23% had a BMI ≥30 kg/m^2. The majority of subjects (76%) had never smoked and < 15% were current smokers. More than half of the subjects (58%) were 'starters' with approximately 17% of subjects classified as true new users; approximately 42% of subjects were switchers from a previous hormonal contraceptive method.

There were no remarkable findings with respect to medical history, or prior and concomitant medications in either of the studies, reflecting a relatively young and healthy population.

Efficacy results

In **Study C301**, there were two pre-treatment pregnancies, five on-treatment pregnancies and four post-treatment pregnancies reported in the ITT Population. Of the five on-treatment pregnancies, two were considered user failures.

This resulted in a Pearl Index of **0.44** (95% CI: 0.14, 1.03) in subjects aged 18 to 35 years with at-risk cycles; the primary efficacy variable. The corresponding PI in the whole age group (18-50 years) was **0.38** (95% CI: 0.12, 0.89).

Several other Pearl index values were also presented. The 'typical use' PI (in which all cycles are included in the denominator regardless of other methods of birth control, occurrence of sexual intercourse or compliance with the protocol) in the 18-35-year-old age group was **0.42** (95% CI: 0.14, 0.99).

The 'method failure PI' (excluding pregnancies due to user failures from the numerator) was **0.26** (95% CI: 0.05, 0.77) in the 18-35-year group and **0.23** (95% CI: 0.05, 0.67) in the whole population. These Pearl index values are all low and comply with the requirement for precision in accordance with the EMA Guideline on Steroid Contraceptives, since the difference between the upper limit of the corresponding 2-sided 95% CI for the Pearl Index and the point estimate was < 1. Life-table analyses (based on Kaplan-Meier estimates) were consistent with the Pearl Index results. The Kaplan Meier curves were fully in line with the Pearl Indices.

In **study C302**, the total number of pregnancies was much higher, with four pre-treatment pregnancies, 28 on-treatment pregnancies and nine post-treatment pregnancies reported in the ITT Population. There were 7 cases of spontaneous abortions, which is discussed in the safety section.

Of the 28 on-treatment pregnancies, 26 occurred in subjects aged 16 to 35 years at screening. Twelve pregnancies were considered user failures and 16 Method Failures.

For the defined primary efficacy variable, the Pearl Index in subjects aged 16 to 35 years with at-risk cycles, the PI for E4/DRSP 15/3 mg was **2.42** (**95% CI: 1.58, 3.54**). Thus, the requirement for precision of the PI was <u>not</u> met in accordance with the EMA Guideline on Steroid Contraceptives, since the difference between the upper limit of the corresponding 2-sided 95% CI for the Pearl Index and the point estimate was > 1.

In the whole group (up to 50 years of age) and with alternative calculation methods, the Pearl Indices ranged from **2.09 to 2.52** and the difference between the point estimates and the upper limit of the corresponding 2-sided 95% CIs was in most cases above 1.

The PI for Method failure was **1.30** (95% CI 0.71, 2.18) for the age group 16-35 years and **1.32** (95% CI 0.75, 2.14) for the whole study population, both with acceptable precision according to the EMA guideline.

The life-table analyses (based on Kaplan-Meier estimates) were consistent with the Pearl Index results. The Kaplan-Meier curves are fully in line with the Pearl Indices also for the US study population, with larger decrease in the US study as expected.

Comparison Pearl Indices between the EU and US phase 3 trials

Based on the findings of the Pearl Indices, the Phase 3 clinical study MIT-Es0001-C301 (EU/Russia) was conducted with appropriate contraceptive efficacy as the primary objective, involving the inclusion of a sufficient number of subjects at-risk of pregnancy, with adequate assessment of compliance and pregnancies. Even the most strictly calculated Pearl Index (overall PI; FDA definition) was considered to be adequate with 0.47 (95% CI: 0.15-1.11), as this is well below 1 and therefore comparable to other widely used COCs. The two-sided 95% confidence intervals are sufficiently precise, such that the difference between the upper limit of the confidence interval and the point estimate did not exceed 1 (in any of the Pearl Index calculations in study MIT-Es0001-C301), which fulfils the criterion on the precision of the estimate in the EMA Guideline on Clinical Investigation of Steroid Contraceptives in Women.

In the US/Canada study (MIT-Es0001-C302), which is actually a US study considering that only 158 of women were from Canada, all the Pearl Indices were higher than noted in the EU study and in several cases insufficiently precise, such that the difference between the upper limit of the confidence interval and the point estimate exceeded 1. The exposure and pregnancy rates generated in the Phase 3 study MIT-Es0001-C302 in the US/Canada meet the FDA requirements only but does not fulfil the criterion on the precision of the estimate of EMA.

Although the definition for the date of conception of the FDA on-treatment pregnancies was more extended (7 days) than the definition applied in the EU study (2 days), i.e. none of the pregnancies in the US study had a date of conception between 2 and 7 days after last intake, this did not explain the higher PI.

The high Pearl Indices obtained in the US study should not be compared with the Pearl Indices of previous COC applications, as Pearl Indices increased over the last 15 years. High Pearl Indices could therefore most likely be due to more frequent pregnancy testing with more sensitive tests and less adherent study populations. Further, the point estimate of 2.65 is therefore higher than reported for Yaz back in 2007 (1.41), but slightly lower than the ones provided in 2017 for the EE-containing COCs LoLoestrin (2.92) and Quartette (3.19). The Pearl Index (95% CI) is, however, lower than recently reported for the DRSP 4 mg progestin-only pill Slynd (4.0), all based on US contraception studies. Whether or not more pregnancy testing with more sensitive testing and less adherent study populations could be explanations for the higher Pearl Indices, cannot be assessed. However, this phenomenon is known since contraception dossiers have been filed with both EU and US studies. Examples are NuvaRing (EU trial 0.65 (0.237 - 1.407), US 1.7 (0.979 -2.885)) and Zoely (EU trial 0.571 ([0.1555, 1.4614]) US trial 1.963 ([0.9798, 3.5119]. Both these COCs have been approved based on the data of the EU trial, as these were large enough to fulfil the EMA requirements on precision of the estimate. This is also the case for the EU trial in support of E4 15mg/DRSP 3mg, therefore the EU trial prevails, regardless of the higher Pearl Index noted in the US trial.

It is acknowledged that higher Pearl Index estimates observed in US vs. EU (non-US) studies is a common phenomenon found for several contraceptives and non-compliance was identified as one of the main factors impacting the efficacy of oral contraceptives in clinical trials. This would fit with the observation that for user-independent contraceptive methods (e.g. IUDs), the PI difference was small or absent. The following was described concerning compliance in the pivotal studies:

In study **C301**, the majority of the subjects (> 87%) in each cycle did not miss any pills. The percentage of subjects who missed 1 pill ranged from 4% to 8% across cycles, the percentage who missed 2 pills ranged from 1% to 3% and the percentage of subjects who missed > 2 pills was rather low, ranging up to 2.5%. Mean compliance over the study was > 99%, ranging from 99.3 to 100% per cycle, with a median compliance of 100% overall and for each cycle.

In study **C302**, the majority of subjects (> 78%) in each cycle did not miss any pills. Missed pills were more commonly reported in early Cycles 1 to 3 than in later cycles of use. The percentage of subjects who missed more than two pills ranged from 2% to 7% across cycles. Mean compliance over the study based on the subjects' diaries was 98.7%, ranging from 98.6 to 99.8% per cycle, with a median compliance of 100% overall and for each cycle.

Thus, a slightly lower compliance was observed in the US vs. the EU study, although it is unclear if this difference would be large enough to lead to the observed PI difference. A trend was observed for an increase of the Pearl Index with increasing BMI. The mean BMI as well as the number of women with high BMI was higher in the US vs. the EU study and this may also have contributed to the different PI results between the studies.

The EU study C301 was a large study (the ITT population comprised 1553 subjects) and the Pearl Index of 0.44 in subjects aged 18 to 35 years with at-risk cycles is low, with an adequate precision (95% CI: 0.14, 1.03). Hence, major focus will be on this study and the higher PI in the US study can merely be noted.

Vaginal bleeding pattern

In comparative study ES-C02, comparing E4/DRSP 15/3 mg with 4 other combinations (E4/DRSP 20/3 mg, E4/LNG 15/0.15 mg, E4/LNG 20/0.15 mg and E2V)/DNG (Qlaira), E4/DRSP 15/3 mg had a lower incidence of unscheduled bleeding/spotting than the other combinations. The rate of absence of withdrawal bleeding was also low for E4/DRSP 15/3 mg, thus suggesting a reasonably predictable bleeding pattern.

In non-comparative study C301, the rate of women recording unscheduled bleeding/spotting was well below 20% except during the first treatment cycle. The mean number of bleeding/spotting days recorded was just under 4 throughout the treatment year, mostly spotting. Absence of scheduled bleeding was reported in 5.6% to 8.1% of subjects per cycle.

In non-comparative study C302, the rate of women recording unscheduled bleeding/spotting was close to or slightly below 20% except during the first treatment cycle. In comparison with data from study C301, data from the USA and Canada included more women with unscheduled bleeding. The number of bleeding/spotting days recorded was just above or around 4 throughout the treatment year. Absence of scheduled bleeding occurred in 13.0% to 17.1% of subjects per cycle.

Discontinuation due to bleeding pattern-related TEAEs was low in both studies 301 and 302, reflecting good tolerability in the majority of women.

Although it should be noted that the sample size of the phase 3 study was much greater and duration was twice as long, i.e. 13 cycles, the phase 3 trial data on cycle control show a better bleeding profile, as compared with the findings of cycle 6 of the comparative phase 2 dose-finding and selection study on cycle control (ES-C02) (see table below). An adequate comparison of the bleeding pattern endpoints was shown between the comparative phase 2 dose-finding and selection study on cycle control (ES-C02) and the phase 3 studies over time.

Summary of endpoints of study MIT-Es0001-C301 and comparative phase 2 trial ES-C02

	Comparative phase 2 trial ES-C02		**Phase 3 trial MIT-Es0001-C301**
	1/2/3 mg E2V and 0/2/3 mg DNG (Qlaira)	**E4/DRSP 15/3mg**	**E4/DRSP 15/3 mg**
Unscheduled bleeding/spotting at cycle 6 (n/N (%))	32/67 (47.8)	22/65 (33.8)	207/1,331 (15.6)
Unscheduled bleeding at cycle 6 (n/N (%))	24/67 (35.8)	11/65 (16.9)	11/1,331 (0.8)
Absence of withdrawal bleeding at cycle 6 (n/N (%))	16/59 (27.1)	2/57 (3.5)	91/1,331 (6.8)

This indirect comparison of bleeding data show that cycle control of E4/DRSP 15/3 mg is similar in the phase 2 and the phase 3 studies. Further, although data should be interpreted with caution, as subject numbers are small, cycle control was most favourable for E4/DRSP 15/3 mg as compared to the other E4 combinations and

the approved CHC (EV/DNG) used as active control. This supports the conclusion that E4/DRSP 15/3 mg demonstrates adequate cycle control, as shown by a bleeding pattern with a low percentage of unexpected breakthrough bleeding/spotting and a low incidence of missed scheduled bleeding (i.e. high percentage of withdrawal bleeding).

Sub-group analyses

Sub-group analyses have been performed based on integrated data for the two studies as well as for each study separately. The sub-groups investigated are considered relevant, e.g. based on BMI, previous contraceptive use, smoking status, age and region. For several subgroups, both the number of pregnancies and numbers of evaluable cycles were too low to achieve meaningful results. This often resulted in estimated PI:s with very wide confidence intervals.

Concerning BMI, a trend was observed for an increase of the Pearl Index with increasing BMI. Smokers also tended to have higher PI vs. non-smokers. Black and Asian women had higher Pearl Index compared to white women and a higher Pearl Index was observed in starters compared to switchers. No major causes for concern are observed based on the data, although firm conclusions are difficult to make due to small sample sizes for some subgroups.

Assessment of paediatric data on clinical efficacy

No paediatric (adolescent) studies have yet been completed, but an adolescent study is included in the PIP. In study C302, 13 subjects aged below 18 years were enrolled and treated.

2.5.4. Conclusions on the clinical efficacy

An adequate ovulation inhibitory effect and cycle control has been observed for the proposed dose regimen of E4/DRSP 15/3 mg in the clinical pharmacology programme.

The pivotal studies had an adequate design and an acceptably low Pearl index value with adequate precision has been demonstrated, at least in the EU/Russian study. The EU study C301 was a large study (the ITT population comprised 1553 subjects) and the Pearl Index of 0.44 in subjects aged 18 to 35 years with at-risk cycles is low, with an adequate precision (95% CI: 0.14, 1.03). Hence, major focus will be on this study and the higher PI in the US study can merely be noted.

The vaginal bleeding pattern was as expected for a combined hormonal contraceptive and raised no cause for concern. There are no outstanding issues related to efficacy.

2.6. Clinical safety

Safety data set

The safety data set, summarised in the Applicant's Integrated Summary of Safety (ISS) contains data from the two Phase 3 studies (MIT-Es0001-C301; MIT-Es0001-C302) and from three Phase 2 studies (MIT-Es0001-C201; MIT-Es0001-C202; ES-C02) (Table 46), which met the following criteria:

- conducted in the target population: healthy pre-menopausal women 16 to 50 years old (18 to 35 years in two Phase 2 studies), without contraindications to the use of COCs;

- dosage and regimen of E4/DRSP 15/3 mg, 24/4-day regimen including 24 days of active tablets followed by 4 days of placebo tablets;
- duration of treatment at least three 28-day cycles.

Other studies, such as dose-finding studies and clinical pharmacology studies with subjects from other populations and/or exposed to other dose regimens were considered less relevant from a Safety perspective and have not been included in the ISS.

Table 19. Summary of key clinical studies providing safety information for E4/DRSP 15/3 mg

Study ID	No of study centers Location Study start	Study Phase Objective	Study design Diagnosis	Subjects (treated / completed)	Mean age (range)	Test product, dosage regimen, route of administration	Duration of treatment
MIT-Es0001-C301 June 2016	59 Europe: B-8, CZ-12, F-8, D-7, H-11, N-4, PL-6, S-3, RUS-10	3 Efficacy / safety	OL, single arm, MC Healthy WOCBP (18 to ≤50 years) Requesting contraception	1553/1218	27.1 years (18-49)	E4/DRSP 15/3 mg: n=1553	13 cycles
MIT-Es0001-C302 Aug 2016	77 70 sites USA, 7 sites Canada	3 Efficacy / safety	OL, single arm, MC Healthy WOCBP (16 to ≤50 years) Requesting contraception	1864/1016	27.3 years (16-50).	E4/DRSP 15/3 mg: n=1864	13 cycles
ES-C02 Oct 2010	10 FI	2b Efficacy / safety (dose-finding) -PD	R, OL, five-arm, MC Healthy WOCBP (18 to ≤35 years) requesting contraception	389/316	24.1 years (18-35)	E4/DRSP 15/3 mg: n=79* E4/DRSP 20/3 mg: n=75* E4/LNG 15/0.15 mg: n=80* E4/LNG 20/0.15 mg: n=77* E2V/DNG 1/2/3 0/2/3 mg: n=78	6 cycles

Study ID	No of study centers Location Study start	Study Phase Objective	Study design Diagnosis	Subjects (treated / completed)	Mean age (range)	Test product, dosage regimen, route of administration	Duration of treatment
MIT-Es0001-C201 Sep 2016	1 NL	2 Safety, PD	R, OL, three-arm, SC Healthy WOCBP (18 to ≤ 50 years) requesting contraception	100/88	26.2 years (18 – 47)	E4/DRSP 15/3 mg: n=38 EE/LNG 0.03/0.15 mg: n=30 EE/DRSP 0.02/3 mg: n=32	6 cycles
MIT-Es0001-C202 Feb 2017	1 NL	2 Safety / efficacy	R, OL, two-arm, SC Healthy WOCBP (18 to ≤35 years) requesting contraception	82/71	25.6 years (19-35)	E4/DRSP 15/3 mg: 41 EE/DRSP 0.02/3 mg: 41	3 cycles

Patient exposure

The overall exposure to E4 during the clinical development (ISS dataset and supportive studies) is summarised in Table 47.

Table 20. Total Exposure to E4 in the E4 Clinical Program

Category	N
Total number of subjects exposed to at least one dose of E4 with or without progestin	4,318**
Total number of subjects exposed to at least one dose of E4/progestin	4,177**
Total number of subjects exposed to one or two single doses of E4/progestin	219*
Total number of subjects exposed to repeated doses of E4/progestin	3,996*,**
Total number of subjects exposed to at least one dose of E4/DRSP 15/3 mg	3,700**
Total number of subjects exposed to one or two single doses of E4/DRSP 15/3 mg	94*
Total number of subjects exposed to repeated doses of E4/DRSP 15/3 mg	3,616*,**

DRSP = drospirenone; E4 = estetrol
* According to the design of study MIT-Es0001-C103, 39 subjects received a single dose of E4/DRSP; 38 of these subjects then received multiple doses (separated from the single dose by a 14-day washout period). Of the 39 subjects, 10 received both a single dose and multiple doses of E4/DRSP 15/3 mg; these subjects are counted in both 'single dose' and 'repeated dose' categories, but only once in the total.
** One subject in the Phase 3 MIT-Es0001-C302 had a post-treatment pregnancy reported in a pregnancy narrative but did not have any diary date from which the exposure could be derived. This subject is included in the Safety Population but has missing data for exposure.

The Integrated Safety Population (ISS dataset) included 3,790 subjects from studies with the recommended dose regimen and in which at least three treatment cycles were planned. From the enrolled population, 94 subjects were excluded who were confirmed not to have taken any study medication. At the request of FDA the Safety Population does however include 215 subjects who were dispensed study medication, but for whom the

actual intake of study medication was not confirmed; they had neither provided information on drug intake in the subject diary, nor was there any record of returned medication.

The distribution of subjects who were exposed to any number of cycles of study medication is presented in Table 48.

Table 21. Extent of Exposure to E4/DRSP 15/3 mg – Phase 3 and 2 Studies (Safety Population)

-	Phase 3 and 2 Studies E4/DRSP 15/3 mg		
Characteristic	**Subjects Aged ≥16-≤35 Years (N=3,381)**	**Subjects Aged >35-≤50 Years (N=409)**	**All Subjects (N=3,790)***
Duration of Total Exposure in Days			
n	3,180	394	3,574**
Mean (SD)	276.6 (122.49)	303.3 (108.28)	279.5 (121.28)
Total Extent of Exposure in Years	2,408	327	2,735
Duration of Actual Exposure in Days			
n	3,180	394	3,574
Mean (SD)	272.7 (121.71)	300.5 (107.91)	275.7 (120.57)
Total Extent of Actual Exposure in Years	2,374	324	2,698
Subjects exposed for at least 26 weeks [n (%)]***	2,272 (67.2)	317 (77.5)	2,589 (68.3)
Subjects exposed for at least 52 weeks [n (%)]***	838 (24.8)	155 (37.9)	993 (26.2)
Number of cycles of study medication taken			
n	3,180	394	3,574 §
Mean (SD)	9.9 (4.29)	10.9 (3.75)	10.0 (4.24)
Number (%) of subjects who had at least *x* cycles of study medication, where *x* =			
1 cycle	3,180 (94.1)	394 (96.3)	3,574 (94.3) §
2 cycles	2,994 (88.6)	382 (93.4)	3,376 (89.1)
3 cycles	2,903 (85.9)	372 (91.0)	3,275 (86.4)
4 cycles	2,691 (79.6)	356 (87.0)	3,047 (80.4)
5 cycles	2,593 (76.7)	351 (85.8)	2,944 (77.7)
6 cycles	2,532 (74.9)	339 (82.9)	2,871 (75.8)

-	Phase 3 and 2 Studies E4/DRSP 15/3 mg		
Characteristic	**Subjects Aged ≥16-≤35 Years (N=3,381)**	**Subjects Aged >35-≤50 Years (N=409)**	**All Subjects (N=3,790)***
7 cycles	2,304 (68.1)	320 (78.2)	2,624 (69.2)
8 cycles	2,236 (66.1)	313 (76.5)	2,549 (67.3)
9 cycles	2,182 (64.5)	309 (75.6)	2,491 (65.7)
10 cycles	2,063 (61.0)	295 (72.1)	2,358 (62.2)
11 cycles	2,002 (59.2)	292 (71.4)	2,294 (60.5)
12 cycles	1,973 (58.4)	287 (70.2)	2,260 (59.6)
13 cycles	1,930 (57.1)	282 (68.9)	2,212 (58.4)

DRSP = drospirenone, E4 = estetrol, n = number of subjects with data, N = number of subjects in the Safety Population and is the denominator for the percentages, SD = standard deviation
* The ISS Safety Population includes 3,575 subjects with confirmed exposure to E4/DRSP 15/3 mg and 215 subjects for whom neither exposure nor non-exposure could be confirmed. All 215 subjects were part of the Phase 3 studies. See Section 3.3.1.
** It is noted that one subject in the Phase 3 MIT-Es0001-C302 had a post-treatment pregnancy reported in a pregnancy narrative but did not have any diary data from which the exposure could be derived. This subject is included in the Safety Population but has missing data for exposure.
*** Refers to subject for which exposure to the study drug is documented in the diary for at least 26 or 52 complete weeks.
§ It is noted that one subject in the Phase 3 MIT-Es0001-C302 had a post-treatment pregnancy reported in a pregnancy narrative but did not have any diary data from which the exposure could be derived. This subject is included in the Safety Population but has missing data for exposure.
Note: Duration of total exposure = the last dose date – the first dose date + 1.
Duration of actual exposure = duration of total exposure – the total number of days with no pills taken.
The total extent of exposure in years was the sum of the duration of total exposure across all subjects in the Safety Population divided by 365.25.
The total extent of actual exposure in years was the sum of the duration of exposure in days across all subjects in the Safety Population divided by 365.25

Thus, **a total of 3,574 subjects were confirmed treated**. A total of 2,212 subjects completed 13 cycles of treatment in the two Phase 3 studies. Treated subjects contributed **a total of 2,735 woman-years** (WY) or 35,677* cycles of exposure. Within the treated population, 3,180 women aged 16 to 35 years contributed 2,408 WY or 31,412* cycles, while 394 women aged 36 to 50 years contributed 327 WY or 4,266* cycles.

Out of the confirmed treated population **1,198 subjects (33.5%) prematurely discontinued**. The reasons for discontinuation included lost-to-follow up (n=328), withdraw consent (n=261), TEAE not related to bleeding (n=245), protocol deviation (n=107), TEAE related to bleeding (n=104), pregnancy (n=39), pregnancy wish (n=32) and death (n=1).

Adverse events

Overview of TEAEs

Overall, at least one TEAE was reported by 50.8% of subjects in the pooled ISS (Phase 3 and Phase 2 studies); at least one TEAE related to study drug was reported by 27.9% of subjects; and at least one serious TEAE was reported by 1.1% of subjects (Table 49).

One TEAE in the pooled Phase 3 and Phase 2 studies led to death. The death was not related to the study drug (accidental overdose with fentanyl and alprazolam). For more information, see below.

Frequent TEAEs

TEAEs reported in ≥ 2 % of subjects are listed in Table 50.

The **most frequent TEAEs by SOC** were infections and infestations (21.2%), reproductive system and breast disorders (19.0%), gastrointestinal disorders (9.9%), nervous system disorders (9.1%), skin and subcutaneous tissue disorders (6.4%), and investigations (5.1%).

The **most frequent TEAEs by PT** were headache (6.4%), metrorrhagia (4.6%), viral upper respiratory tract infection (3.9%), acne (3.7%), dysmenorrhea (3.3%), vaginal hemorrhage (3.1%), nausea (2.7%), urinary tract infection (2.5%), weight increased (2.6%), breast pain (2.3%), and abdominal pain (2.1%).

Table 22. Overall Summary of TEAEs – Pooled Phase 2 and Phase 3 (ISS, Safety Population)

	Phase 3 Studies E4/DRSP 15/3 mg (N=3,632)*			Phase 3 and 2 Studies E4/DRSP 15/3 mg (N=3,790)*		
Adverse event category	**n**	**%**	**m**	**n**	**%**	**m**
Any TEAEs	1,803	49.6	4877	1,924	50.8	5323
Any TEAEs related to study drug	986	27.1	2001	1056	27.9	2148
Any TEAEs of severe intensity	125	3.4	185	130	3.4	191
Any Serious TEAEs	41	1.1	45	41	1.1	45
Any Serious TEAEs related to study drug	4	0.1	4	4	0.1	4
Any TEAEs leading to study discontinuation	347	9.6	383	357	9.4	402
Any serious TEAEs leading to study discontinuation	6	0.2	6	6	0.2	6
Any TEAEs leading to death	1	0.0	1	1	0.0	1
Any Serious TEAEs leading to death	1	0.0	1	1	0.0	1

TEAE = treatment emergent adverse event, n = number of subjects, m = number of events.
* The ISS Safety Population includes 3,575 subjects with confirmed exposure to E4/DRSP 15/3 mg and 215 subjects for whom neither exposure or non-exposure could be confirmed. All 215 subjects were included in Phase 3 studies.

Table 23. TEAEs reported in ≥2% of the Subjects by SOC and PT (Safety Population)

	Phase 3 Studies E4/DRSP 15/3 mg (N=3,632)			Phase 3 and 2 Studies E4/DRSP 15/3 mg (N=3,790)*		
System Organ Class Preferred Term	n	(%)	m	n	(%)	m
Any Treatment-Emergent Adverse Events**	1,803	(49.6)	4,877	1,924	(50.8)	5,323

	Phase 3 Studies E4/DRSP 15/3 mg (N=3,632)			Phase 3 and 2 Studies E4/DRSP 15/3 mg (N=3,790)*		
System Organ Class Preferred Term	n	(%)	m	n	(%)	m
Infections and infestations**	738	(20.3)	1,114	8,04	(21.2)	1,213
Viral upper respiratory tract infection	120	(3.3)	147	148	(3.9)	180
Urinary tract infection	94	(2.6)	106	95	(2.5)	107
Reproductive system and breast disorders	680	(18.7)	1,094	721	(19.0)	1,161
Metrorrhagia	172	(4.7)	245	174	(4.6)	247
Dysmenorrhoea	113	(3.1)	143	124	(3.3)	158
Vaginal haemorrhage	117	(3.2)	198	117	(3.1)	198
Breast pain	68	(1.9)	78	89	(2.3)	110
Gastrointestinal disorders	342	(9.4)	535	377	(9.9)	591
Nausea	92	(2.5)	101	101	(2.7)	110
Abdominal pain	77	(2.1)	93	81	(2.1)	98
Nervous system disorders	310	(8.5)	424	344	(9.1)	497
Headache	214	(5.9)	271	241	(6.4)	333
Skin and subcutaneous tissue disorders	215	(5.9)	252	241	(6.4)	280
Acne	128	(3.5)	138	140	(3.7)	151
Investigations	192	(5.3)	235	195	(5.1)	238
Weight increased	99	(2.7)	99	100	(2.6)	100

DRSP = drospirenone, E4 = estetrol, m = number of events, n = number of subjects with data, N = number of subjects in the Safety Population and is the denominator for the percentages
*The ISS Safety Population includes 3,575 subjects with confirmed exposure to E4/DRSP 15/3 mg and 215 subjects for whom neither exposure nor non-exposure could be confirmed. All 215 subjects were part of the Phase 3 studies.
** This table includes one subject who never started the treatment. Two AEs occurring to this subject should not have been accounted in the TEAEs. For more information, see the Analysis Data Reviewers Guide (ADRG).

Drug-related TEAEs

Drug-related TEAEs (adverse drug reactions; ADRs) occuring in ≥ 2 % of the study population are presented in Table 51.

Overall, drug-related TEAEs were reported in 27.9% of subjects in pooled Phase 3 and Phase 2 studies (Category B).

The most frequent drug-related TEAEs by SOC were reproductive system and breast disorders (15.8%), followed by psychiatric disorders (5.6%), nervous system disorders (4.5%), skin and subcutaneous tissue disorders (4.1%), gastrointestinal disorders (3.6%), and investigations (3.2%).

The most frequent drug-related TEAEs by PT were metrorrhagia (4.3%), headache (3.2%), acne (3.2%), vaginal hemorrhage (2.7%), dysmenorrhea (2.4%), breast pain (2.1%), and weight increased (2.0%).

Table 24. Drug-related TEAEs reported in ≥2% of subjects by SOC and PT (Safety Population)

	Phase 3 Studies E4/DRSP 15/3 mg (N=3,632)			Phase 3 and 2 Studies E4/DRSP 15/3 mg (N=3,790)*		
System Organ Class Preferred Term	n	(%)	m	n	(%)	m
Any Drug-Related TEAEs**	986	(27.1)	2,001	1056	(27.9)	2,148
Reproductive system and breast disorders	565	(15.6)	887	599	(15.8)	943
Metrorrhagia	160	(4.4)	230	162	(4.3)	232
Vaginal hemorrhage	103	(2.8)	181	103	(2.7)	181
Dysmenorrhea	85	(2.3)	107	92	(2.4)	115
Breast pain	60	(1.7)	69	79	(2.1)	98
Psychiatric disorders	195	(5.4)	252	211	(5.6)	273
Nervous system disorders	154	(4.2)	206	170	(4.5)	233
Headache	109	(3.0)	132	123	(3.2)	156
Skin and subcutaneous tissue disorders	142	(3.9)	162	155	(4.1)	177
Acne	112	(3.1)	120	122	(3.2)	131
Gastrointestinal disorders**	123	(3.4)	160	138	(3.6)	177
Investigations	120	(3.3)	145	122	(3.2)	147
Weight increased	74	(2.0)	74	75	(2.0)	75

DRSP = drospirenone, E4 = estetrol, m = number of events, n = number of subjects with data, N = number of subjects in the Safety Population and is the denominator for the percentages, TEAE = treatment-emergent adverse event

*The ISS Safety Population includes 3,575 subjects with confirmed exposure to E4/DRSP 15/3 mg and 215 subjects for whom neither exposure nor non-exposure could be confirmed. All 215 subjects were part of the Phase 3 studies.

** Including one event of acute pancreatitis which was subsequently considered as not related to the study drug.

Supportive studies

Overall, the safety profile from supportive studies investigating E4/DRSP (any dose) was aligned with the safety profile obtained from the pooled Phase 3 and Phase 2 studies.

Studies investigating E4 alone did not evidence any safety risk preventing further use as an oral contraceptive. A potential dose-relationship with safety was observed in study PR3050, where the percentage of subjects reporting TEAEs and drug-related TEAEs was higher in subjects receiving a single dose of E4 100 mg compared to other dose levels (E4 0.1 mg to E4 10 mg). A clear safety dose-relationship, in terms of number of TEAEs, could not be established with E4/DRSP in studies MIT-Es0001-C106 and MIT-Es0001-C103 (doses tested ranging from E4/DRSP 15/3 mg to 75/15 mg). However, severe and serious TEAEs were more frequently reported with the highest dose tested, including a VTE considered as related to study drug.

The safety profile of E4 alone and E4/DRSP was similar in Caucasian subjects and Japanese subjects in study MIT-Es0001-C109.

Following concomitant administration of valproic acid (VAL), an UGT2B7 inhibitor (UGT2B7 being the main enzyme responsible for metabolization of E4), with E4/DRSP, an increase in the number of TEAEs and drug-related TEAEs was observed (study MIT-Es0001-C110). However, the frequency of TEAEs related to E4/DRSP only (not to VAL) was similar in both groups (E4/DRSP and E4/DRSP/VAL) (MIT-Es0001-C110).

No impact of food intake (fasting *vs*. fed) on the safety of the combination E4 + progestin (DRSP or LNG) was observed in studies Es0001-C101 and 0031CA002.

Serious adverse event/deaths/other significant events

ISS population

Deaths

There was a total of one (1) death in all clinical studies performed with E4 (with or without progestin). It was reported in Study MIT-Es0001-C302 (with E4/DRSP 15/3 mg) and evaluated as not related to the study drug.

Serious adverse events

A total of 45 serious TEAEs were reported in 41 subjects (1.1%) in the pooled Phase 3 and Phase 2 studies (Table 52). The most frequent serious TEAEs by PT were spontaneous abortion (n=9, 0.2%), ectopic pregnancy (n=2, 0.1%), appendicitis (n=2, 0.1%), depression (n=2, 0.1%). Other serious TEAEs were not reported for more than 1 subject.

Of the 45 serious TEAEs, 3 were assessed by Investigator as related to the study drug:

- One subject experienced VTE in study MIT-Es0001-C301, and event resolved without any sequelae;
- One was a worsening of depression in study MIT-Es0001-C302. Due to the event occurring 4 months after initiating the study drug, the relatedness of this event to the study drug was disagreed by the Sponsor.
- One was an ectopic pregnancy in study MIT-Es0001-C302. Due to absence of any potential causality between the use of COCs and the occurrence of ectopic pregnancy in the literature, the relatedness of this event to the study drug was disagreed by the Sponsor.

Of note, in study MIT-Es0001-C302 there was a report of a non-serious TEAE of acute pancreatitis, which led to the creation of a serious TEAE of acute pancreatitis after event worsened and the subject had to be hospitalized. Only the initial TEAE was considered drug related by the investigator.

Table 25. Serious TEAEs by SOC, PT, – Pooled Phase 2 and Phase 3 (ISS, Safety Population)

	Phase 3 and 2 Studies E4/DRSP 15/3 mg (N=3,790)*		
System Organ Class Preferred Term	**n**	**(%)**	**m**
Any Serious Treatment-Emergent Adverse Events**	41	(1.1)	45
Pregnancy, puerperium and perinatal conditions**	11	(0.3)	11
Abortion spontaneous**	9	(0.2)	9
Ectopic pregnancy	2	(0.1)	2
Infections and infestations	7	(0.2)	7

	Phase 3 and 2 Studies E4/DRSP 15/3 mg (N=3,790)*		
System Organ Class Preferred Term	**n**	**(%)**	**m**
Appendicitis	2	(0.1)	2
Abscess limb	1	(0.0)	1
Bacterial pyelonephritis	1	(0.0)	1
Campylobacter gastroenteritis	1	(0.0)	1
Gastroenteritis	1	(0.0)	1
Infection parasitic	1	(0.0)	1
Psychiatric disorders	6	(0.2)	7
Depression	2	(0.1)	2
Affective disorder	1	(0.0)	1
Alcohol withdrawal syndrome	1	(0.0)	1
Bipolar I disorder	1	(0.0)	1
Psychotic disorder	1	(0.0)	1
Suicidal ideation	1	(0.0)	1
Injury, poisoning and procedural complications	5	(0.1)	5
Accidental overdose	1	(0.0)	1
Concussion	1	(0.0)	1
Rib fracture	1	(0.0)	1
Spinal column injury	1	(0.0)	1
Upper limb fracture	1	(0.0)	1
Gastrointestinal disorders	3	(0.1)	3
Abdominal pain	1	(0.0)	1
Colitis	1	(0.0)	1
Pancreatitis acute	1	(0.0)	1
Hepatobiliary disorders	2	(0.1)	2
Cholecystitis	1	(0.0)	1
Hepatic hematoma	1	(0.0)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(0.1)	2
Acute myeloid leukemia	1	(0.0)	1
Thyroid neoplasm	1	(0.0)	1
Ear and labyrinth disorders	1	(0.0)	1

	Phase 3 and 2 Studies E4/DRSP 15/3 mg (N=3,790)*		
System Organ Class Preferred Term	**n**	**(%)**	**m**
Vertigo	1	(0.0)	1
General disorders and administration site conditions	1	(0.0)	1
Pyrexia	1	(0.0)	1
Immune system disorders	1	(0.0)	1
Drug hypersensitivity	1	(0.0)	1
Nervous system disorders	1	(0.0)	1
Migraine without aura	1	(0.0)	1
Renal and urinary disorders	1	(0.0)	1
Renal cyst	1	(0.0)	1
Reproductive system and breast disorders	1	(0.0)	1
Hemorrhagic ovarian cyst	1	(0.0)	1
Respiratory, thoracic and mediastinal disorders	1	(0.0)	1
Pneumomediastinum	1	(0.0)	1
Vascular disorders	1	(0.0)	1
Venous thrombosis	1	(0.0)	1

DRSP = drospirenone, E4 = estetrol, m = number of events, n = number of subjects with data, N = number of subjects in the Safety Population and is the denominator for the percentages
*The ISS Safety Population includes 3,575 subjects with confirmed exposure to E4/DRSP 15/3 mg and 215 subjects for whom neither exposure nor non-exposure could be confirmed. All 215 subjects were part of the Phase 3 studies.
**This table includes one subject who never started the treatment. One serious AE occurring to this subject should not have been accounted in the serious TEAEs. For more information, see the Analysis Data Reviewers Guide (ADRG).

Supportive studies

In total, 3 serious TEAEs were reported among 512 subjects receiving at least one dose of E4 in the supportive clinical studies. Two of these events, occurring in study MIT-Es0001-C106, were considered related to the study drug:

- One subject treated with E4/DRSP 15/3 mg for 10 days then E4/DRSP 75/15 mg for 10 days experienced a deep vein thrombosis (DVT) the day after receiving the last dose of E4/DRSP 75/15 mg. This event was considered as a serious TEAE due to it being an important medical event, severe, likely related to the study drug, and resolving (no longer in need of follow-up).
- One subject treated with E4/DRSP 15/3 mg for 10 days then E4/DRSP 75/15 mg for 10 days experienced complicated migraine. The subject was considered as withdrawn from the study. This event was considered by the investigator to be moderate in severity, possibly related to the study drug, and resolved.

The other serious TEAE was reported in study PR3054 in a subject who had received one cycle of E4 10 mg. The subject experienced a cerebral haemorrhage 31 days after the last E4 dose and 15 days after the last progestogen dose (lynestrenol). This event was considered by the investigator to be severe, not related to the study drug, and resolved with sequelae.

TEAEs of special interest

In the pooled ISS analysis (Phase 3 and Phase 2 studies), 10 categories of TEAEs of special interest (TEAESIs) were retrospectively defined:

- Venous thromboembolic events (VTE) (or suspected)
    - Deep vein thrombosis (DVT)
    - Pulmonary embolism
- Arterial thromboembolic events
    - Stroke and myocardial infarction
- Mood changes (for example, depression, suicide, worsening of depression, emotional lability, mood swings, etc.)
- Bleeding irregularities
- Acne, seborrhoea, oily skin
- Sexual interest (increase/loss of libido)
- Breast complaints (pain, tenderness, masses, galactorrhoea)
- Headache / migraine
- Potassium related AEs (hyperkalaemia)
- Weight gain/loss

Overall, at least one TEAESI was reported by 24.8% of subjects. Around 75% of TEAESIs were considered related to the study drug (19.2 % of subjects). See Table 53.

Table 26. Overall Summary of TEAESIs (Safety Population)

	Phase 3 and 2 Studies E4/DRSP 15/3 mg (N=3,790)*		
Adverse Event Category	**n**	**(%)**	**m**
Any TEAEs	1,924	(50.8)	5,323
Any TEAESIs	941	(24.8)	1,524
Any TEAESIs related to study Drug	728	(19.2)	1,127
Any TEAESIs of severe intensity	39	(1.0)	54
Any Serious TEAESIs	7	(0.2)	7
Any Serious TEAESIs related to Study Drug	2	(0.1)	2
Any TEAESIs leading to study discontinuation	209	(5.5)	224
Any Serious TEAESIs leading to study discontinuation	3	(0.1)	3
Any TEAESIs leading to death	0	(0.0)	0
Any Serious TEAESIs leading to death	0	(0.0)	0

DRSP = drospirenone, E4 = estetrol, n = number of subjects with data, N = number of subjects in the Safety Population and is the denominator for the percentages, m = number of events, TEAESI = treatment-emergent adverse event of special interest
* The ISS Safety Population includes 3,575 subjects with confirmed exposure to E4/DRSP 15/3 mg and 215 subjects for whom neither exposure nor non-exposure could be confirmed. All 215 subjects were part of the Phase 3 studies. See **Section** 3.3.1.

TEAESIs were most frequently reported in the SOC reproductive system and breast disorders (11.8%), nervous system disorders (7.3%), skin and subcutaneous tissue disorders (4.2%) and investigations (2.9%). When evaluated by PT, the most frequently reported TEAESIs were headache (6.4%), metrorrhagia (4.6%), acne (3.7%), weight increased (2.6%) and breast pain (2.3%).

The most frequent **drug-related TEAESIs by SOC** were reproductive system and breast disorders SOC (10.8%), nervous system disorders (3.9%), skin and subcutaneous disorders (3.5%), psychiatric disorders (2.9%) and investigations (2.1%). The most frequent **drug-related TEAESIs by PT** were metrorrhagia (4.3%), headache (3.2%), acne (3.2%), breast pain (2.1%), weight increased (2.0%), breast tenderness (1.8%), libido decreased (1.5%) and menorrhagia (1.3%). All other drug-related TEAESIs were reported in less than 1% of subjects.

Serious TEAESIs were reported by 7 subjects in the ISS population. Out of these 7 events, 5 were part of the psychiatric disorders SOC (0.1% of subjects), including 2 events of depression. The other 2 serious TEAESIs were a migraine and a venous thrombosis. Two 2 events were considered as related to the study drug (depression and venous thrombosis, respectively, further described above). No TEAESI had a fatal outcome.

By Severity

Overall, mild TEAESIs were reported in 15.2% of subjects, moderate TEAESIs were reported in 8.6% of subjects and severe TEAESIs were reported in 1.0% of subjects (Phase 2 and Phase 3 population). The most frequent severe TEAESIs by PT were headache (n=11, 0.3%), libido decreased (n=6, 0.2%), breast pain (n=3, 0.1%), anxiety (n=3, 0.1%), depression (n=3, 0.1%), migraine (n=2, 0.1%), migraine without aura (n=2, 0.1%), suicidal ideation (n=2, 0.1%) and weight increased (n=2, 0.1%). Other severe TEAESIs were not reported by more than 1 subject.

By Treatment duration

A gradual decrease in the frequency of TEAESIs was observed from Cycle 1 to Cycle 13. This trend was observed in the full Safety Population and in both age groups. This trend can be partially explained by the gradual decrease in the number of subjects in the study over time.

Venous thromboembolic Events

Over the clinical program of E4, including 4,319 subjects treated with at least one dose of E4, 2 cases of VTE were reported (0.05% of subjects). These have already been mentioned above.

- One case of venous thrombosis of vena fibularis was reported in a subject while being on her 4th cycle of E4/DRSP 15/3 mg. This event was considered by the investigator as moderate in intensity and probably related to the study drug, required withdrawal from the study drug and resolved without any sequelae.
- The second event was a deep vein thrombosis (DVT) of the lower right extremity reported in a subject who received E4/DRSP 15/3 mg for 10 days and then a supratherapeutic dose with E4/DRSP 75/3 mg for another 10 days. This event was considered by the investigator to be severe, likely related to study drug, and resolved without any sequelae.

The Applicant attempted to calculate the incidence of VTE observed in the pooled clinical Phase 2 and 3 studies (one event). The proposed incident amounted to 2.80 (95% CI: 0.68, 15.59) per 10,000 women and the incidence rate, in view of 2,735 woman years of (confirmed) exposure, was 3.66 (0.89, 20.37) per 10,000 woman years. These numbers must be interpreted with extreme caution.

Endometrial Safety Sub-study

In the Europe/Russia Phase 3 clinical study (Study MIT-Es0001-C301) endometrial biopsies were obtained from a subset of subjects at screening and at Cycle 11, 12, or 13, between Days 12 and 19 of the cycle. For a total of 108 subjects paired endometrial biopsies were available.

The endometrial tissue obtained by endometrial biopsy was processed by the central laboratory. Two independent pathologists assessed the slides from the endometrial biopsies. In case of discrepancy between both pathologists' assessments, a third independent pathologist assessed the slide. If concurrence was not reached, the worst diagnosis was used. Due to some discrepancies between the initial reading of the slides and re-evaluation by an external pathologist, which was subsequently confirmed by the initial reader as well as a third reader, the Sponsor initiated an overall reread of the slides by three new, independent readers. This new analysis confirms the results of the initial endometrial safety assessment. The results are shown in Table 54.

Table 27. Endometrial biopsy data at screening and after 13 months (visit 7).

Histological Category [n (%)]	15 mg E4/3 mg DRSP (N=108)	
	Screening Visit	Visit 7a
No tissue	0	0
Tissue insufficient for diagnosis	1 (0.9)	9 (8.3)
Benign Histology		
Atrophic	2 (1.9)	11 (10.2)
Inactive	7 (6.5)	61 (56.5)
Proliferative	76 (70.4)	22 (20.4)
Weakly proliferative	30 (27.8)	10 (9.3)
Active proliferative	24 (22.2)	1 (0.9)
Disordered proliferative	22 (20.4)	11 (10.2)
Secretory	22 (20.4)	5 (4.6)
Cyclic type	16 (14.8)	1 (0.9)
Progestational type (including stromal decidualization)	6 (5.6)	4 (3.7)
Menstrual type	0	0
Simple hyperplasia without atypia	0	0
Complex hyperplasia without atypia	0	0
Pre-malignant/Malignant Histology		
Simple hyperplasia with atypia	0	0
Complex hyperplasia with atypia	0	0
Carcinoma	0	0

Source: Table 14.3.12.1

DRSP = drospirenone; E4 = estetrol

Only subjects who signed the informed consent form for the Endometrial Safety Substudy and who had 2 biopsies (one at screening and one at Visit 7a) were included in this table.

Subjects who were pregnant at the time that the biopsies were taken were excluded from the table.

Pregnancies

The distribution of pregnancy outcomes in each category is presented in descriptive statistics in Table 55. No pregnancy was reported during the Phase 2 studies.

In total in the phase 3 trials, 39 pregnancies were exposed to E4/DRSP 15/3 mg, either on-treatment pregnancies or pre-treatment pregnancies. Amongst those, 9 subjects (23.1%) carried the pregnancy to term and delivered a healthy child; 4 subjects (10.3%) had a late preterm delivery of a healthy child; 11 subjects (28.2%) had an elective abortion; 8 subjects (20.5%) had a spontaneous abortion; 2 subjects (5.1%) an ectopic pregnancy; and 5 subjects (12.8%) were lost to follow-up.

Pregnancy narratives are available in MIT-Es0001-C301 and MIT-Es0001-C302.

Table 28. Pregnancy Outcomes – Pooled Phase 3 studies (ISS, Safety Population)

	Pregnancies in Phase 3 Studies	
Pregnancy Outcomes	**Proportion based on known outcomes (n=34)**	**Proportion based on total pregnancies (N=39)**
Term live Birth -	9 (26.5)	9 (23.1)
Elective Abortion	11 (32.4)	11 (28.2)

Late preterm live birth -	4 (11.8)	4 (10.3)
Spontaneous abortion	8 (23.5)	8 (20.5)
Ectopic pregnancy	2 (5.9)	2 (5.1)
Lost to follow-up	--	5 (12.8)

Laboratory findings

Serum chemistry

In the ISS, effects on serum chemistry values were presented as shift analysis, i.e. the percentage of patients showing a shift of category (low, normal, high) for the parameter.

Shifts values (low, normal and high) outside of the reference range were presented by parameter and visit and are summarized by the number and percentage of subjects with evaluable shifts. An evaluable shift is one where both the baseline value and the on-treatment, end of treatment or early termination value is recorded for subjects in the Safety Population. The denominator for calculating the percentages is the number of subjects with an evaluable shift.

Shift summaries from baseline to EoS of the serum chemistry parameters were presented for pooled Phase 3 studies (Category A). For the full ISS population (Category B) shifts from baseline to EoS for Phase 2 studies and to Cycle 7 for Phase 3 studies were presented.

Parameters with the highest proportion of shifts from one category (low, normal or high) at baseline to another category at EoS were bicarbonate and LDH isoenzyme 2 concentrations in both categories. For both cases the shift was from low to normal or from normal from low and the shifts were within the range 15-24% of the subjects and 12-19% of the subjects for bicarbonate and LDH isoenzyme 2, respectively. Creatinine shifted from normal to high in 6.5% of the ISS population. For all other tested parameters, no shifts in more than 5% of the subjects were seen.

Adverse events related to serum chemistry or lipid profile

In study C301, TEAEs related to serum chemistry or lipid profile parameters were reported in 18 subjects (1.2%). These adverse events were considered treatment-related in 12 subjects (0.8%) with increased LDL cholesterol, 4 subjects (0.3%) with increased ALT, 2 subjects (0.1%) with increased AST, 1 subject (0.1%) with increased cholesterol and 1 subject (0.1%) with increased blood creatinine plus the subject (0.1%) who had the event mistakenly coded as increased blood creatine.

In study C302, TEAEs related to serum chemistry or lipid profile parameters were reported in 14 subjects (0.8%). These TEAEs were considered related to study treatment in 12 subjects (0.6%) with increased LDL, 11 subjects (0.6%) with increased blood cholesterol, 5 subjects (0.3%) with increased blood triglycerides, 3 subjects with hyperlipidemia (0.2%), 3 subjects (0.2%) with increased ALT, 2 subjects (0.1%) with increased AST, 2 subjects (0.1%) with increased blood potassium and 1 subject (0.1%) with increased GGT, 1 subject (0.1%) with increased blood glucose, 1 subject (0.1%) with decreased LDL and 1 subject (0.1%) with decreased serum ferritin.

Hyperkalaemia

Due to the potassium-sparing properties of DRSP, hyperkalaemia was specifically evaluated.

Hyperkalaemia was defined as a potassium level more than 5.3 mmol/L.

Of the 3,790 subjects included in the pooled Phase 3 and Phase 2 studies, 120 subjects (3.2%) recorded this level at some point during treatment. The majority of these 120 subjects (84.2%, 101 subjects) had potassium levels less than 6.0 mmol/L, while 15 subjects (12.5%) had a level between 6.0 and 7.9 mmol/l. Only 4 subjects (3.3%) had a potassium level 8.0 mmol/L or greater. Hyperkalaemia due to haemolysis of the sample occurred for 3 subjects.

In 72 subjects (60.0%) hyperkalaemia was discovered during Days 169 to 192 of treatment, while 29 subjects (24.1%) exhibited hyperkalaemia, usually between 11 and 28 days after the last study drug intake. Almost 60% (58.3%, 70 subjects) of the 120 subjects completed the study with a normal potassium level. Of note, 29 of the 120 subjects were enrolled with hyperkalaemia (protocol deviation), and 11 of these completed the study treatment without hyperkalaemia.

From the 120 subjects, no subject received treatment for hyperkalaemia and 7 cases were reported as TEAE by the investigator; all were considered mild and 5 were deemed related to the study drug. The potassium level for one of these events was 5.2 mmol/L but was credited as hyperkalaemia by the Investigator. Only one subject, with a potassium level of 6.0 mmol/L, had the study treatment withdrawn because of hyperkalaemia; the potassium level during the early termination evaluation, 21 days after the last study drug intake, had returned to normal. The chronic use of medications likely to precipitate a rise in the potassium level was prohibited during the study, however there was reported use of NSAIDS in 28 of the subjects with hyperkalaemia, all of whom were chronic users apart from five. The past medical history of 3 subjects may have also played a role in their development of hyperkalaemia.

Haematology

The highest proportion of shifts from one category (low, normal or high) at baseline to another category at EoS were observed for haemoglobin, erythrocytes and for the lymphocytes/leucocytes ratio.

Adverse events related to haematology

In study C301, TEAEs related to haematology parameters were reported in 1 subject (0.1%) with anaemia (Table 14.3.2.2). This event was considered not related to the investigational product

In study C302, TEAEs related to haematology parameters were reported in 6 subjects (0.3%) with anaemia, 1 subject (0.1%) with leukocytosis, 1 subject (0.1%) with leukopenia, 1 subject (0.1%) with neutropenia, 1 subject (0.1%) with decreased haemoglobin and 1 subject (0.1%) with increased platelet count (Table 14.3.2.2). Only the TEAE of decreased haemoglobin was considered related to the investigational product.

Metabolic control and haemostasis

The effects on haemostasis, endocrine function, lipid and carbohydrate metabolism parameters were studied in healthy female subjects randomized to 15 mg E4/3 mg DRSP (n=39) or 30 mcg EE/150 mcg LNG (n=30) or 20 mcg EE/3 mg DRSP (n=32) during 6 treatment cycles.

Subjects were stratified by previous hormonal contraception use (2 menstrual cycles or more than 2 menstrual cycles without hormonal contraceptive use before starting study treatment) and by age (≤35 years or >35 years of age). Subjects using hormonal contraception had a washout period of 1 menstrual cycle. Thereafter, each subject underwent 1 pre-treatment cycle, followed by 6 treatment cycles.

A total of 98 female subjects between 18 and 47 years of age and with a body mass index (BMI) between 18.3 and 30.0 kg/m^2 used the study medications. A total of 93 (95%) subjects were of white race, 3 (3%) subjects

were of mixed race (1 subject was white + black and 2 subjects were white + Asian), 1 (1%) subject was black or African American, and 1 (1%) subject was Asian. None of the subjects were of Hispanic or Latino ethnicity. No apparent group differences were observed for any of the parameters measured at pre-treatment/baseline.

Inhibitors of coagulation generally showed statistically significant decreases from baseline as observed for Protein S activity, free Protein S, and free tissue factor pathway inhibitor (TFPI), while Protein C was increased. Changed fibrinolysis was indicated by increased plasminogen and decreased t-PA not counterbalanced by decreased plasminogen activator inhibitor-1 (PAI-1), although D-dimer was unchanged.

Results

Haemostasis: The E4/DRSP 15/3 mg combination was associated with the smallest changes. The resistance to APC, a functional coagulation test measuring the generation of thrombin in the presence and absence of APC (ETP-based APC resistance), was considerably less with E4/DRSP than observed with EE/LNG and EE/DRSP, with respective changes from baseline of 30%, 165% and 219%. Similarly, the change in F1+2 (+23.0%) was smaller than observed with EE/LNG (+71.0%) and EE/DRSP (+64.0%).

No statistically significant changes from baseline were observed in coagulation inhibitors, while the changes in fibrinolytic parameters plasminogen (+12.0%), D-dimer (+4.0%), t-PA (-7.0%) and PAI-1 (+20.0%) are clinically irrelevant and not at all indicative of fibrinolytic activation to the extent observed for the two reference COCs. E4/DRSP 15/3 mg does not affect soluble E-selectin, an endothelial adhesion molecule involved in inflammation and haemostasis, in contrast to EE/LNG and EE/DRSP.

Table 29. Percentages change from baseline in haemostatic parameters. Median and length of interquartile range. (PP Population Study MIT Es0001 C201.)

Parameter	E4/DRSP 15/3 mg N=34	EE/LNG 0.03/0.15 mg N=27	EE/DRSP 0.02/3 mg N=30
Coagulation			
Activated Protein C Resistance - (ETP based)	30.0 [370] *,1,2	164.5 [126.0] *,1,3	218.5 [145.0] *,2,3
Activated Protein C Resistance - (APTT based)	0.0 [22.0]	5.0 [26.0] *	-1.0 [23.0]
Fibrinogen (mg/dL)	10.0 [26.0] *	5.0 [34.0]	16.0 [31.5] *
Factor VII Activity (%)	-3.0 [19.0] 2	-5.0 [14.0] *	20.0 [24.0]*
Factor VIII Activity (%)	5.0 [18.0]	3.0 [42.0]	9.0 [35.0]
von Willebrand Factor (%)	5.0 [22.0]	-2.0 [18.0] 3	13.0 [24.0]*,3
Prothrombin Activity (%)	7.0 [12.0] *	13.0 [13.0] *	7.0 [14.5] *
Prothrombin Fragments 1+2 (nmol/L)	23.0 [56.0] *,1,2	71.0 [55.0] *,1	64.0 [54.0] *,2
Coagulation Inhibitors			
Antithrombin (%)	-1.0 [7.0]	-5.0 [11.0] *	-3.5 [13.5]
Protein S activity (%)	-4.0 [17.0] 2	-5.0 [21.0] 3	-30.5 [12.5] *,2,3
Protein S, Free (%)	5.0 [14.0] 2	-3.0 [25.0] 3	-22.5 [16.5] *,2,3
Protein C (Factor XIV Activity) (%)	2.0 [10.0] 2	7.0 [22.0] *	17.5 [21.5]*,2
Free tissue factor pathway inhibitor (U/mL)	-8.5 [29.0]	-6.0 [39.0]	-20.0 [30.0] *
Fibrinolysis			
Plasminogen (%)	12.0 [12.0] * 1,2	40.0 [18.0] *,1	35.5 [17.5] *,2
Tissue Plasminogen Activator Antigen (ng/mL)	-7.0 [32.0] 1,2	-33.0 [30.0] *,1	-39.5 [36.0] *,2
Plasminogen Activator Inhibitor-1 (U/mL)	20.0 [78.0]	0.0 [50.0]	0.0 [63.0]
D-Dimer (mcg/mL FEU)	4.0 [32.0] *	7.0 [38.0]	0.0 [33.5]
Endothelial adhesion factor			
Soluble E-Selectin (ng/mL)	2.5 [24.0] 1,2	-31.0 [15.0] *	-21.0 [19.0] *

DRSP = drospirenone, E4 = estetrol, EE=ethinylestradiol, LNG = levonorgestrel, PP = per protocol
* Statistically significant ($p<0.05$) change from baseline; 1,2,3 Statistically significant ($p<0.05$) between treatments: 1 = E4/DRSP vs EE/LNG; 2 = E4/DRSP vs EE/DRSP; 3 = EE/LNG vs EE/DRSP

Treatment with E4/DRSP 15/3 mg generally resulted in minor apparent changes from baseline in the haemostatic parameters. Changes seen with EE/LNG were less pronounced than those seen with EE/DRSP and, in general least pronounced with E4/DRSP 15/3 mg, which is considered reassuring. The clinical significance of the effects on haemostatic parameters with regard to VTE risk is, however, only speculative. Whereas EE/LNG has been reported from large epidemiological studies to have the lowest risk of VTE, the association with laboratory results, which are surrogate biomarkers, and VTE risk is weak. At best, it can be concluded that treatment with E4/DRSP 15/3 mg has less effect on haemostatic parameters than EE/LNG and EE/DRSP, possibly reflecting that E4 is a less potent oestrogen than EE.

As estetrol is a new oestrogen in a CHC, it is important to establish the magnitude of VTE risk. Therefore, VTE is included as an identified risk in the RMP and it is proposed to monitor the VTE occurrence post-marketing as an additional pharmacovigilance activity.

Androgens and liver proteins: Treatment was associated with a decrease in androgen concentrations. Median testosterone levels decreased by more than 30% and free testosterone levels decreased by 50% in the E4/DRSP and EE/LNG groups, and by 71% in the EE/DRSP group. In parallel, an increase in the median concentration of

SHBG by 55%, 74% and 251% in groups treated with E4/DRSP, EE/LNG and EE/DRSP, respectively, was observed. Decreases in median concentrations of androstenedione, dehydroepiandrosterone and dihydrotestosterone were also observed.

Treatment with E4/DRSP 15/3 mg resulted in less pronounced increases from baseline for all liver proteins assessed. The effects of E4/DRSP and EE/LNG on TBG (+17.0% vs +37.0%) were comparable, but the effects on CBG (+40% vs +152%), angiotensinogen (+75% vs +170%) and CRP (0% vs +30%) were all much less pronounced with E4/DRSP 15/3 mg. The changes with EE/DRSP 0.02/3 mg were much larger for all parameters compared to E4/DRSP 15/3 mg, and to a lesser extent larger than with EE/LNG 0.03/0.15 mg too for SHBG, TBG, and angiotensinogen.

The changes that were observed with regard to androgens and liver proteins were those expected for a COC, inhibiting ovulation. The modest increase from baseline in SHBG reported in the E4/DRSP group compared to the EE/DRSP group supports that E4 in the given dose exerts weak oestrogen activity.

Lipids and lipoproteins: The effects on lipids and lipoproteins by the 3 different COCs studied were generally modest, and as expected according to what has been reported in numerous previous studies on various COCs. No changes that are considered clinically important were seen.

Carbohydrate metabolism: The effects on carbohydrate metabolism by the 3 different COCs studied were generally modest with little difference between them, and as expected according to what has been reported in previous studies on various COCs. No changes that are considered clinically important were seen.

Cardiac function parameters

Due to the cardiac toxicity observed in non-clinical studies (see above), cardiac function parameters LDH 1 and LDH 2 serum concentrations were measured in the Phase 3 clinical trials at baseline, during treatment and shortly after treatment completion. The evaluation of LDH, although considered an unspecific marker, was by the Applicant suggested justified as in the animals showing interstitial fibrosis and vacuolization of cardiomyocytes in non-clinical studies, LDH was increased.

For LDH 1 mean ± standard deviation baseline concentrations (N=3,625) were 0.239 ± 0.0356 U/L and similar values were found at Cycle 7 and after treatment; corresponding changes from baseline were 0.0002 ± 0.0315 and -0.003 ± 0.0318, respectively. For LDH 2 (U/L) the baseline value was 0.296 ± 0.039 (U/L) and the changes from baseline were 0.005 ± 0.0401 and 0.005 ± 0.0371, respectively. Upward shifts from normal to high LDH 1 values at Cycle 7 were observed in 22 subjects (0.8%) and the reverse, downward shifts from high to normal, by 21 subjects (0.8%); at the post-treatment measurement these shifts from baseline were observed by 14 (0.4%) and 17 (0.5%) subjects, respectively. For LDH 2 normal to high shifts were observed in 2 subjects (0.1%) at Cycle 7 and in one subject post-treatment.

LDH1, LDH2, as well as troponin, were also measured in Study MIT-Es0001-C201 between Days 18 and 21 of the baseline cycle and the last treatment cycle. No trend was observed and no clinically relevant changes in any of the parameters was noted in 34 subjects treated for 6 cycles. Similar results were obtained in in 41 subjects treated for 3 cycles in Study MIT-Es0001-202. In Study MIT-Es001-C103 the same parameters were studied at baseline, and on Days 1 and 29 of one treatment cycle, at dose levels of one, two, four or five times the intended therapeutic dose in 10 subjects per dose group. Again, no effects were noted.

The potential of a E4/DRSP to delay cardiac repolarization was specifically assessed in two clinical studies by testing the effects on the QT/QTc interval. Study MIT-Es001-C103 was a placebo-controlled study, in which E4/DRSP was tested as both a single dose and in 14-day daily doses of 15/3 mg, 30/6 mg, 60/12 mg and 75/15

mg, equivalent to up to 5 times the therapeutic dose. In Study MIT-Es0001-C106 the single dose and multiple dose (10 days) effects of E4/DRSP 15/3 mg and 75/15 mg (5 times therapeutic) were again tested, but in this study a positive control, i.e., moxifloxacin 400 mg, was also included in addition to placebo.

By-timepoint analyses did not indicate that E4/DRSP in the studied doses had a clinically relevant effect on ECG parameters and a mean QT effect exceeding 10 msec could be excluded within the observed range of E4 and DRSP plasma concentrations. None of the E4/DRSP combinations had a relevant effect on heart rate or echocardiography results either.

Measurement of the cardiac function was also performed in studies MIT-Es0001-C201 and MIT-Es0001-C202. Overall, no changes or trends of clinical significance were seen for the heart rate, PR interval, QRS duration, QT interval and QTcF interval.

Echocardiography was performed in studies MIT-Es0001-C103, MIT-Es0001-C201 and MIT- Es0001-C202. In studies MIT-Es0001-C103 and MIT-Es0001-C202, no clinically relevant findings were observed on the echocardiograms. In study MIT-Es0001-C201, no clinically relevant findings were observed, except for 3 subjects who had an abnormal result at screening.

In the ISS Safety population, 11 subjects (0.3%) reported a total of 12 TEAEs in the SOC Cardiac disorders. Most events were palpitations (m=7). Out of the 12 TEAEs, one (palpitations) was assessed as potentially related to the treatment and none was considered as serious. No trends in the shift from one category (low, normal or high) to another was observed between baseline and the end of study (EoS) for any of the cardiovascular parameters investigated (blood pressure, heart rate or BMI).

Safety in special populations

Age

When evaluated by age group (subjects aged ≥16 – ≤35 years and subjects aged >35 – ≤50 years), the relative TEAE distributions was similar to the larger 'all subjects' Phase 3 and Phase 2 pooled study populations. Also the proportion of subjects reporting TEAEs of Special interest was similar in subjects aged ≥16 - ≤35 years and in subjects aged >35-≤50 years.

BMI

Over the BMI categories (underweight, normal, overweight and obese), the percentage of subjects reporting any TEAE ranged from 50.1% to 51.6% and the percentage of subjects reporting any drug-related TEAE ranged from 23.8% to 28.8%, indicating that BMI did not appreciably alter the distribution of TEAEs. Due to the small sample size in some categories, especially underweight (n=126), no reliable conclusion could be drawn. For the category with the highest number of serious TEAEs, obese, the following serious TEAEs by PT were reported by 1 patient each: abortion spontaneous, ectopic pregnancy, gastroenteritis, campylobacter gastroenteritis, depression, psychotic disorder, bipolar I disorder, alcohol withdrawal syndrome, affective disorder, pancreatitis acute, abdominal pain, cholecystitis, thyroid neoplasm, acute myeloid leukaemia, and pneumomediastinum.

Smoking status

The percentage of subjects reporting any TEAE ranged from 47.8% to 53.1%, and the percentage of drug-related TEAEs ranged from 25.6% to 31.7%, with no appreciable differences noted between current smokers, former smokers, and never smokers (ISS population). However, due to the low number of subjects

with TEAEs in current smokers and former smokers compared to never smokers, no reliable conclusion could be drawn.

The **serious TEAEs** by SOC and PT evaluated by smoking status varied between 0.9 to 2.2%, with the highest percentages noted in the current smoker population (Category B). However, given the small number of subjects with serious TEAEs in current smokers (n=12), former smokers (n=4), and n ever smokers (n=25), no reliable conclusions could be drawn.

Race

An analysis of TEAEs by race was performed on the pooled Safety Populations from Phase 3 and Phase 2 studies (ISS). The distribution of subjects of the different races in the study population was the following: White: n=3,094 (81.6%); Black or African American: n=467 (12.3%); Asian: n=100 (2.6%); Other: n=129 (3.4%).

The percentage of subjects reporting any TEAE ranged from 38.1% to 61.0% and the percentage of subjects reporting any drug-related TEAE ranged from 20.8% to 31.0%, with black or African American subjects showing the lowest percentage and Asians the highest percentage. However, due to the low sample sizes of non-white subjects in the Safety Population, results should be considered with caution.

The percentage of subjects with **serious TEAEs** varied between 0.9% to 2.1%, with the highest percentages noted in the Black or African American population (Category B). However, given the small number of subjects with serious TEAEs in the White (n=28), Black or African American (n=10), Asian (n=1), and Other Race (n=2), no reliable conclusions could be drawn.

Paediatric subjects

The safety and efficacy of E4/DRSP have been established in women from 16 years of age (US/Canada Phase 3 study, C302) or from 18 years of age (European/Russian Phase 3 study, C301). In both studies, approximately half of the subjects (45 % and 51 % in study C302 and C301, respectively) were ≤ 25 years.

A Phase 3 study to evaluate the efficacy and safety of Drovelis in post-menarcheal subjects aged 12 to 17 years is proposed as part of the Paediatric Investigation Plan.

Hepatic or renal impairment

No clinical studies have been performed with Drovelis in patients with renal or hepatic insufficiency. Drovelis is contraindicated in women with severe hepatic disease or severe renal insufficiency.

Immunological events

Drug hypersensitivity was reported as TEAE in one subject in the ISS population. It was considered related to treatment with E4/DRSP.

Study PR3054: After repeated-dose administration of 10 mg E4 alone to 10 post-menopausal women for 28 days, no clinically relevant changes were observed in total T cells (CD3 positive) and CD4- and CD8- positive T cells, the corresponding CD4/CD8 ratio as well as the complement factors C3 and C4 and the antibody levels of IgA, IgG and IgM.

Safety related to drug-drug interactions and other interactions

No TEAEs of drug-drug interactions were reported in the ISS.

Discontinuation due to adverse events

Overall, **9.4% of subjects (n=357) in the ISS population discontinued the study due to a TEAE**, and the TEAE was considered **related to study treatment in in 7.7% of subjects (n=290)**.

The TEAEs leading to discontinuation can be divided into TEAEs not related to vaginal bleeding (n=250, 6.6%) and related to vaginal bleeding (n=106, 2.8%).

The most frequent TEAEs leading to discontinuation by SOC were reproductive system and breast disorders (3.6%), psychiatric disorders (2.5%), skin and subcutaneous tissue disorders (1.1%), nervous system disorders (0.8%), gastrointestinal disorders (0.6%), investigations (0.6%), general disorders and administration site conditions (0.2%) and vascular disorders (0.2%). All other TEAEs leading to withdrawal by SOC were reported by ≤0.1% of subjects.

The most frequent TEAEs leading to discontinuation by PT, were metrorrhagia (1.1%), acne (0.9%), vaginal haemorrhage (0.7%), menorrhagia (0.6%), libido decreased (0.5%), mood swings (0.5%), weight increased (0.4%), mood altered (0.4%), headache (0.4%), depression (0.2%), irritability (0.2%), breast pain (0.2%), anxiety (0.2%), menstruation irregular (0.2%), dysmenorrhea (0.2%), abdominal pain (0.2%), migraine with aura (0.2%), migraine (0.2%), and nausea (0.2%). All other TEAEs leading to discontinuation by PT were reported by ≤0.1% of subjects.

Results by age group (≥16 to <35 years old and ≥35 to ≤50 years old) were similar to results obtained in the full Safety Population.

Overall, the TEAEs leading to discontinuation evaluated by BMI category showed relatively equal distributions, ranging from 8.5% to 9.8% (Phase 2 and 3 population). Due to the small sample sizes in some BMI categories (e.g. underweight, n=126), no meaningful conclusions could be drawn on the role of BMI in regard to discontinuation due to AE.

Overall, **5.5% of subjects discontinued the study due to a TEAE of special interest**. The most frequent events in this category by PT were metrorrhagia (1.1%), acne (0.9%), libido decreased (0.5%), menorrhagia (0.6%), weight increased (0.4%), headache (0.4%), depression (0.2%), breast pain (0.2%), anxiety (0.2%), menstruation irregular (0.2%), migraine with aura (0.2%), and migraine (0.2%).

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

Drovelis is a new CHC including a new oestrogen, estetrol (E4), and a previously known progestogen, drospirenone (DRSP).

Safety population

The safety evaluation was made primarily based on integrated data from subjects included in Phase 2 or Phase 3 studies, treated with the recommended dose (15 mg E4 and 3 mg DRSP) and in which the planned treatment duration was at least three 28-day cycle, which is considered adequate. The phase 3 studies contributed to about 95% of the total number of treated subjects.

The integrated safety population included 3,574 fertile women 16-50 years of age with confirmed treatment. A total of 2,212 subjects completed 13 cycles of treatment in the two Phase 3 studies. The safety database is considered sufficiently large and mirrors the target population. For a CHC with a previously known progestogen, 13 cycles of treatment are considered enough for assessing the effects of long-term treatment.

Treatment-emergent adverse events

Overall, the AE profile appears similar to what is known for other CHCs and what would be expected from the mode of action an oestrogen and a progestogen. The system organ class (SOC) within which the highest frequency of TEAEs that were considered related to treatment was reported was Reproductive system and breast disorders (15.8%), where the most common preferred terms (PTs) were metrorrhagia, vaginal hemorrhage, dysmenorrhea, and breast pain (each reported in ≥ 2% of subjects). Psychiatric disorders that were considered treatment-related were reported in 5.6% of subjects. Nervous system disorders was reported in 4.5% of subjects where headache was the most common PT. Acne was reported in 3.5%, weight increased in 2.6% and abdominal pain in 2.1% of subjects.

The Applicant provided an overview of drug-related AEs in the phase 2 trials in which E4/DRSP 15/3 mg was compared with other E4 combinations and licensed CHCs. A disbalance in breast pain with E4/DRSP 15/3 mg as compared with other licensed CHCs was seen in the smaller phase 2 studies, but this was not confirmed neither in the larger phase 2 study ES-C02, where different E4 combinations were compared with the licensed CHC Qlaira (estradiol/dienogest), nor in the phase 3 studies. In the ES-C02 study, the safety profile of E4/DRSP 15/3 mg seemed to be generally similar to that for Qlaira. No relevant disbalances in AEs were revealed from these data.

Serious adverse events and deaths

One death was reported within the clinical studies of E4/DRSP, but was not considered related to study treatment.

Serious adverse events occurring in either the integrated safety population or in supportive studies and that were considered related to study treatment by study investigators included two cases of VTE, one case of worsening of depression, one case of ectopic pregnancy and one case of complicated migraine, i.e. a total of five cases. The case of worsening of depression and the case of ectopic pregnancy were unlikely to be related to treatment with E4/DRSP. These events do not affect the overall assessment of the safety profile. Depression/mood changes is a known risk for CHCs, and the risk is described in section 4.4 as well as 4.8 of the SmPC for Drovelis. Ectopic pregnancy is listed in section 4.8, also as a class effect for CHCs.

The two events of VTE were both considered related to study treatment. The currently available clinical safety database is too small to draw conclusions regarding the magnitude of the risk for/incidence of VTEs at treatment with E4/DRSP, and the Applicant's attempt to calculate an incidence based on the ISS population is not considered conclusive. Treatment with E4/DRSP 15/3 mg resulted in the least apparent changes from baseline in the haemostatic parameters compared to EE/LNG and EE/DRSP, which is considered reassuring. The clinical significance of the effects on haemostatic parameters with regard to VTE risk can, however, only be hypothetical. The association with laboratory results, which are surrogate biomarkers, and VTE risk is weak. VTE is an established risk during use of a CHC and usually associated with the oestrogen content of the CHC. Altogether, no claims regarding the relative risk for VTE with Drovelis in comparison with other CHCs can be made based on the currently available data.

One drug-related additional serious TEAE of acute pancreatitis was reported as an error. The case was judged as not related to the study drug based on the absence of increased triglycerides, which is agreed.

In eight out of 39 on-treatment pregnancies, a spontaneous abortion occurred. None of the spontaneous abortions were considered related to study treatment. Five of the eight spontaneous abortions occurred during week 5-6 of pregnancy, which would be considered normal. No concern is raised based on the reported rate of spontaneous abortions.

Discontinuations due to adverse events

Overall, 9.4% of subjects in the ISS population discontinued the study due to a TEAE, and the TEAE was considered related to treatment with E4/DRSP in in 7.7% of subjects. The most common AEs leading to discontinuation were as expected for a CHC and included e.g. metrorrhagia, menorrhagia, dysmenorrhea, libido decreased, mood swings/depression, acne, headache/migraine and abdominal pain/nausea.

Special safety parameters

In non-clinical studies, some effects on lymphatic organs were seen (see Non-clinical Aspects). In the ISS population, the most frequent TEAEs were reported within the SOC "Infections and infestations". However, the overall frequency (21%) and the pattern of PTs within this SOC is not apparently different from what would be expected in a young, sexually active, female population. The most commonly reported PTs were viral upper respiratory tract infection and UVI, reported in about 3.9% and 2.5% of the ISS population, respectively. Other similar PTs included upper respiratory tract infection, viral respiratory tract infection, rhinitis, otitis. Vulvovaginal infections of different kind were commonly reported. The SAES reported within the SOC infections and infestations included appendicitis (2 cases), abscess limb, bacterial pyelonephritis, campylobacter gastroenteritis and parasitic infection (one case each). None of these were considered treatment related.

In the specific evaluation of endometrial safety, the findings were as expected for a CHC, with mostly atrophic or inactive endometrium.

Other special safety parameters that were investigated included effects on androgens, liver proteins, lipid metabolism, haemostasis (discussed above), bone parameters and cardiac effects. The data did not reveal any unexpected effects. In particular, the currently available clinical data do not indicate that the cardiac toxicity observed in non-clinical studies are clinically relevant.

Special populations

The pivotal Phase 3 studies included women from 18 years (Study C301) or 16 years (Study C302).

When safety data from the ISS population was analysed based on age, there were no apparent differences in distribution of TEAEs between subjects aged ≥16 – ≤35 years and subjects aged >35 – ≤50 years. Data are considered too limited to draw firm conclusions on the effect of weight/BMI, smoking status or race on the safety of E4/DRSP.

The currently proposed SmPC includes a warning in section 4.2 that efficacy and safety has not been established in paediatric patients < 16 years, which is adequate although it may be considered unlikely that the safety profile in post-menarcheal, sexually active women < 16 years differs relevantly from that in the current Phase 3 study population. A Phase 3 study in adolescent women 12-17 years of age is planned (PIP).

Known risks with CHCs in hepatic impairment and the potentially increased risk of hyperkaliaemia from DRSP in patients with renal impairment are handled by standard contraindications and warnings in the SmPC.

SmPC

Class effects of CHCs and the known risk of hyperkalaemia at treatment with DRSP are adequately handled in the proposed SmPC. Of note, no statements on the magnitude of the risk for thromboembolic events can be made based on the currently available data.

2.6.2. Conclusions on the clinical safety

The TEAE pattern at treatment with E4 15 mg + DRSP 3 mg, including the pattern of TEAEs leading to discontinuation, appears to be as expected for a CHC. The safety database is overall considered sufficient as a basis for providing relevant information in the SmPC, and the available clinical safety data does not give raise to any specific concerns regarding this new CHC.

No conclusions regarding the magnitude of the risk for/incidence of VTEs at treatment with E4/DRSP can be drawn based on available data. Additional post-marketing data is considered necessary in order to further characterise the risk. The CHMP considers the following measure necessary to address issues related to safety: a category 3, prospective non-interventional comparative cohort observational study, with a primary objective to characterize and compare the risks of E4/DRSP with COC-LNG in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is VTE, specifically DVT and PE.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Venous thromboembolism
	Arterial thromboembolism
Important potential risks	None
Missing information	Exposure during pregnancy

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
International Active Surveillance Study Prospective non-interventional comparative cohort observational study	Primary objectives To characterize and compare the risks of E4/DRSP with COC-LNG in a study population that is representative of the actual users of these preparations. The main clinical outcome of interest is VTE, specifically DVT and PE. Secondary objectives Measuring the occurrence of unintended pregnancy, assessing the risk of ATE, describing the drug utilization pattern, describing the baseline risk for VTE and ATE and investigating outcomes associated with fetal exposure to E4/DRSP	VTE ATE Exposure during pregnancy	Protocol submission	07/2021
			Start of study	EMA approval of protocol and medical drug commercially available
			Interim reports[1]	Annually (First Interim report: 12 months following start of data collection)
			Final report	7.5 years after EMA agreement on protocol (2029)

[1]To be harmonized with the PSURs, where applicable

Risk minimisation measures

Safety concern	Risk minimisation measures
Venous thromboembolism	Routine risk minimisation measures: *SmPC section 4.1, 4.3, 4.4, 4,6, 4.8* *PL section 2, 4* Additional risk minimisation measures: *Educational materials:* **Important information for women:** • *Information card for women* **Physician educational material:** • *Checklist for prescribers*
Arterial thromboembolism	Routine risk minimisation measures: *SmPC section 4.3, 4.4, 4.8* *PL section 2, 4* Additional risk minimisation measures: *Educational materials:* **Important information for women:** • *Information card for women* **Physician educational material:** • *Checklist for prescribers*
Exposure during pregnancy	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Additional risk minimisation measures: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.7 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.
The MAH submitted the summary of the pharmacovigilance system (dated: 12th September 2019 for Gedeon Richter Plc. for the Drovelis application, which fulfils the requirements of Directive 2001/83/EC, article 8 and GVP Module II revision 2, in the scope of this procedure in principle.

The summary includes the following elements:

- Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance
- The Member States in which the qualified person resides and carries out his/her tasks
- The contact details of the qualified person
- PSMF reference number

The Pharmacovigilance System Master File (PSMF) is located in Budapest, Hungary for Drovelis.

The CHMP, having considered the data submitted in the application, as well as observations of the Inspectors performing the Good Clinical Practice inspections in relation to the overall robustness of the quality management system and management of safety data, concluded that the assessments of the PSMF and PhV system raised no concern regarding the PhV system of Gedeon Richter.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

The PSUR frequency should be 6 months as it is the first time that the component estetrol is being used as estrogen in a combined hormonal contraceptive. Furthermore, the VTE/ATE risk of this combined hormonal contraceptive is still uncertain.

2.9. New Active Substance

The applicant compared the structure of estetrol with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

Based on the information provided by the applicant, it can be concluded that treatment with the applied substance estetrol monohydrate (E4) will not expose the patient to the same therapeutic moiety as an already authorised active substance in the EU. It has been satisfactorily addressed that E4 is not a prodrug or a metabolite of any other active substance in a medicinal product authorised in the EU. E4 is therefore not

considered as a derivative of an already approved substance based on the definition of the term 'derivative' given in the EMA reflection paper on new active substance (NAS) status (EMA/CHMP/QWP/104223/2015)]. Taken together, it considers that estetrol monohydrate (E4) is qualified as a NAS.

The CHMP, based on the available data, considers estetrol to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Drovelis (drospirenone/estetrol) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Combined oral contraceptives (COCs) are medicinal products that include two types of hormones, a progestin and an estrogen. The progestin primarily prevents pregnancy by decreasing luteinizing hormone (LH) secretion by the pituitary gland, which results in ovulation inhibition. The estrogen component also contributes to contraceptive activity by inhibiting follicle stimulating hormone (FSH) and LH secretion, thereby impacting ovarian follicle development. However, its major function in combined hormonal contraception is to balance the effects of the progestin on the endometrium to provide an acceptable bleeding pattern during the use of a COC.

The claimed indication is oral contraception. The fixed dose combination of drospirenone 3 mg / estetrol monohydrate 15 mg/ (DRSP/E4 3/15 mg) is to be used in a 24 days active treatment and 4 days placebo regimen. The new COC contains the estrogen E4 in combination with the progestin DRSP.

E4, a natural estrogen produced by the liver in the human foetus during pregnancy only. E4 reaches the maternal circulation through the placenta. DRSP is a well-characterized and widely used progestogen in other COCs combined with EE (Yasmin, Yaz) that are on the EU market since 2000.

3.1.2. Available therapies and unmet medical need

Several contraceptive methods for use by females are already available, both hormonal and non-hormonal. However, since women have different needs and experiences (e.g. side effects, and poor bleeding patterns) with some methods, there can still be a place for a new combined hormonal contraceptive even if there is no large unmet medical need.

Recent figures show that contraceptive use is above 70% in Europe, and Northern America (WHO, Contraception, Evidence brief 2019). Combined oral contraception (COC) is used by over 20% of women of reproductive age in 27 countries worldwide, with the highest prevalence in European countries (United Nations, Contraceptive Use by Method 2019, data booklet).

The choice of available contraceptive methods has increased in recent years. COC, first introduced in the 1960s, remains the method of choice for many women in Europe and the US. COCs are generally classified by 'generations', reflecting the point in time when they were developed and authorised for use. The first generation of contraceptive pills, developed in the 1960s, used a high concentration of oestrogen sometimes with a progestogen component. Later, a second generation of hormonal contraceptives was introduced. These medicines combined lower levels of oestrogens with various progestogens in different concentrations, often levonorgestrel. Since the late 1980s, further COC products with different progestogens have been developed, i.e. the third generation COCs, containing desogestrel or gestodene. In the nineties, norgestimate and dienogest-containing COCs were approved, which were not clearly categorized into a particular generation.

Since 2000, the first COC product with DRSP was introduced, EE/DRSP 0.03 mg/3 mg (Yasmin), and can be called a fourth generation pill. The second DRSP-containing COC, EE/DRSP 0,03 mg/3 mg with a different dose

regimen (Yaz), was registered in 2007. In recent years, some new contraceptives have been developed, for which estradiol is used and not EE, and dosing regimen (Zoely, Qlaira).

Next to COC, a combined hormonal contraceptive vaginal ring (NuvaRing) and a combine hormonal contraceptive patch are approved in the EU.

All combined hormonal contraceptives have the same contraceptive efficacy, i.e. a Pearl index below 1.

Other forms of hormonal contraception are the progestogen-only contraceptives. Levonorgestrel-containing IUD (Mirena) and the etonogestrel-containing implant (Implanon) are considered two of the most effective forms of hormonal contraception, as they are not dependent of treatment-compliance.

The high EE-dosed early contraceptives were associated with a variety of side-effects, including some rare but serious venous thrombotic effects. To improve the clinical profile, the EE dose was reduced step-wise and more selective progestins were developed. The activity of the newer progestins also allowed further EE dose reduction. However, reductions of EE dose are associated with less acceptable bleeding profiles.

More recently, use of more natural hormones has been attempted with the goal of further improving the safety profile of CHCs, with a potentially less impact on haemostasis, lipid and carbohydrate metabolism compared to their synthetic analogues.

3.1.3. Main clinical studies

The application for E4/DRSP is supported by two Phase 3, multi-centre, open-label, single-arm studies; Study MIT-Es0001-C301 (conducted in Europe/Russia) and Study MIT-Es0001-C302 (conducted in the US/Canada).

The studies included heterosexually active females at risk for pregnancy and requesting contraception, and who were willing to use the investigational product as the primary method of contraception for 13 consecutive cycles. The women were aged 18 to 50 years (inclusive) in Study C301 and 16-50 years in Study C302. Eligible subjects were treated with 15 mg E4/3 mg DRSP for a maximum of 13 consecutive cycles. The treatment was to be taken once daily in a 24/4-day regimen, i.e., 24 active tablets followed by 4 placebo tablets (4-day hormone-free interval). In Study C301, the ITT population comprised 1553 subjects and in C302 1864 subjects.

The studies had a non-comparative, open-label single arm design, hence, there were no objectives related to superiority or non-inferiority and randomisation and blinding were not necessary.

3.2. Favourable effects

Dose confirmation study results (MIT-ES0001-C202 and ES-C02) suggest that the E4/DRSP 15/3 mg 24/4 regimen may provide as acceptable contraceptive efficacy as the already marketed product EE/DRSP 0,02/3 mg (YAZ) as well as an adequate bleeding pattern, in comparison with Qlaira.

In **Study C301**, five on-treatment pregnancies resulted in a Pearl Index of **0.44** (95% CI: 0.14, 1.03) in subjects aged 18 to 35 years with at-risk cycles; the primary efficacy variable. The corresponding PI in the whole age group (18-50 years) was **0.38** (95% CI: 0.12, 0.89).

Several other Pearl index values were also presented. The 'typical use' PI (in which all cycles are included in the denominator regardless of other methods of birth control, occurrence of sexual intercourse or compliance with the protocol) in the 18-35-year-old age group was **0.42** (95% CI: 0.14, 0.99). These Pearl index values were all low and comply with the requirement for precision in accordance with the EMA Guideline on Steroid

Contraceptives, since the difference between the upper limit of the corresponding 2-sided 95% CI for the Pearl Index and the point estimate was < 1.

Life-table analyses (based on Kaplan-Meier estimates) were consistent with the Pearl Index results.

In **study C302**, 28 on-treatment pregnancies resulted in a Pearl Index in subjects aged 16 to 35 years with at-risk cycles, of **2.42** (95% CI: 1.58, 3.54).

In the whole group (up to 50 years of age) and with alternative calculation methods, the Pearl Indices ranged from **2.09 to 2.52**. The PI for Method failure was **1.30** (95% CI 0.71, 2.18) for the age group 16-35 years and **1.32** (95% CI 0.75, 2.14) for the whole study population, both with acceptable precision according to the EMA guideline.

The bleeding pattern was overall acceptable and as expected for a CHC. Less than 20% of women reported unscheduled bleeding with a tendency of improvement over the year. The vast majority of women reported scheduled bleeding, occurring in association with the hormone-free days. Few women (around 3%) discontinued for bleeding/spotting related adverse events.

3.3. Uncertainties and limitations about favourable effects

It was not clearly mentioned in the inclusion criteria of both studies whether women had established ovulatory cycles. The women were not checked for having ovulatory cycles due to low feasibility, but it was sufficiently clarified that the approach of including heterosexually active female at risk for pregnancy, with 'at risk' to be judged by the investigator on clinical grounds, comes closest to clinical practice of prescribing women a CHC.

In the US/Canadian study C302, the total number of pregnancies was higher than in Study C301. Of the 28 on-treatment pregnancies, twelve pregnancies were considered user failures and 16 Method Failures.

The requirement for precision of the PI (**2.42**, **95% CI: 1.58, 3.54** was not met in accordance with the EMA Guideline on Steroid Contraceptives, since the difference between the upper limit of the corresponding 2-sided 95% CI for the Pearl Index and the point estimate was > 1. Also for the PI values in the whole group (up to 50 years of age) and with alternative calculation methods, the difference between the PI point estimates and the upper limit of the corresponding 2-sided 95% CIs was in most cases above 1.

The defined primary Pearl index value as well as the secondary PIs were higher in the US/Canadian study C302 compared with the European/Russian study C301. Although a similar pattern has been observed for other hormonal contraceptives, i.e. a higher Pearl index in studies performed in the US compared with studies performed in the EU, the Applicant was asked to discuss and explain these results. This difference has been the subject of many reviews with different outcomes. Amongst others, less adherence is most often indicated, as is also briefly pointed out by the Applicant. However, the Applicant was requested to present a thorough review of recent public literature reflecting the latest insights on this discrepancy in Pearl Indices between the US and Europe. The Applicant refers to non-compliance as one of the main factors impacting the efficacy of oral contraceptives in clinical trials. This would fit with the observation from literature data that for user-independent contraceptive methods (e.g. IUDs), the PI difference was small or absent.

Although it should be noted that the sample size of the phase 3 study was much greater and duration was twice as long, i.e. 13 cycles, the phase 3 trial data on cycle control show a slightly better bleeding profile, as compared with the findings of cycle 6 of the comparative phase 2 dose-finding and selection study on cycle control

(ES-C02). An indirect comparison of the bleeding pattern endpoints between phase 3 and phase 2 studies including a comparison with bleeding patterns observed for COCs used for active controls. showed that cycle control of E4/DRSP 15/3 mg was similar in the phase 2 and the phase 3 studies. Further, although data should be interpreted with caution, as subject numbers are small, cycle control was most favourable for E4/DRSP 15/3 mg as compared to the other E4 combinations and the approved CHC (EV/DNG) used as active control. This supports the conclusion that E4/DRSP 15/3 mg demonstrates adequate cycle control, as shown by a bleeding pattern with a low percentage of unexpected breakthrough bleeding/spotting and a low incidence of missed scheduled bleeding (i.e. high percentage of withdrawal bleeding).

Sub-group analyses based on integrated data for the two studies as well as for each study separately showed that for BMI, a trend was observed for an increase of the Pearl Index with increasing BMI. Smokers also tended to have higher PI vs. non-smokers. Black and Asian women had higher Pearl Index compared to white women and a higher Pearl Index was observed in starters compared to switchers. Firm conclusions are difficult to make due to small sample sizes for some subgroups resulting in wide confidence intervals.

Follow-up of pregnancies was not complete at time of CSR finalization in all cases, but further data have been provided. These do not give cause for concern, however, due to re-categorizations of some pregnancies, confirmation was requested that these amendments did not have any impact on the study outcomes, taking into account the Pearl Indices of the studies. It was confirmed that these corrections did not impact the calculations of the Pearl Indices.

The outcome of the requested GCP inspection was that, despite some findings, the conclusion was that the data obtained at the sites inspected are reliable and can be accepted as support of the Marketing Authorisation Application submitted to the EMA for approval.

3.4. Unfavourable effects

The pooled safety population consisted of subjects from studies designed to include at least three cycles of E4 at 15 mg + DRSP at 3 mg, i.e. the two phase 3 studies (MIT-Es0001-C301; MIT-Es0001-C302) or in three phase 2 studies (MIT-Es0001-C201; MIT Es0001-C202; ES-C02). In total, the pooled safety population included 3,574 subjects who were confirmed treated with 1 to 13 cycles of E4 15 mg + DRSP 3 mg.

The clinical safety database is overall considered sufficient as a basis for providing relevant information in the SmPC and RMP, and the available clinical data does not give raise to specific concerns regarding this new CHC. The TEAE pattern at treatment with E4 15 mg + DRSP 3 mg, including the pattern of TEAEs leading to discontinuation, appears similar to what is known for other CHCs and what would be expected from the mode of action an oestrogen and a progestogen.

The most commonly reported AEs were from the system organ classes (SOCs) infections and infestations, reproductive system and breast disorders, gastrointestinal disorders, psychiatric disorders and nervous system disorders.

The SOC within which the highest frequency of *treatment-related* TEAEs was reported was Reproductive system and breast disorders (15.8%). Psychiatric disorders that were considered treatment-related were reported in 5.6% of subjects. The most commonly reported treatment-related preferred terms (PTs) were metrorrhagia (4.3%), headache (3.2%), acne (3.2%), vaginal haemorrhage (2.7%), dysmenorrhea (2.4%), breast pain

(2.1%), weight increased (2.0%), breast tenderness (1.8%), libido decreased (1.5%), nausea (1.4%), menorrhagia (1.3%) and mood swings (1.3%).

In only 10% of the subjects (n=398), discontinuation was due to a medical reason, which is considered low. This included TEAEs (n=356, 9.4%) of which 2.8% were related to vaginal bleeding (n=106). Other medical reasons included pregnancy (n=41, 1.1%; n=8 pre-treatment; n=33 on-treatment) and death (n=1, 0.03%). No relevant safety concerns have been identified from these data.

A total of 45 serious TEAEs were reported in 41 subjects (1.1%) in the pooled Phase 3 and Phase 2 studies. The incidence of serious TEAEs can be considered low with 1.1%, of which only a few (n=3, 0.1%) were considered related to E4/DRSP 15/3 mg. These concerned one case each for ectopic pregnancy, (worsening of) depression, and venous thrombosis. The latter two are known safety events with the use of CHCs. One subject died due to a fatal serious TEAE of accidental drug overdose with fentanyl and alprazolam, which was considered unlikely related to E4/DRSP.

Regarding thromboembolic events, one case of VTE was reported in the pooled safety population (<0.05% of subjects), which was considered possibly related to the study drug. Another VTE was reported in a postmenopausal woman who participated in a phase 1 study, who received a high dose of E4 75 mg monotherapy. This case was considered possibly related to the high E4 dose. As all CHCs are associated with an increased risk of venous thromboembolism, the event is not unexpected.

The effect on existing acne in a subgroup of patients was evaluated in the comparative PD study versus EE/LNG and EE/DRSP. Although differences were small and data should therefore be interpreted with caution, the effect of any worsening of acne in the DRSP groups appeared to be smaller than in the LNG groups and there seemed to be an improving effect in the DRSP groups. However, no specific claim have been made on acne in the SmPC, and acne is included in section 4.8 of the SmPC as an adverse event.

Despite the marked effect on lymphatic organs in some non-clinical studies, the frequency and pattern of infections observed in the ISS population was not apparently different from what would be expected in a young, sexually active, female population and does not give raise to concern. The most commonly reported PTs were viral upper respiratory tract infection and UVI, reported in about 3.9% and 2.5% of the ISS population, respectively. Other similar PTs included upper respiratory tract infection, viral respiratory tract infection, rhinitis, otitis. Vulvovaginal infections of different kind were commonly reported. The SAES reported within the SOC infections and infestations included appendicitis (2 cases), abscess limb, bacterial pyelonephritis, campylobacter gastroenteritis and parasitic infection (one case each). None of these were considered treatment related.

During the non-clinical development, a potential impact of E4/DRSP on cardiac function was highlighted, with cases of interstitial fibrosis and hypertrophy reported in cynomolgus monkeys. The effects were suggested to be species-specific. However, based on these data, a close follow-up of cardiac changes was performed in the clinical studies by monitoring parameters indicative of these changes. Laboratory parameters of cardiac fibrosis (LDH 1, LDH 2 and troponin), ECG and echocardiography appeared not to be influenced by treatment E4/DRSP 15/3 mg. The three subjects with abnormal results at screening all recovered by the end of the study.

3.5. Uncertainties and limitations about unfavourable effects

Drovelis contains a new oestrogen, E4. The available clinical data indicate that the AE profile is as expected for a low-dose, combined oestrogen and progestogen, and the safety database is overall considered sufficient for approval. However, the data is not considered sufficient to draw any conclusions on the magnitude of the risk for VTE, as compared with other CHCs.

PD studies have shown that effects on haemostatic balance were less pronounced with E4/DRSP in comparison with EE 003 mg/LNG 0.150 mg and EE 0.03 mg/DRSP 3mg, with the latter CHC having the most pronounced effects. However, as none of the haemostatic parameters assessed in the PD studies is validated for the clinical endpoint of VTE, no conclusions can be drawn from these data. The currently available clinical safety database is too small to draw conclusions regarding the magnitude of the risk for/incidence of VTEs at treatment with E4/DRSP. VTE and ATE are included in the RMP as identified risks and will be followed in future PSURs, but in order to better estimate the magnitude of the risk of thromboembolic events, a PASS study is agreed by the Applicant.

3.6. Effects Table

Table 30. Effects Table for Drovelis

Favourable Effects						
Effect	**Short Description**	**Unit**	**15 mg E4/ 3 mg DRSP**	**Control**	**Uncertainties/ Strength of evidence**	**References**
PI	Pearl index (in subjects aged 18 to 35 years with at-risk cycles)	N/A	**0.44**	N/A	95% CI: 0.14, 1.03	Study C301
PI	Pearl index (in subjects aged 16 to 35 years with at-risk cycles)	N/A	**2.42**	N/A	95% CI: 1.58, 3.54	Study C302
PI	Method failure Pearl index (in subjects aged 18 to 35 years with at-risk cycles)	N/A	**0.26**	N/A	95% CI: 0.05, 0.77	Study C301
PI	Method failure Pearl index (in subjects aged 16 to 35 years with at-risk cycles)	N/A	**1.30**	N/A	95% CI: 0.71, 2.18	Study C302
Unfavourable Effects						

Effect[1)]	Short Description	Unit	15 mg E4/ 3 mg DRSP	Control	Uncertainties/ Strength of evidence	References
Reproductive system and breast disorders	Main PTs[2)]: metrorrhagia (4.3%), vaginal haemorrhage (2.7%), dysmenorrhea (2.4%), breast pain (2.1%)	%	15.8	N/A	Considered as class effect	ISS population[3)]
Psychiatric disorders	Incl. e.g. mood disorders, libido disturbances, depression, anxiety disorder (each < 2%)	%	5.6	N/A	Considered as class effect	ISS population
Nervous system disorders	Main PT: headache (3.2%)	%	4.5	N/A	Considered as class effect	ISS population
Skin and subcutaneous tissue disorders	Main PT: Acne (3.2%)	%	4.1	N/A	Considered as class effect	ISS population
Gastrointestinal disorders	Incl e.g. abdominal pain, nausea (each < 2%)	%	3.6	N/A	Considered as class effect	ISS population
Investigations	Main PT: Weight increase (2%)	%	3.2	N/A	Considered as class effect	ISS population
VTE		n	2	N/A	Considered as class effect. No epidemiological data available.	All clinical studies

Abbreviations: PI: Pearl index
[1)] SOCs reported in ≥2% of the ISS population are listed
[2)] Main PTs = PTs reported in ≥ 2% of the ISS population
[3)] ISS population included subjects receiving E4 15 mg/DRSP 3 mg for at least three cycles in studies MIT-Es0001-C301, MIT-Es0001-C302, MIT-Es0001-C201, MIT-Es0001-C202, and ES-C02.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The contraceptive efficacy results in Study C301 show that E4/DRSP is a combined hormonal contraceptive with low Pearl index. This was true for all definitions of Pearl index, including the Method failure PI, as well as for the group of women 18-35 years and the whole study population up to 50 years of age. The precision in the PI estimates was high, thus, fulfilling the requirements in the EMA guideline.

In study C302 on the other hand, the primary PI as well as other Pearl indices were much higher and had lower precision, not fulfilling the EMA guideline requirements.

The bleeding pattern was overall acceptable and as expected for a CHC. The use of E4/DRSP 15/3 mg appeared to be associated with a predictable vaginal bleeding pattern, with a majority of women having their scheduled bleedings each cycle without experiencing unscheduled bleeding requiring the use of sanitary protection. These findings are highly relevant for the woman's treatment compliance and continuation. Although no formal phase 3 comparison was performed, cycle control thus seems comparable to or even slightly better than other, such as commonly used EE-containing COCs.

The TEAE pattern at treatment with this new oestrogen and DRSP, including the pattern of TEAEs leading to discontinuation, appears similar to what is known for other CHCs and what would be expected from the mode of action an oestrogen and a progestogen. Further, studies into cardiac function did not show a clinical effect on ECG parameters, including QTc interval length, and no trends in routine haematology and blood biochemistry were observed. Also, the patient's well-being was not found to be affected by the use of E4/DRSP 15/3 mg.

The known risks with CHCs are described in the SmPC and are considered manageable by routine risk minimisation, including the risk for VTE. The available clinical safety database as presented does therefore not give raise to any objections against approval. However, the currently available database is too small to draw conclusions on the risk for VTE in comparison with other CHCs and cannot support any claims regarding the magnitude of this risk.

3.7.2. Balance of benefits and risks

A clinically relevant contraceptive efficacy has been demonstrated, at least in the EU/Russian study C301. This study was sufficiently large to demonstrate a Pearl index of adequate precision. The bleeding pattern is acceptable. The AE profile appears similar to other CHCs and the clinical safety profile is overall not concerning. The known risks with CHCs can be managed by routine pharmacovigilance measures. The VTE risk for this new CHC will be characterised post-marketing in a PASS. Altogether, on clinical grounds no major issues have been identified that preclude conclusions on the balance of benefits and risks at the present time. Furthermore, in the GCP inspection it was concluded that the data obtained at the sites inspected are reliable and can be accepted as support of the Marketing Authorisation Application submitted to the EMA for approval.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Drovelis is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Drovelis is favourable in the following indication:

"Oral contraception.

The decision to prescribe Drovelis should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Drovelis compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4)."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to the launch of Drovelis in each Member State, the Marketing Authorization Holder (MAH) will agree about the content and format of the educational material, including communication media, distribution modalities and any other aspects of the programme with the National Competent Authority.

The educational materials are aimed at providing guidance on how to manage risk of thromboembolic events.

The MAH shall ensure that in each Member State where Drovelis is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use the product have access to:

- Prescriber's checklist;
- Information card for women.

The prescriber's checklist should aim at initiating a discussion between the prescriber and woman to assess their suitability to receive Drovelis, particularly with respect to the presence of any contraindications or risk factors for thromboembolic events.

The prescriber's checklist should contain the following key elements:

- points to cover in the consultation (risk of thromboembolism with the CHC, effect of intrinsic risk factors, to be alert for signs and symptoms of a thrombosis);
- checklist of contraindications;
- checklist for risk factors;
- reminder to inform women of situations when the risk of thromboembolism is increased and to advise women to tell healthcare professionals that they are taking a CHC.

The Information card for women is provided as part of the product packaging, the text of which is included in Annex III. The Information card for women aims to provide women with information on the risk of thromboembolism associated with combined oral contraceptive pills, the known risk factors, as well as signs and symptoms of venous and arterial thromboembolism and to emphasize the significance of the early detection of any thromboembolic event.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that estetrol is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0478/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.