LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kelzyn
(ethinylestradiol, dienogest)

SE/H/2381/01/DC

This module reflects the scientific discussion for the approval of Kelzyn. The procedure was finalised on 2024-02-28. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Kelzyn, 2 mg/0,02 mg, Prolonged-release tablet.

The active substance are ethinylestradiol and dienogest. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Dienogest/Ethinylestradiol (DNG/EE), 2 mg/0.02 mg, Prolonged-release tablet (LPRI-424), is a complete application submitted according to Article 8(3) of Directive 2001/83/EC (known active substance). The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and these CMSs:
SE/H/2381/01/DC: DK, FI, NO
The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

Paediatric Regulation
Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision [P/0092/2022] on the agreement of a paediatric investigation plan (PIP). The applicant has obtained a partial PIP waiver for some subsets of the paediatric population.
At the time of submission of the application, the PIP [EMEA-002229-PIP01-17] was not yet completed as some measures were deferred.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substances have been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of dienogest (DNG) and ethinylestradiol (EE) are well known. As DNG and EE are widely used, well-known active substances, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate. There are no objections to approval of LPRI-424 from a non-clinical point of view.

Environmental Risk Assessment (ERA)
Regarding the ERA, both DNG and EE are endocrine active substances, with a mechanism of action of relevance to reproduction. Therefore, a tailored phase II Tier A assessment that addresses the specific mechanism of action for each substance is required according to the Q&A on CHMP 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010). As the submitted ERA(s) for the product(s) were not complete (e.g., for EE Phase IIA and IIB assessment, for DNG missing OECD TG106 and OECD TG209 studies, the most sensitive aquatic toxicity study and NOEC/LOEC value remains to be determined, incomplete Phase IIB assessment), the applicant has committed to submit a new ERA within 2 years post-approval for the product Dienogest / Ethinylestradiol 2/0.02 mg prolonged-released Tablets. A Letter of Access to existing relevant ERA's would also be acceptable within this context.

Table 1. Summary of main study results and calculations for dienogest (DNG).

Substance (INN/Invented Name): dienogest			
CAS-number (if available): 65928-58-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential - log K_{ow}		log K_{ow} =	Potential PBT? Study report pending
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		Not B
	BCF		
Persistence	DT50 or ready biodegradability	DT50 total system > 120d Not readily biodegradable	P
Toxicity	NOEC fish	< 0.01 mg/L	T
PBT-statement:	Not PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$ default	0.01	µg/L	> 0.01 threshold (Y)
Other concerns (e.g., chemical class)			EAS, sex hormone

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD TG106	K_{oc} sludge 1 = K_{oc} sludge 2 = K_{oc} soil 1 = K_{oc} soil 2 = K_{oc} soil 3 =			Study report pending
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50, water}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Study report pending
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG 201 Cited report in Fass	EC10 Growth rate	>16.3	mg/L	*Desmodesmus subspicatus*
Daphnia sp. Reproduction Test	OECD TG 211 Cited report in Fass	NOEC	≥ 491	µg/L	*D. magna*
Fish,		NOEC	pending	µg/L	Study report pending
Activated Sludge, Respiration Inhibition Test	OECD TG 209			mg/L	pending
Phase IIb Studies					
Sediment dwelling organism	OECD TG 218	EC10 Developmental rate	44	mg/kg dry sediment	pending

NA = Not applicable

Table 2. Summary of main study results and calculations for ethinylestradiol (EE)

Substance (INN/Invented Name): ethinylestradiol			
CAS-number (if available): 57-63-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential - log K_{ow}		log K_{ow} =	Potential PBT Y Study report pending
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		
	BCF		
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC fish	< 0.01 mg/L	T
PBT-statement:	Not PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$ default	0.0001	µg/L	> 0.01 threshold (N)

Other concerns (e.g., chemical class)					EAS, sex hormone
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD TG106	K_{oc} sludge 1 = K_{oc} sludge 2 = K_{oc} soil 1 = K_{oc} soil 2 = K_{oc} soil 3 =			Study report pending
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50, water}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Study report pending
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG 201	EC10 Growth rate		mg/ L	Study report pending
Daphnia sp. Reproduction Test	OECD TG 211	NOEC		µg/L	Study report pending
Fish,		NOEC		µg/L	Study report pending
Activated Sludge, Respiration Inhibition Test	OECD TG 209			mg/ L	Study report pending
Phase IIb Studies					
Bioconcentration test					Study report pending
Sediment dwelling organism	OECD TG 218			mg/ kg dry sed.	

NA = Not applicable

Conclusions on the ERA

The reported data indicate risks to the aquatic environment for both DNG and EE but as a consequence of the above-mentioned issues, it is currently not possible to draw conclusions on the PBT potential or risks of DNG or EE to the environment.

IV. CLINICAL ASPECTS

I.1.1 Pharmacokinetics

Two pharmacokinetic studies were submitted with the applied prolonged-release tablet, one single-dose food effect study (LPRI-424/102) and one multiple-dose relative bioavailability study (LPRI-421/101). In addition, sparse PK sampling was performed in a phase III study. A population PK analysis was performed including data from the two PK studies (LPRI-421/101 and LPRI-424/102) and from the phase III study (LPRI-424/301). No human in vitro studies have been submitted. Data on PK characteristics, special populations and interactions from the literature and other products containing DNG, EE or its combination have been included to supplement the data from the clinical trials.

Absorption

Ethinylestradiol has an oral bioavailability of about 45% and dienogest has an oral bioavailability of over 90%.

A single dose food effect study (Study LPRI-424/102) was conducted with the prolonged-release tablets DNG 2 mg/ EE 20 µg. The plasma exposure of dienogest and ethinylestradiol following single-dose administration in the fasted and fed state are shown in Table 3 and Table 4. There was no food effect observed for the prolonged release formulation (2 mg dienogest and 20 µg ethinylestradiol) in the single dose study following intake of a standard high-fat breakfast 30 minutes before administration compared to fasted state.

Table 3. PK endpoints of dienogest following single-dose in the fasted and fed state (Study LPRI-424-102).

Test	Variable	Geom. mean	Arithm. mean	SD	CV	Range	Median	N
'A' under fasting conditions	$AUC_{(0-72h)}$ [ng*h/mL]	596.98	604.64	103.60	17.1	483.24 - 859.36	600.16	18
	C_{max} [ng/mL]	38.04	38.78	7.90	20.4	26.77 - 54.69	38.45	18
	t_{max} [h]	-	4.038	0.695	17.2	3.000- 6.000	4.017	18
'B' under fed conditions	$AUC_{(0-72h)}$ [ng*h/mL]	616.17	626.36	120.75	19.3	435.97 - 938.03	594.21	18
	C_{max} [ng/mL]	43.44	44.08	7.70	17.5	30.21 - 58.36	44.76	18
	t_{max} [h]	-	3.254	0.814	25.0	1.500 - 4.533	3.000	18

Abbreviations: $AUC_{(0-72h)}$=Area under the concentration-time curve from 0-72h; C_{max}=Maximum observed plasma concentration; t_{max}=Time until C_{max} is reached; CV=Coefficient of variance; DNG=Dienogest; EE=Ethinyl estradiol; h=Hour; N=Number; SD=Standard deviation

Source: Table TT 1 in section 2 of study report LPRI-424/102

Table 4. PK endpoints of ethinylestradiol following single-dose in the fasted and fed state (Study LPRI-424/102).

Test	Variable	Geom. mean	Arithm. mean	SD	CV	Range	Median	N
'A' under fasting conditions	$AUC_{(0-72h)}$ [pg*h/mL]	454.85	483.11	169.34	35.1	241.40 - 788.22	479.39	18
	C_{max} [pg/mL]	30.32	32.42	12.11	37.4	11.69 - 57.77	29.33	18
	t_{max} [h]	-	4.255	0.550	12.9	3.000- 5.017	4.500	18
'B' under fed conditions	$AUC_{(0-72h)}$ [pg*h/mL]	484.82	510.45	162.84	31.9	269.29 - 781.86	514.16	18
	C_{max} [pg/mL]	32.02	33.50	10.07	30.1	18.53 - 51.11	33.82	18
	t_{max} [h]	-	3.754	0.943	25.1	2.000 - 5.000	4.250	18

Abbreviations: $AUC_{(0-72h)}$=Area under the concentration-time curve from 0-72h; C_{max}=Maximum observed plasma concentration; t_{max}=Time until C_{max} is reached; CV=Coefficient of variance; DNG=Dienogest; EE=Ethinyl estradiol; h=Hour; N=Number; SD=Standard deviation

Source: Table TT 2 in section 2 of study report LPRI-424/102

A multiple-dose study (LPRI-421/101) was performed comparing the plasma exposure following administration of different strengths of the prolonged-release tablet (of which one was the strength applied for-test 1; 2 mg dienogest/20µg ethinylestradiol) with an immediate-release formulation. The results are shown in Table 5, Figure 1 and Figure 2. In comparison to the immediate release formulation, Tmax was observed later, 3.8 hours (PR, 2 mg dienogest/ 20 µg ethinylestradiol) compared to 1.3 hours (IR, 2 mg dienogest/ 30 µg ethinylestradiol) for both dienogest and

ethinylestradiol. The fluctuations in drug concentrations at steady state was lower following prolonged release formulation compared to immediate release formulation for both dienogest and ethinylestradiol. The AUC0-24h was similar for dienogest but the Cmax was lower following repeated administration of prolonged release formulation compared to immediate release formulation with the same strength of 2 mg. For ethinylestradiol, the strengths differed and both the AUC_{0-24h}, C_{max} and Cmin was lower for the prolonged release formulation (20 µg) compared to the immediate release formulation (30 µg).

Table 5. Study LPRI-421/101: Mean plasma concentration of DNG and EE prior to tablet intake over 7 days of daily treatment

	AUC_{0-24h}	C_{AV}	C_{max}	C_{min}	PTF (%)	T_{max} (h)
DNG (ng*h/mL)						
Test 1	731.6	30.5	59.3	12.5	156.02	3.75
Test 2	366.5	15.3	28.6	6.7	147.28	3.857
Test 3	735	30.6	56.2	14.3	139.76	3.754
Reference	720.3	30	75.4	11.6	219.62	1.321
EE (pg*h/mL)						
Test 1	706.3	29.4	63.6	14.9	164.14	3.754
Test 2	351.9	14.7	32.3	7.8	169.05	3.571
Test 3	338.4	14.1	33.2	7.8	180.22	3.468
Reference	1072.8	44.7	135.2	20.8	258.03	1.345

Test 1=DNG 2 mg /EE 20 µg PR; Test 2=DNG 1 mg /EE 10 µg PR; Test 3=DNG 2 mg /EE 10 µg PR; Reference product=DNG 2 mg /EE 30 µg IR. (N=14).
Abbreviations: AUC(0-24h)=Area under the concentration-time curve from 0-24h; C_{AV}=Average concentration during dosing interval of length $\tau\tau$ (steady state); C_{max}=Maximum observed plasma concentration; C_{min}=Minimum observed plasma concentration; DNG=Dienogest; EE=Ethinyl estradiol; PTF=Peak-trough fluctuation; T_{max}=Time until C_{max} is reached.
Source: Table 22 to Table 39 and Table 62 to Table 78 in section 14.2.3.1 of study report LPRI-421/101

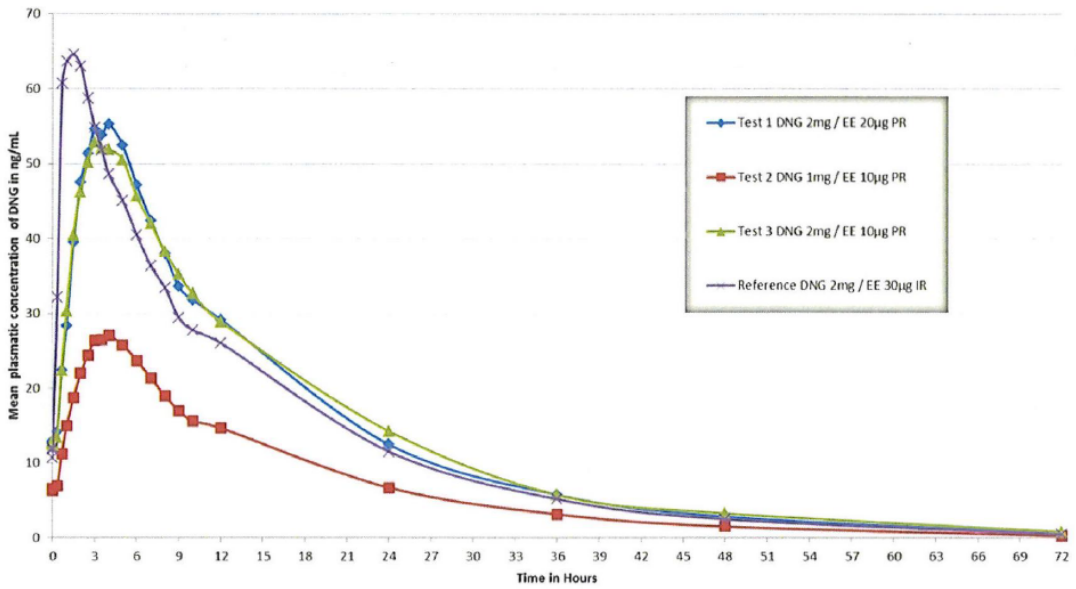


Figure 1. Study LPRI-421/101: Mean DNG plasma concentration compared to reference.

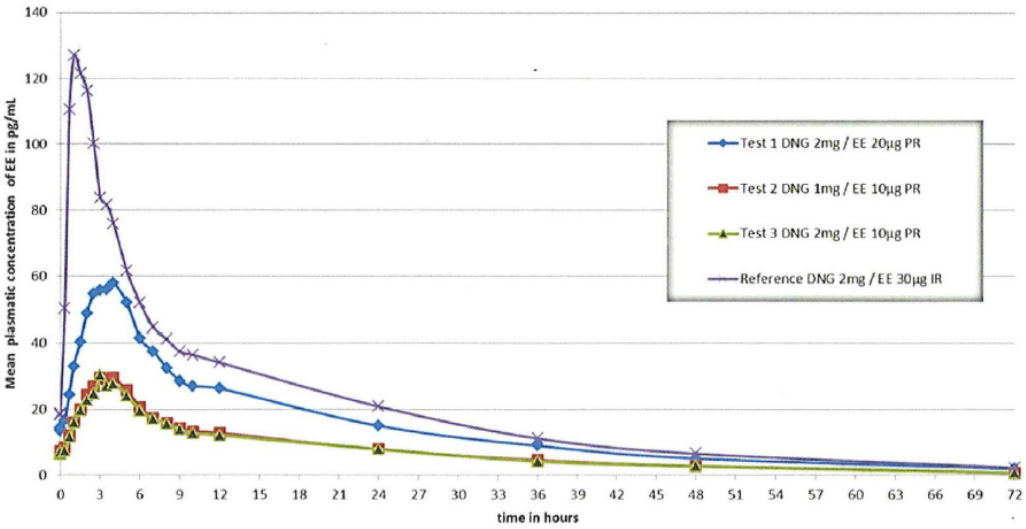


Figure 2. Study LPRI-421/101: Mean EE plasma concentration compared to reference.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98%) and induces an increase in the serum concentrations of SHBG (sex hormone-binding globulin). Dienogest is bound to serum albumin and does not bind to SHBG or corticoid binding globulin (CBG). The apparent volume of distribution of dienogest is about 40 L after a single oral dose of 1 mg.

Elimination

Ethinylestradiol serum levels decrease in 2 phases characterized by half-lives of about 1 hour and 10–20 hours, respectively. Hydroxylation of ethinylestradiol is catalyzed by cytochromes of the CYP2C, CYP2E and CYP3A gene families, being CYP3A4 the most important. Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronides and sulfate. Ethinylestradiol is not excreted in unchanged form. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The elimination half-life of the metabolites is about one day.

Dienogest is a substrate of cytochrome P450 (CYP) 3A4. Dienogest is metabolized predominantly through hydroxylation and conjugation, with the formation of endocrinologically largely inactive metabolites. These metabolites are very quickly cleared from plasma so that in human plasma no important metabolite is observed besides unchanged dienogest. The serum clearance of dienogest is ~ 64 mL/min, and the $T_{1/2}$ for excretion of urinary metabolites is ~ 14 hours. Most of the metabolites are eliminated in the first 24 hours, and approximately 86% of the administered dose is eliminated within 6 days.

Special populations

The prolonged release formulation has not been studied in patients with renal or hepatic impairment. Oestrogens and oral contraceptives are both associated with several liver related complications and the

product is contraindicated in women with severe hepatic impairment. No other dose recommendations are suggested in patients with impaired renal or hepatic impairment.

I.1.2 Pharmacodynamics

The contraceptive effect of DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet is based on the interaction of various factors, the most important are the inhibition of ovulation and changes in cervical mucus.

Dienogest has no glucocorticoid, no anti-mineralocorticoid activity and no antiestrogenic activity. The combination of dienogest and ethinylestradiol has minor influences on lipid and carbohydrate metabolism, adrenal hormones, blood pressure, serum parameters and appears to have a balanced effect on the haemostatic system, based on literature data.

The performed Phase 2 study evaluated inhibition of ovulation by three different doses of DNG/EE. The product proposed for marketing, DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet (87-day treatment period) inhibited the ovarian activity most effectively of the tested doses, inducing 100% inhibition of ovulation and resulted in no or minimum ovarian activity in the largest number of subjects (per Hoogland score).

Both substances have been used in contraceptive settings before, but not in the proposed dose combination and prolonged release formulation.

I.1.3 Discussion on Clinical Pharmacology

Pharmacokinetics

According to Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Rev1) the pharmacokinetics should be characterised for a new modified release formulation and a comparison with an immediate-release formulation should be performed following single-dosing and if there is accumulation also following repeated dosing. In addition, influence of food on the bioavailability of the prolonged-release formulation must be investigated in a single dose study. A comparison with an immediate-release formulation was performed only in the multiple-dose study (study LPRI-421/101). The results for both dienogest and ethinylestradiol showed a lower fluctuation in drug concentrations at steady state and a later t_{max} of 3.8 hours for the prolonged release formulation compared to the immediate release formulation (t_{max} 1.3 hours). The single-dose study (LPRI-424/102) evaluated the food effect, resulting in no observed food effect for the prolonged release formulation. The results from single-dose study LPRI-424/102 have also been compared with historical data showing lower C_{max} and later t_{max} for the applied product (both dienogest and ethinylestradiol) but similar AUC.

According to Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017), a DDI study between the active substances in the fixed combination medicinal product should be conducted unless the presence or absence of a pharmacokinetic interaction can be established through other evidence (knowledge from *in vitro* data, mechanistic understanding or other published clinical trials). No specific drug-drug interaction (DDI) study to investigate potential interaction between the two compounds has been performed. In this case absence of a DDI study is acceptable as clinical phase III studies have been performed with the applied fixed combination prolonged release formulation.

The popPK analysis has identified an impact of body weight on exposure for both dienogest and ethinylestradiol. In theory, higher body weight patients could have a potential lack of efficacy. However, the clinical data does not indicate lack of efficacy for patients with higher body weight. 109 kg appear to be the highest body weight included. Thus, the popPK analysis is considered to have low regulatory impact and the issues regarding the models were not pursued.

The submitted PK studies are considered sufficient and the pharmacokinetics of the applied prolonged release formulation of dienogest/ethinylestradiol has been adequately characterised.

Pharmacodynamics

In the Phase 2 studies, the dosing regimen was 87 + 4 days and in the Phase 3 studies the regimen 24 +4 was chosen.

The rational for the prolonged-release properties is the intention of less fluctuation in plasma levels than for the IR products, with the aim of obtaining better cycle control. Further, the Applicant suggests that the lower dose of EE and less fluctuation in plasma levels might also possibly lead to an improved safety profile as compared with the immediate-release product.

I.1.4 Clinical efficacy

A total of six clinical trials were concluded by the Applicant, including two Phase 1 studies, two Phase 2 studies and two Phase 3 studies conducted in the EU (one study with adults and 1 study with adolescents and adults). A third Phase 3 study conducted in the USA and aiming at evaluating the contraceptive efficacy, safety and tolerability of DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet (LPRI-424) in subjects between 13-45 years old, was not yet finished by the time of the present MAA, and no data from this study were included in the initial submission. The study was completed and data submitted during the procedure, but since the study was not pivotal for efficacy evaluation, data was not used for primary assessment of efficacy. (**Table 6**).

Table 6. Tabular listing of all studies conducted with LPRI-421 and LPRI-424

Study Identifier	Study Design	Treatment	Num. Subjects	Objectives	Status
Biopharmaceutic studies					
LPRI-424/101	Phase 1, single center, open-label, multiple dose, crossover, randomized, four-treatment, four-period	Three Test IMP- DNG/EE PR tablets: Test 1: DNG/EE 2 mg/20 µg Test 2: DNG/EE 1 mg/10 µg Test 3: DNG/EE 2 mg/10 µg RP: Valette® (DNG/EE 2 mg/30 µg) IR tablet Once daily for 7 days under fasting conditions with 240 mL water, in four different periods, at least 7 days apart	19 healthy pre-menopausal female volunteers (18-39 years)	To assess the relative bioavailability and safety of three oral test IMPs compared to a RP	Completed; Full report
LPRI-424/102	Phase 1, open-label, single dose, randomized, two-period crossover	IMP: DNG 2 mg/EE 20 µg film-coated tablets Single dose under fasting and fed conditions in two different periods, at least 7 days apart	18 healthy post-menopausal females (46-64 years)	To assess the PK, safety and tolerability of the oral test IMP under fasting and fed conditions	Completed; Full report
Human Pharmacodynamic studies					
LPRI-424/201	Phase 2, single center, open-label, randomized, active- controlled	Three Test LPRI-421-DNG/EE PR tablets: Test 1: DNG/EE 1 mg/10 µg Test 2: DNG/EE 2 mg/10 µg Test 3: DNG/EE 2 mg/20 µg	100 healthy women (18-35 years)	Evaluate the inhibition of ovulation and safety of three prolonged-release formulations containing a combination of DNG and EE versus a RP	Completed; Full report

Study Identifier	Study Design	Treatment	Num. Subjects	Objectives	Status
		RP: Velmari® Langzyklus (DRSP/EE 3 mg/20 µg) 119 days of treatment (once daily for 87 days, followed by 4 HFI, followed by once daily for 28 days)			
LPRI-424/202	Phase 2, multicenter, open-label, randomized, active- controlled	Three test LPRI-421 of DNG/EE PR tablets: -D1: DNG/EE 1 mg/10 µg -D2: DNG/EE 2 mg/10 µg -D3: DNG/EE 2 mg/20 µg RP: Velmari® Langzyklus 0.02/3 mg tablets (EE 20 µg/DRSP 3 mg) 182 days of treatment (once daily for 87 days, followed by 4 HFI, followed by once daily for 87 days)	338 healthy females (18-35 years)	To assess vaginal bleeding pattern, tolerability and safety of three different doses of LPRI-421 compared with a RP	Completed; Full report
Efficacy and Safety studies					
LPRI-424/301	Phase 3, multicentre, open-label, uncontrolled	LPRI-424 (DNG/EE 2 mg/20 µg) and placebo PR tablets 364 days of treatment (13 cycles of 28 days) once daily tablet	Approx 1000 sexually active, postmenarcheal and premenopausal female subjects between the ages of 15-45 years (inclusive)	To demonstrate the contraceptive efficacy, safety, tolerability and PK of LPRI-424	Completed; Full report
LPRI-424/302	Phase 3, multicentre, double-blind, double- dummy, randomised	LPRI-424 (DNG/EE 2 mg/20 µg) PR tablets RP: DRSP/EE 3 mg/20 µg film-coated tablets 252 days of treatment (9 cycles of 28 days) two tablets per da	Approx 1250 sexually active, postmenarcheal and premenopausal female subjects between the ages of 18-45 years (inclusive)	To demonstrate the contraceptive efficacy, safety and tolerability of LPRI-424 in comparison to DRSP 3ºmg//EE 20 µg, especially regarding bleeding pattern	Completed; Full report
LPRI-424/303	Phase 3, multicentre, open-label, non-controlled	LPRI-424 (DNG/EE 2mg/20 µg) and placebo ER tablets 364 days of treatment (13 cycles of 28 days) once daily tablet	Approx 1750 sexually active, postmenarcheal and premenopausal female subjects between the ages of 13-45 years (inclusive)	To demonstrate the contraceptive efficacy, safety and tolerability of LPRI-424	Ongoing at initial submission, Completed during the procedure; Full report submitted (not part of efficacy assessment)

Abbreviations: DNG=dienogest; DRSP=drospirenone; EE=ethinylestradiol; HFI=Hormone-Free Interval; IMP=investigational medicinal product; PK=pharmacokinetics; PR=prolonged-release; RP=reference product, IR=immediate release

Design and conduct of clinical studies

Phase 3 study LPRI-424/302

The study design was multicentre, double-blind, double-dummy randomised trial. Subjects fulfilling all the eligibility criteria were randomised to one of the following treatment groups by randomisation ratio of 5:2:

- LPRI-424 (DNG 2 mg / EE 0.02 mg) plus DRSP/EE placebo

- DRSP 3 mg / EE 0.02 mg plus DNG/EE, 2 mg/0.02 mg (LPRI-424) placebo

The primary endpoint was overall Pearl Index (PI) in women aged ≤ 35 years (at the time of trial enrolment).

Secondary endpoints were:

1) Overall PI in all women and in women aged > 35 years (at the time of trial enrolment)
2) PI after correction for back-up contraception and sexual activity (evaluable cycles) in all women
3) PI after correction for back-up contraception and sexual activity (evaluable cycles) in women aged ≤ 35 years and in women aged > 35 years (at the time of trial enrolment)
4) PI for method failures in all women
5) PI for method failures in women aged ≤ 35 years and in women aged > 35 years (at the time of trial enrolment)
6) Pregnancy ratio by life table analysis in all women
7) Pregnancy ratio by life table analysis in women aged ≤ 35 years and in women aged > 35 years (at the time of trial enrolment)

Statistical considerations

Efficacy analysis is based on the Full Analysis Set (FAS), which is comprised of all subjects who were randomised to treatment, took at least one dose of IMP and who were not pregnant at the date of first IMP intake.

Following definitions of terms are used in the analyses:

On-drug pregnancy	An on-drug pregnancy includes all conceptions that occur from Day 1 (the initiation of trial medication) through seven days after the final tablet (active or placebo) is taken.
Confirmed pregnancy	Subject reported a positive urine home pregnancy test and the pregnancy was confirmed by qualitative urine pregnancy test (beta human chorionic gonadotropin [ß-hCG]) and quantitative serum pregnancy test (ß-hCG)
User failure pregnancy	Pregnancy where the subject failed to comply with IMP dosing near the time of conception and estimated date of conception was during the treatment period
Method failure pregnancy	An on-drug pregnancy that occurred during the perfect cycle, i.e. which occurred during the perfect use of IMP and cannot be associated with non-compliance or protocol deviation that might have an impact on the conception.
Suspected, non-confirmed pregnancy	Subject reported a positive urine home pregnancy test but confirmatory qualitative urine pregnancy test (ß-hCG) and/or quantitative serum pregnancy test (ß-hCG) are missing.

Suspected, subject confirmed not pregnant	Subject reported a positive urine home pregnancy test but confirmatory qualitative urine pregnancy test (ß-hCG) and/or quantitative serum pregnancy test (ß-hCG) are negative.
Medication cycle	Twenty-eight days starting with the administration of the first two tablets from a wallet and ending with the last tablet from the wallet. For each medication cycle, one wallet with two blister packs inside will be administered. Each blister pack contains 28 tablets.
Exposure cycle	A 28-day cycle, where at least one treatment diary entry of IMP intake is available. In addition, a cycle is an exposure cycle if the subject becomes pregnant during this cycle regardless of whether this cycle is a 28-day cycle or not.
Evaluable cycle	Exposure cycle with confirmed sexual activity and without back-up contraception use. A cycle is also to be defined as evaluable if: - Subject becomes pregnant at the respective cycle regardless of whether back-up contraception was used or not. - Cycle has a missing answer about sexual activity or sexual activity was not confirmed in the electronic diary (e-diary) but subject becomes pregnant in the respective cycle.
Evaluable cycle (modified*) * not in accordance with evaluable cycle definition in CTP 2.0	Exposure cycle with confirmed sexual activity and at least once without back-up contraception use. A cycle is also to be defined as evaluable if: - Subject becomes pregnant at the respective cycle regardless of whether back-up contraception was used or not. - Cycle has a missing answer about sexual activity or sexual activity was not confirmed in the electronic diary (e-diary) but subject becomes pregnant in the respective cycle.
Perfect cycle	Evaluable cycles without: - >48 h tablet free interval during the second IMP intake until Day 24 of each cycle or >144 h interval between the last IMP intake and the first IMP intake in the consecutive cycle. Tablet free interval calculation will not take into account cycle Days 25-28. - four or more days with forgotten intake of tablets during cycle Days 1-24. - protocol deviations having effect on this cycle.

The primary efficacy endpoint is overall Pearl Index (PI) in women aged ≤35 years (at the time of trial enrolment) which is defined as follows:

$$Overall\ PI_{CPExP\leq 35} = \frac{n_{CPExC\leq 35}}{n_{ExC\leq 35}} \times 1300$$

where n_{CPExC} is number of confirmed on drug pregnancies in exposure cycles, and n_{ExC} is number of exposure cycles. Pregnancies following premature termination of IMP are excluded from the calculations if the estimated date of conception occurs later than seven days after the last tablet intake.

Two-sided 95% confidence intervals (CIs) for the overall PI in women aged ≤35 years (at the time of trial enrolment) are calculated assuming that events of pregnancy have a Poisson distribution. No hypothesis testing is performed for the primary and secondary efficacy endpoints.

Secondary analysis included: PI based on confirmed on-drug pregnancies and on evaluable cycles, and PI for method failures based on confirmed on-drug pregnancies that occurred during the perfect cycle, both in women aged ≤ 35 years at the time of trial enrolment. In addition to PI analysis, overall life table analysis based on exposure cycles, method failure life table analysis based on perfect cycles and life table analysis based on evaluable cycles are performed in order to have the pregnancy rate at each cycle and cumulative pregnancy rates for 6 and 9 cycles. Life table analyses are based on on-drug pregnancies. Two-sided 95% CIs are calculated for all PI parameters using the same method as for the primary analysis.

Cumulative pregnancy rate is calculated by using the PROC LIFETEST procedure. Logarithmic transformation is used for 95% CI of the cumulative pregnancy rate. The Kaplan-Meier method is used to estimate the cumulative pregnancy ratio, and the Clopper-Pearson 95% CI calculated for the pregnancy ratios. Cycles from the first on-treatment cycle until the cycle in which subject became pregnant are the time variable in this analysis. Subjects who did not become pregnant will be right censored at the cycle when the last IMP is taken.

The tolerability assessment includes vaginal bleeding pattern. Analysis of tolerability is based on the Safety Set (SS), which is comprised of all subjects who were randomised to treatment and received at least one dose of IMP. The Clopper-Pearson 95% CI is calculated for rates of subjects with frequent, irregular or prolonged bleeding/spotting. The proportion of subjects with unscheduled bleeding/spotting in cycles 2 to 6 treated with LPRI-424 and DRSP/EE are compared by a non-inferiority (NI) test with a NI margin of 9 percentage points. The test is at a 1-sided 2.5% level.

Phase 3 study LPRI-424/301

The trial was a prospective, multicentre, open-label, uncontrolled trial in female subjects, who presented to the clinic seeking contraception and who were postmenarcheal and premenopausal.

During each 28-day cycle, all subjects received orally one active tablet containing DNG 2 mg/ EE 0.02 mg for 24 consecutive days followed by one hormone-free tablet for 4 consecutive days.

The primary endpoint was overall Pearl Index in women aged ≤ 35 years (at the time of trial enrolment).

Secondary endpoints were:

1. PI after correction for back-up contraception and sexual activity (evaluable cycles) in women aged ≤ 35 years (at the time of trial enrolment)
2. PI for method failures in women aged ≤ 35 years (at the time of trial enrolment)
3. Pregnancy ratio (life table analysis) in women aged ≤ 35 years (at the time of trial enrolment)
4. Overall PI, PI after correction for back-up contraception and sexual activity (evaluable cycles), PI for method failures and pregnancy ratio (life table analysis) in all women
5. Overall PI, PI after correction for back-up contraception and sexual activity (evaluable cycles), PI for method failures and pregnancy ratio (life table analysis) in women aged > 35 years (at the time of trial enrolment)

Statistical considerations

Similar definitions of terms and same methods of primary and secondary analysis are used in the analyses as presented for the randomized pivotal study (LPRI-424/302). No hypothesis testing was performed.

Efficacy data and additional analyses

Brief summary of the Phase 2 study LPRI-421/201

The study LPRI-421/201 was a single centre, Phase 2, open-label randomized clinical trial to evaluate the inhibition of ovulation of three PR formulations containing a combination of DNG and EE versus a flexible regimen contraceptive containing DRSP 3 mg and EE 20 µg (Velmari®). A total of 150 subjects were enrolled in the study and screened. One hundred subjects were randomized and received at least 1 dose of IMP, and 84 subjects completed the study. The study population was healthy without uncontrolled concomitant diseases at screening.

A Hoogland score 1 to 4 was defined as "inhibition of ovulation" for the efficacy assessment. The inhibition rates in the treatment groups T3 and Velmari® was 100% in TC 1 and TC 4. For T2, the inhibition rates were 100% and 95.5% in TC 1 and TC 4; respectively, and for T1, the inhibition rates were 96.0% and 90.9% in TC 1 and TC 4, respectively.

No or minimum ovarian activity in TC 1/TC 4 was achieved in 91.7%/95.0% of Velmari® subjects, 88.0%/81.8% of T3 subjects, 83.3%/68.2% of T2 subjects, and 56.0%/31.8% of T1 subjects. Residual ovarian activity was detected in the majority of other subjects, but high ovarian activity including ovulation was also found in T1 (4.0%/9.1%) and T2 (0/4.5%). For all groups except Velmari®, the proportion of subjects with residual or high ovarian activity increased from TC 1 to TC 4; being highest in T1, followed (in ascending order) by T2, T3, and Velmari®.

TC No	Inhibition	T1 N=25 n (%)	T2 N=24 n (%)	T3 N=25 n (%)	Velmari® N=24 n (%)	Total N=98 n (%)
TC 1	No	1 (4.0)	0	0	0	1 (1.0)
	Yes	24 (96.0)	24 (100.0)	25 (100.0)	24 (100.0)	97 (99.0)
	CI for yes	79.6; 99.9	85.8; 100.0	86.3; 100.0	85.8; 100.0	-
TC 4	No	2 (9.1)	1 (4.5)	0	0	3 (3.5)
	Yes	20 (90.9)	21 (95.5)	22 (100.0)	20 (100.0)	83 (96.5)
	CI for yes	70.8; 98.9	77.2; 99.9	84.6; 100.0	83.2; 100.0	-

Abbreviations: CI=Clopper-Pearson confidence interval; DNG=Dienogest; DRSP=Drospirenone; EE=Ethinyl estradiol; N=Number of subjects; n (%)=Number and percentage of subjects in the category; No.=Number; T1=DNG/EE 1mg/10 µg; T2=DNG/EE 2 mg/10 µg; T3=DNG/EE 2ºmg/20 µg; Velmari®=Velmari® Langzyklus 0.02/3 mg tablets (EE 20 µg/DRSP 3 mg); TC=Treatment cycle
Source: Table 11.4 in section 11.4.1 of study report LPRI-421/201

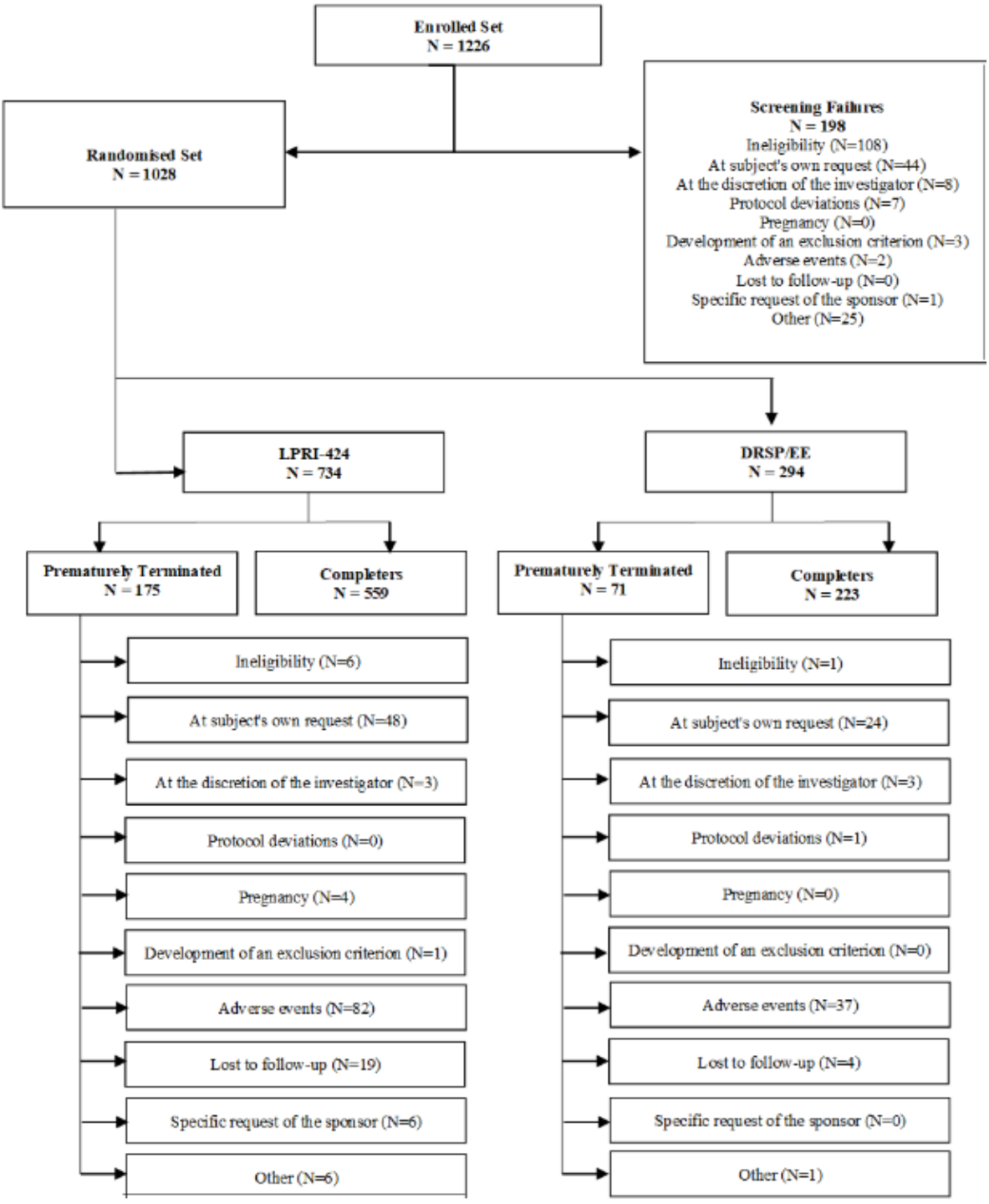
Phase 3 study LPRI-424/302

A total of 1226 subjects were enrolled at 54 active trial centres in Europe. Of these, 198 subjects failed screening (enrolled in the trial but discontinued from the trial before first IMP intake).

Overall, 1028 subjects were randomised to IMP including 734 DNG/EE (LPRI-424) group subjects and 294 DRSP/EE group subjects. A total of 1004 subjects received at least one dose of IMP including 716 subjects in the DNG/EE (LPRI-424) group and 288 subject in the DRSP/EE group. Of these, a total of 782 (76.1%) subjects completed the trial (559 [67.2%] subjects in the DNG/EE (LPRI-424) group and 223 [75.9%] subjects in the DRSP/EE group), and 246 (23.9%) subjects prematurely terminated the trial (175 [23.8%] subjects in the DNG/EE (LPRI-424) group and 71 [24.1%] subjects in the DRSP/EE group). The most common primary reason for discontinuation in the total population were AEs (119 subjects, 11.6%) and at subject's own request (withdrawal of consent) (72 subjects, 7.0 %) with similar percentages in both treatment groups.

Of the included subjects who received at least one dose of IMP, the majority were 35 years of age or younger (84.8%) and 15.2% were older than 35 years. Age range was 18-45 years. Similar percentages of women by age group were reported in both treatment groups.

Figure 3. Subject disposition (enrolled set)



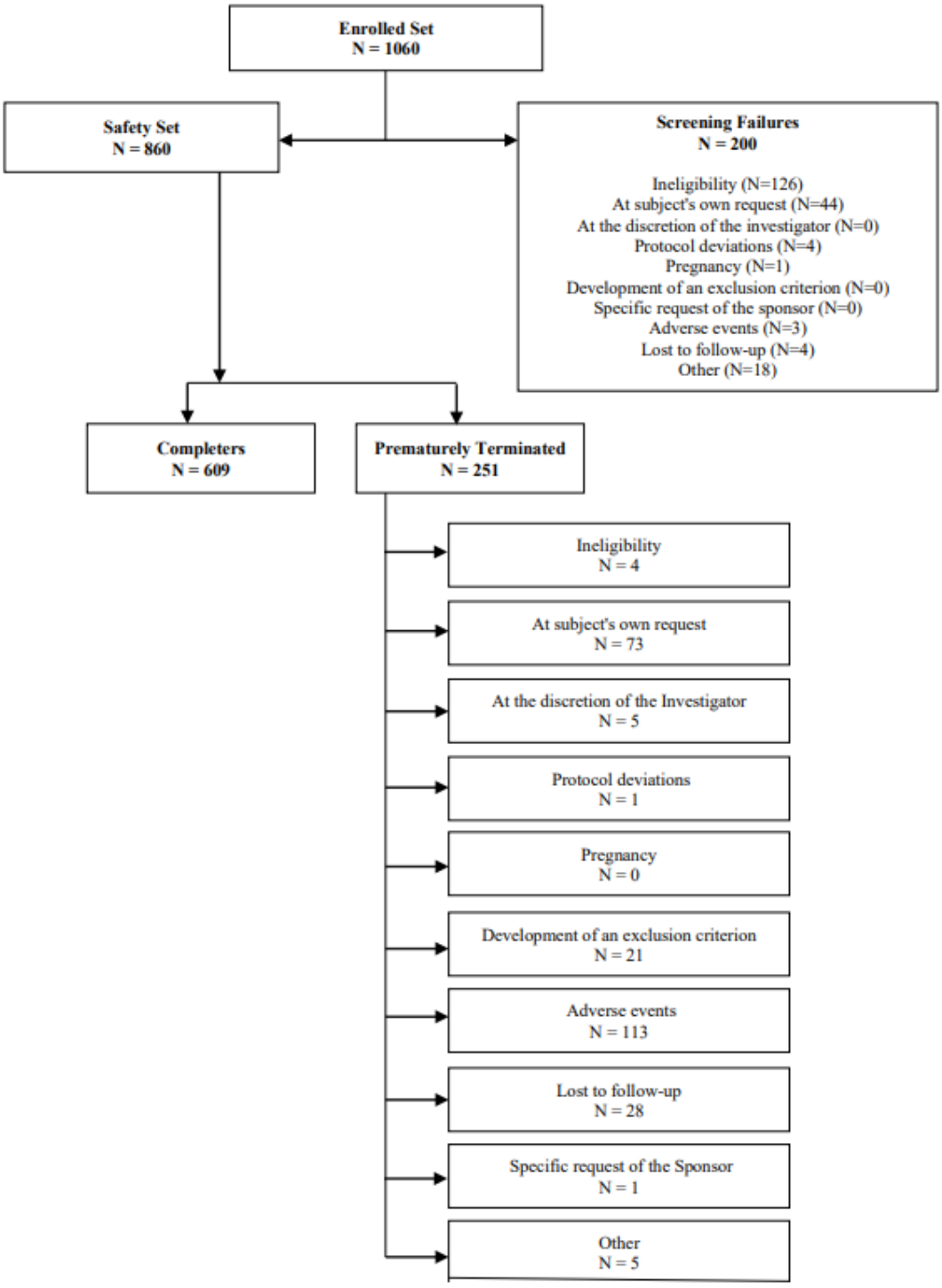
Phase 3 study LPRI-424/301

A total of 1060 subjects were enrolled at 53 active trial centres in Europe. Of these, 200 subjects failed screening (enrolled in the trial but discontinued from the trial before first IMP intake).

Overall, 860 subjects received at least one dose of IMP. Of these, a total of 609 (70.8%) subjects completed the trial and 251 (29.2%) subjects prematurely terminated the trial. The most common primary reasons for discontinuation were adverse events (113 subjects, 13.1%) and at subject's own request (withdrawal of consent) (73 subjects, 8.5%).

Of the included subjects who received at least one dose of IMP, the majority were 35 years of age or younger (704 subjects, 81.9%), 156 (18.1%) were older than 35 years. A total of 15 subjects (1.7%) were adolescents.

Figure 4. Subject disposition



Efficacy results – Phase 3 study LPRI-424/302

A total of 7725 (100.0%) exposure cycles were documented, 6361 (82.3%) of these cycles were evaluable cycles. Most reported reasons for exclusion from evaluable cycles were cycles with no intercourse (9.7%) and cycles with intercourse with additional contraception (6.7%). A total of 4028

(52.1%) perfect medication cycles were documented. Most reported reasons for exclusion from perfect cycles were cycles with an active tablet free interval of more than 48 hours (37.0%) and at least 4 days where the intake of tablet was forgotten by the subject (22.0%). Similar percentages were observed in both treatment groups.

Overall, 2 (0.2%) subjects of the full analysis set reported an on-drug pregnancy, both subjects were in the DNG/EE (LPRI-424) group (0.3%). One of these subjects had a method failure pregnancy, the other one a user failure pregnancy. She was excluded from method failure PI calculation as she failed to comply with IMP dosing near the time of conception.

The mean (SD) subjects' age in the total population was 27.4 (6.87) years ranging from 18 to 45 years. The majority of women (84.8 %) were 35 years of age or younger, 15.2 % were older than 35 years. Similar mean ages and similar percentages of women by age group were reported in both treatment groups.

The mean (SD) subjects' age at menarche in the total population was 12.9 (1.37) years and ranged from 9 to 17 years. In total 416 (41.4%) women reported having had any deliveries, miscarriages and/or abortions. In the DNG/EE (LPRI-424) group, the percentage of subjects with no deliveries and 2 deliveries was lower (8.9% and 35.7%, respectively) compared to the DRSP/EE group (12.8% and 41.6%, respectively), whereas the percentage of subjects with 1 and 3 or more deliveries was higher in the DNG/EE (LPRI-424) group (46.7% and 8.6%, respectively) than in the DRSP/EE group (41.6% and 4.0%, respectively).

The majority of subjects reported no miscarriages (356 subjects, 85.6%) and no abortions (326 subjects, 78.4%). Similar mean values and percentages of subjects were reported in both treatment groups for miscarriages and abortions.

Pregnancies

In total, 2 confirmed on-drug pregnancies and 3 confirmed non-on-drug pregnancies were reported in the LPRI-424 group.

Table 7. Pregnancies (Enrolled Set)

Subject No	Treatment group	Age (years)	Race	Ethnicity	Outcome
Method failure pregnancies					
2108033	LPRI-424	34	White	Non-Hispanic or Latino	Healthy, female baby
User failure pregnancies					
2413068	LPRI-424	23	White	Non-Hispanic or Latino	Abortion spontaneous
Not on-drug pregnancies					
2106018	LPRI-424	25	White	Non-Hispanic or Latino	Healthy, female baby
2408038	LPRI-424	27	White	Non-Hispanic or Latino	Unknown
2601025	LPRI-424	22	White	Non-Hispanic or Latino	Unknown

Source: Appendix 16.2, Listing 16.2.6.1 and Listing 16.2.6.2

The primary endpoint was defined as the overall PI from exposure cycles in women aged ≤ 35 years (at the time of trial enrolment) and was based on confirmed on-drug pregnancies. The overall PI (95% CI) in the DNG/EE (LPRI-424) group based on 605 subjects, 2 confirmed on-drug pregnancies and 4650 exposure cycles was 0.6 (0.07, 2.02) compared to an overall PI (95% CI) in the DRSP/EE group of 0 (NC, 2.55) based on 246 subjects, no confirmed on-drug pregnancies and 1883 exposure cycles. In **Table 8** an overview of overall PIs, PIs based on evaluable cycles and method failure PIs (confirmed on-drug pregnancies) is presented for all women, women aged ≤ 35 years and women aged > 35 years is presented.

Table 8. Overview of Overall Pearl Index, method Failure Pearl Index and pearl index Based on evaluable Cycles (Confirmed On-Drug Pregnancies)(Full Analysis Set)

	LPRI-424 (FAS)			DRSP/EE (FAS)		
	All women	Women ≤ 35 years	Women > 35 years	All women	Women ≤ 35 years	Women > 35 years
Overall Pearl Index						
N	716	605	111	288	246	42
Subjects with pregnancy (n [%])	2 (0.3)	2 (0.3)	0	0	0	0
Subjects without pregnancy (n [%])	714 (99.7)	603 (99.7)	111 (100.0)	288 (100.0)	246 (100.0)	42 (100.0)
Exposure Cycles	5502	4650	852	2223	1883	340
Pearl Index (95% CI)	0.5 (0.06, 1.71)	0.6 (0.07, 2.02)	0 (NC, 5.63)	0 (NC, 2.16)	0 (NC, 2.55)	0 (NC, 14.1)
Pearl Index for evaluable cycle						
N	716	605	111	288	246	42
Subjects with pregnancy (n [%])	2 (0.3)	2 (0.3)	0	0	0	0
Subjects without pregnancy (n [%])	714 (99.7)	603 (99.7)	111 (100.0)	288 (100.0)	246 (100.0)	42 (100.0)
Evaluable Cycles	4495	3793	702	1866	1560	306
Pearl Index (95% CI)	0.6 (0.07, 2.09)	0.7 (0.08, 2.48)	0 (NC, 6.83)	0 (NC, 2.57)	0 (NC, 3.07)	0 (NC, 15.67)
Pearl Index for method failures						
N	716	605	111	288	246	42
Subjects with pregnancy (n [%])	1 (0.1)	1 (0.2)	0	0	0	0
Subjects without pregnancy (n [%])	715 (99.9)	604 (99.8)	111 (100.0)	288 (100.0)	246 (100.0)	42 (100.0)
Perfect Cycles	2834	2377	457	1194	1011	183
Pearl Index (95% CI)	0.5 (0.01, 2.56)	0.5 (0.01, 3.05)	0 (NC, 10.49)	0 (NC, 4.02)	0 (NC, 4.74)	0 (NC, 26.21)

Primary endpoint: Overall PI based on exposure cycles and confirmed on-drug pregnancies in women aged ≤ 35 years

In the FAS, 605 DNG/EE (LPRI-424) group subjects with 4650 exposure cycles and 246 DRSP/EE group subjects with 1883 exposure cycles aged ≤ 35 years were analysed. During these cycles 2 (0.3%) DNG/EE (LPRI-424) group subjects and no DRSP/EE group subject reported a confirmed on-drug pregnancy, leading to a PI (95% CI) of 0.6 (0.07, 2.02) and 0 (NC, 2.55), respectively.

Table 9. Pearl Index Based on Exposure Cycles and Confirmed On-Drug Pregnancies in Women Aged ≤35 Years (Full Analysis Set)

	LPRI-424 (N = 605)	DRSP/EE (N = 246)
Total number of exposure cycles	4650	1883
Confirmed on-drug pregnancy		
Subjects with pregnancy (n [%])	2 (0.3)	0
Subjects without pregnancy (n [%])	603 (99.7)	246 (100.0)
Pearl Index (95% CI)	0.6 (0.07, 2.02)	0 (NC, 2.55)

Source: Section 15.2, Table 15.2.1.1.1
N: Number of subjects aged ≤ 35 years in Full Analysis Set; n: Number of subjects with data available;
%: Percentage based on N; CI: Confidence interval, NC: not calculable.

Secondary endpoints

Analyses of secondary endpoints were based on confirmed on-drug pregnancies.

Secondary endpoint Overall pearl index in all women and in women aged ≥35 years:

In the FAS, 716 DNG/EE (LPRI-424) group subjects of all age groups with 5502 exposure cycles and 288 DRSP/EE group subjects with 2223 exposure cycles were analysed. During these cycles 2 (0.3%) DNG/EE (LPRI-424) group subjects and no DRSP/EE group subject reported a confirmed on-drug pregnancy, leading to a PI (95% CI) of 0.5 (0.06, 1.71) and 0 (NC, 2.16), respectively.

A total of 111 DNG/EE (LPRI-424) group subjects aged > 35 years with 852 exposure cycles and 42 DRSP/EE group subjects with 340 exposure cycles were analysed. During these cycles no subject reported a confirmed on-drug pregnancy, leading to a PI (95% CI) of 0 (NC, 5.63) and 0 (NC, 14.1), respectively.

Table 10. Overall Pearl Index in Women of All Age Groups and for Women Aged >35 years (Full Analysis Set)

Age Group	LPRI-424	DRSP/EE
All Women		
N	716	288
Total number of exposure cycles	5502	2223
Confirmed on-drug pregnancy		
Subjects with pregnancy (n [%])	2 (0.3)	0
Subjects without pregnancy (n [%])	714 (99.7)	288 (100.0)
Pearl Index (95% CI)	0.5 (0.06, 1.71)	0 (NC, 2.16)
Women Aged > 35 Years		
N	111	42
Total number of exposure cycles	852	340
Confirmed on-drug pregnancy		
Subjects with pregnancy (n [%])	0	0
Subjects without pregnancy (n [%])	111 (100.0)	42 (100.0)
Pearl Index (95% CI)	0 (NC, 5.63)	0 (NC, 14.1)

Source: Section 15.2, Table 15.2.1.2 and Table 15.2.1.3
N: Number of subjects of respective age in Full Analysis Set; n: Number of subjects with data available;
%: Percentage based on N; CI: Confidence interval, NC: not calculable.

Secondary endpoint: Pearl index after correction for back-up contraception and sexual activity (evaluable cycles) in all women

In the FAS, 716 DNG/EE (LPRI-424) group subjects of all age groups with 4495 evaluable cycles and 288 DRSP/EE group subjects with 1866 evaluable cycles were analysed. During these cycles only in the DNG/EE (LPRI-424) group 2 (0.3%) subjects reported a confirmed on-drug pregnancy, leading to a PI (95% CI) of 0.6 (0.07, 2.09) in the DNG/EE (LPRI-424) group and of 0 (NC, 2.57) in the DRSP/EE group.

Table 11. Pearl Index Based on Evaluable Cycles in Women of All Age Groups (Full Analysis Set)

Women of All Age Groups	LPRI-424 (N = 716)	DRSP/EE (N = 288)
Total number of evaluable cycles	4495	1866
Confirmed on-drug pregnancy		
Subjects with pregnancy (n [%])	2 (0.3)	0
Subjects without pregnancy (n [%])	714 (99.7)	288 (100.0)
Pearl Index (95% CI)	0.6 (0.07, 2.09)	0 (NC, 2.57)

Source: Section 15.2, Table 15.2.2.2
N: Number of subjects in Full Analysis Set; n: Number of subjects with data available;
%: Percentage based on N; CI: Confidence interval, NC: Not calculable.

Secondary endpoint: Pearl index for method failures in women aged ≤35 years and in women aged >35 years

In the FAS, 605 DNG/EE (LPRI-424) group subjects aged ≤ 35 years with 2377 perfect cycles and 246 DRSP/EE group subjects with 1011 perfect cycles were analysed. During these cycles only in the DNG/EE (LPRI-424) group 1 (0.2%) subject reported a method failure pregnancy, leading to a PI (95% CI) of 0.5 (0.01, 3.05) in the DNG/EE (LPRI-424) group and of 0 (NC, 4.74) in the DRSP/EE group.

A total of 111 DNG/EE (LPRI-424) group subjects aged > 35 years with 457 perfect cycles and 42 DRSP/EE group subjects with 183 perfect cycles were analysed. During these cycles no method failure pregnancies were reported, leading to a PI (95% CI) of 0 (NC, 10.49) in the DNG/EE (LPRI-424) group and of 0 (NC, 26.21) in the DRSP/EE group.

Life tables analysis

Overall life table analysis based on exposure cycles, method failure life table analysis based on perfect cycles and life table analysis based on evaluable cycles was performed in all women to have the pregnancy rate at each cycle and cumulative pregnancy rates after Cycle 6 and Cycle 9. Cumulative pregnancy rates were calculated using Kaplan Meier estimates and 95% CIs.

The cumulative 6-cycle and 9 -cycle overall pregnancy ratios (95% CI) based on confirmed on-drug pregnancies (FAS) were 0.16% (0.00%, 0.46%) and 0.33% (0.00%, 0.79%), respectively, in the DNG/EE (LPRI-424) group and 0% (NC, NC) for both cumulative ratios in the DRSP/EE group.

The cumulative 6-cycle and 9-cycle pregnancy ratios (95% CI) based on confirmed on-drug pregnancies and evaluable cycles (FAS) were 0.17% (0.00%, 0.51%) and 0.40% (0.00%, 0.96%), respectively, in the DNG/EE (LPRI-424) group and 0% (NC, NC) for both cumulative ratios in the DRSP/EE group.

The cumulative 6-cycle and 9-cycle method failure pregnancy ratios (95% CI) based on on-drug confirmed pregnancies (FAS) were 0.24% (0.00%, 0.72%) for both cumulative ratios in the DNG/EE (LPRI-424) group and 0% (NC, NC) for both cumulative ratios in the DRSP/EE group.

Pregnancy ratio by life table analysis in women aged ≤35 years and in women aged >35 years

In women aged ≤35 years, the cumulative 6-cycle and 9 -cycle overall pregnancy ratios (95% CI) based on confirmed on-drug pregnancies (FAS) were 0.18% (0.00%, 0.54%) and 0.39% (0.00%, 0.93%), respectively, in the DNG/EE (LPRI-424) group and 0 (NC, NC) for both cumulative ratios in the DRSP/EE group.

The cumulative 6-cycle and 9-cycle pregnancy ratios (95% CI) based on confirmed on-drug pregnancies and evaluable cycles (FAS) were 0.20% (0.00%, 0.60%) and 0.48% (0.00%, 1.14%), respectively, in the DNG/EE (LPRI-424) group and 0 (NC, NC) for both cumulative ratios in the DRSP/EE group.

The cumulative 6-cycle and 9-cycle method failure pregnancy ratios (95% CI) based on confirmed on-drug pregnancies (FAS) were 0.29 (0.00, 0.85) for both cumulative ratios in the DNG/EE (LPRI-424) group and 0 (NC, NC) for both cumulative ratios in the DRSP/EE group.

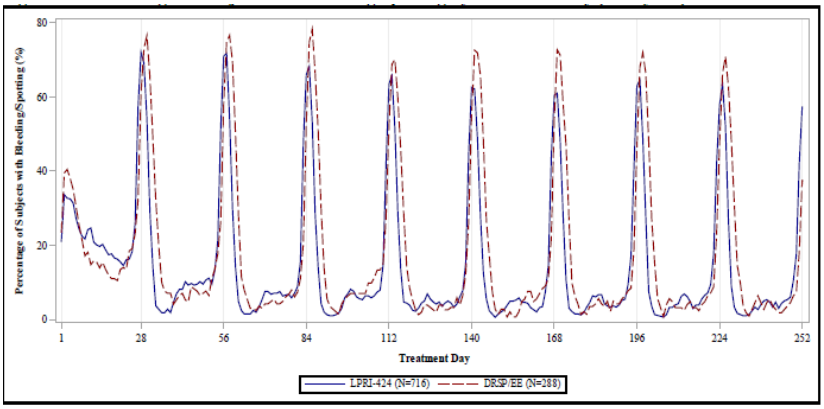
In women aged >35 years, the cumulative 6-cycle and 9-cycle method failure pregnancy ratios (95% CI) based on confirmed on-drug pregnancies (FAS) were 0 (NC, NC) in both treatment groups for both cumulative ratios.

Bleeding pattern

Only cycles without consecutively missing days of active pills and with less than 4 non-consecutively missing days of active pills were used in the bleeding pattern analysis. Data of Cycle 1 were excluded from the analyses by reference cycle because the bleeding pattern in this cycle is distorted due to the change from natural menstruation to cycle control by a hormonal contraceptive.

Percentages of subjects with bleeding/spotting and with spotting by treatment day for the Safety Set are presented in figures below.

Figure 5. Percentage of Subjects with Bleeding/Spotting by Treatment Day (Safety Set)



Source: Section 15.4, Figure 15.4.1.1.1

Scheduled bleeding (spotting) was defined as any bleeding (spotting) that occurred during hormone-free intervals (defined as Days 25-28 ±1) regardless of the duration of the regimen and may continue into the first 4 days (Days 1–4) of the subsequent cycle.

The proportions of subjects with scheduled bleeding/spotting were slightly higher in the DNG/EE (LPRI-424) group at all cycles, except Cycles 6 and 7, compared to the DRSP/EE group.

The proportions of subjects with scheduled bleeding were lower in the DNG/EE (LPRI-424) group at all cycles, except Cycles 3 and 4, compared to the DRSP/EE group. In the DNG/EE (LPRI-424) group, the proportion of subjects with scheduled bleeding by cycle increased from 72.1% during Cycle 1 to 75.2% during Cycle 3 and decreased afterwards to 64.7% during Cycle 9. In the DRSP/EE group the proportion of subjects with scheduled bleeding increased from 72.7% during Cycle 1 to 78.1% during Cycle 6 and decreased afterwards to 66.4% during Cycle 9.

Unscheduled bleeding-spotting

Unscheduled bleeding (spotting) was defined as any bleeding (spotting) that occurred outside the time window defined for scheduled bleeding (spotting). The proportion of subjects with unscheduled bleeding/spotting in cycles 2 to 6 treated with DNG/EE (LPRI-424) or DRSP/EE was compared by a non-inferiority test with a margin of 9% points. The test was a one-sided at the 2.5% type I error level. The non-inferiority test results for the proportion of subject with unscheduled bleeding/spotting in cycles 2 to 6 is presented in Table 12.

Table 12. Number of Subjects with Unscheduled Bleeding/Spotting in Cycles 2 to 6 (Non-inferiority Test)(Safety Set)

	LPRI-424 (N = 716) n/m (%)	DRSP/EE (N = 288) n/m (%)	95% CI	p-value
Cycles 2 - 6	290/574 (50.5)	171/235 (72.8)	(0.159 - 0.286)	<0.0001

Source: Section 15.4, Table 15.4.2

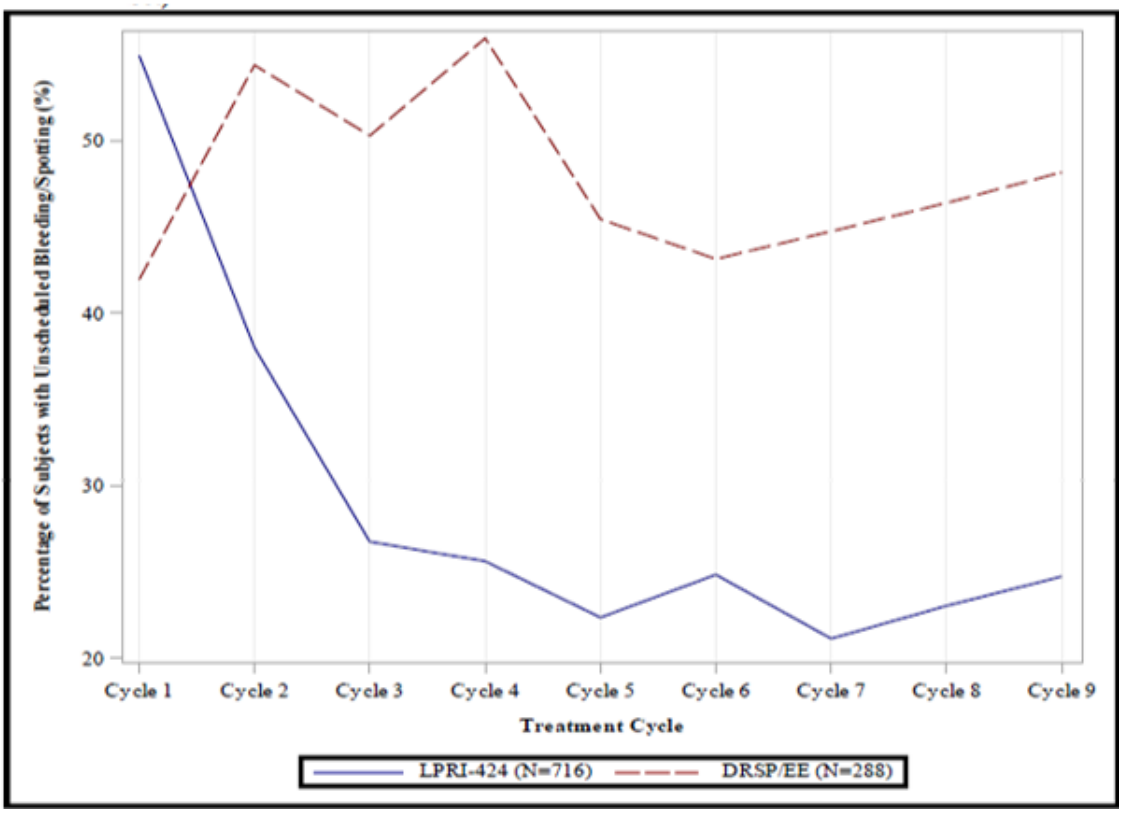
N: Number of subjects in the Safety Set; n: Number of subjects with bleeding data in the respective timepoint
m: Number of subjects with data available in the respective timepoint; %: Percentage based on m.

The proportion of subjects with unscheduled bleeding/spotting days, unscheduled bleeding days and unscheduled spotting days was notably lower in all cycles except Cycle 1 in the DNG/EE (LPRI-424) group compared to the DRSP/EE group.

In the DNG/EE (LPRI-424) group the highest proportion of subjects with unscheduled bleeding/spotting days was observed during Cycle 1 (54.9%), which decreased to 24.8% during Cycle 9.

In the DNG/EE (LPRI-424) group, no clear bleeding/spotting pattern was observed: the highest proportion of subjects with unscheduled bleeding/spotting was observed during Cycle 4 (55.9%) and the lowest in Cycle 6 (43.2%). An increase to 48.2% was seen during Cycle 9.

Figure 6. Percentage of Subjects with Unscheduled Bleeding/Spotting Days by Treatment Cycle (Safety Set)



Efficacy results – Phase 3 study LPRI-424/301

A total of 9095 (100.0%) exposure cycles were documented, 7313 (80.4%) of these cycles were evaluable cycles. Most reported reasons for exclusion from evaluable cycles were cycles with no intercourse (11.9%) and cycles with intercourse with additional contraception (6.6%). A total of 5172 (56.9%) exposure cycles were perfect medication cycles. Most frequently reported reasons for exclusion from perfect cycles were cycles with an active tablet free interval of more than 48 hours (30.1%) and non-evaluable cycles (22.5%).

The mean (SD) subjects' age was 27.8 (7.06) years ranging from 15 to 45 years. The majority of women (704 subjects, 81.9%) were 35 years of age or younger, 156 (18.1%) subjects were older than 35 years. A total of 15 (1.7%) adolescents participated in the trial. This number is smaller than planned in the CTP (approximately 50 adolescents).

The mean (SD) subjects' age at menarche was 13.0 (1.29) years and ranged from 9 to 17 years. In total 341 (39.7%) women reported having had any deliveries, miscarriages and/or abortions. Of these, 156 (45.7%) subjects reported one delivery followed by 128 (37.5%) subjects with 2 deliveries. The majority of subjects reported no miscarriages (291 subjects, 85.3%) and no abortions (253 subjects, 74.2%).

The vast majority of subjects with available data reported scheduled/menstrual bleedings prior to screening (800 subjects, 93.0%). Mean (SD) time since last scheduled/menstrual bleeding was 18.1 (26.33) days and varied from -3 to 595 days. Unscheduled bleeding in the last 6 cycles was reported by 20 (2.3%) subjects. Most frequently reported intensity was unscheduled bleeding of slight intensity

(13 subjects, 65.0%), followed by moderate intensity (4 subjects, 20.0%). The incidence of previous spotting was low and was reported by 28 (3.3%) subjects.

Pregnancies

In total, no confirmed on-drug pregnancy was reported. One confirmed non-on-drug pregnancy was reported for a subject who failed screening due to this pregnancy.

Primary endpoint: Overall Pearl Index (PI) in women aged ≤ 35 years

In the FAS, 704 subjects aged ≤ 35 years with 7476 exposure cycles were analysed. During these cycles no subject became pregnant, leading to a PI (95% CI) of 0 (NC; 0.64). The CI for the PI was calculated assuming that events of pregnancy had a Poisson distribution.

Table 13. Pearl Index Based on Exposure Cycles and Confirmed Pregnancies in women Aged ≤35 Years (Full Analysis Set)

	LPRI-424 (N = 704)
Total number of exposure cycles	7476
Confirmed on-drug pregnancy	
Subjects with pregnancy (n [%])	0
Subjects without pregnancy (n [%])	704 (100.0)
Pearl Index (95% CI)	0 (NC, 0.64)

Source: Section 15.2, Table 15.2.1.1.1 N: Number of subjects aged ≤ 35 years in the Full Analysis Set; n: Number of subjects with data available; %: Percentage based on N; CI: Confidence interval; NC: not calculable.

Secondary endpoint: Pearl Index after correction for back-up contraception and sexual activity (evaluable cycles) in women aged ≤35 years

In the FAS, 704 subjects aged ≤ 35 years with 5831 evaluable cycles were analysed. No subject became pregnant, leading to a PI (95% CI) of 0 (NC; 0.82).

Table 14. Pearl index Based on Confirmed Pregnancies and Evaluable Cycles in Women Aged ≤35 Years (Full Analysis Set)

	LPRI-424 (N = 704)
Total number of evaluable cycles	5831
Confirmed on-drug pregnancy	
Subjects with pregnancy (n [%])	0
Subjects without pregnancy (n [%])	704 (100.0)
Pearl Index (95% CI)	0 (NC, 0.82)

Source: Section 15.2, Table 15.2.2.1.1 N: Number of subjects aged ≤ 35 years in Full Analysis Set; n: Number of subjects with data available; %: Percentage based on N; CI: Confidence interval; NC: not calculable.

The PI based on evaluable modified cycles for women aged ≤ 35 years with a total 704 subjects aged ≤ 35 years with 6127 evaluable cycles were analysed. No subject became pregnant, leading to a PI (95% CI) of 0 (NC; 0.78).

Secondary endpoint: Pearl Index for method failures in women aged ≤35 years

Method failures PI is defined as PI that included all pregnancies of women who used the IMP correctly and is based on perfect cycles.

In the FAS, 704 subjects aged ≤ 35 years with 4038 perfect cycles were analysed. No subject became pregnant, leading to a PI (95% CI) of 0 (NC; 1.19).

Life tables analysis

Overall life table analysis based on exposure cycles, method failure life table analysis based on perfect cycles and life table analysis based on evaluable cycles was performed in women aged ≤ 35 years (at

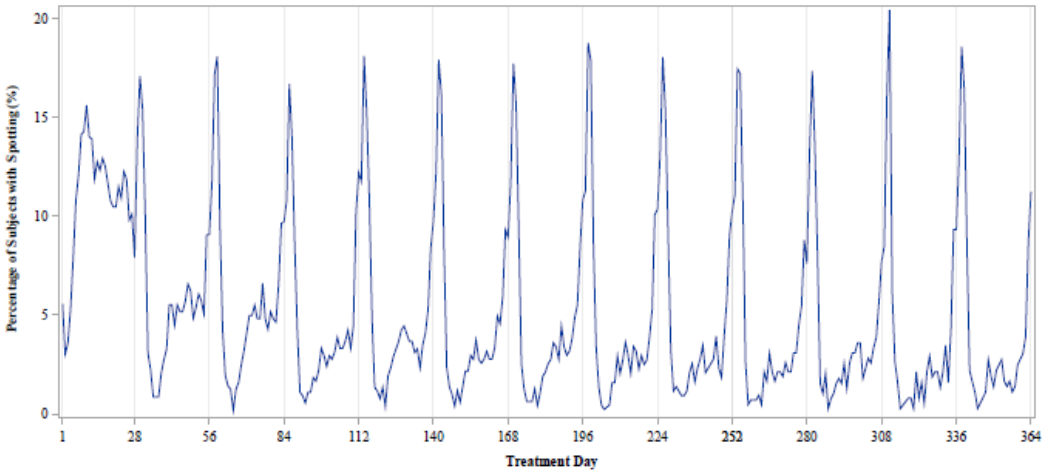
the time of trial enrolment) to have the pregnancy rate at each cycle and cumulative pregnancy rates after Cycle 6 and Cycle 13. Cumulative pregnancy rates were calculated using Kaplan Meier estimates and 95% CIs.

The cumulative 6-cycle and 13-cycle pregnancy ratio (95% CI) in women aged ≤ 35 years for exposure cycles, evaluable cycles and perfect cycles (FAS) was 0% (NC, NC) as no pregnancies were reported.

Bleeding pattern

Only cycles without consecutively missing days of active pills and with less than 4 non-consecutively missing days of active pills were used in the bleeding pattern analysis. Data of Cycle 1 were excluded from the analyses by reference cycle because the bleeding pattern in this cycle is distorted due to the change from natural menstruation to cycle control by a hormonal contraceptive.

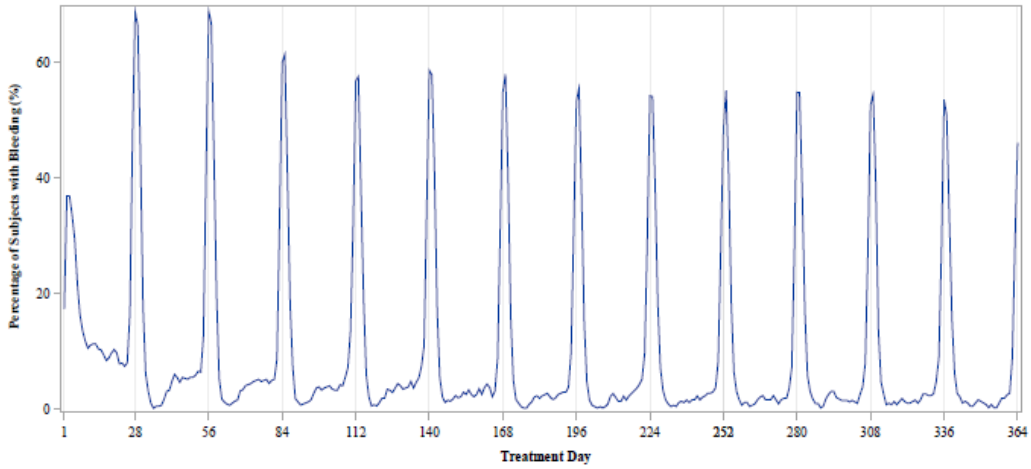
Figure 7. Percentage of Subjects with Spotting by Treatment Day (Safety Set)



Source: Section 15.4, Figure 15.4.1.1.1

The proportions of subjects with bleeding showed maxima on Day 1 or Day 28 of each cycle. With prolonged treatment, the maxima decreased from 68.8% of subjects with bleeding on Day 28 of Cycle 1 and 68.9% of subjects on Day 28 of Cycle 2 to 50.8% of subjects on Day 1 of Cycle 13.

Figure 8. Percentage of Subjects with Bleeding by Treatment Day (Safety Set)



Source: Section 15.4, Figure 15.4.1.1.1

Scheduled bleeding (spotting) was defined as any bleeding (spotting) that occurred during hormone-free intervals (defined as Days 25-28 ±1) regardless of the duration of the regimen and may continue into the first 4 days (Days 1–4) of the subsequent cycle.

During Cycles 2-13, 665 (88.8%) subjects reported scheduled bleeding days.

The highest number and percentage of subjects with scheduled bleeding days (555 subjects, 79.2%) was observed during Cycle 1. The number and percentage of subjects decreased to 241 (65.8%) subjects during Cycle 13. During Cycles 5, 11 and 12, slight increases of percentages of subjects with scheduled bleeding days were observed compared to previous cycles. The number and percentage of subjects with scheduled bleeding days by reference period decreased from 590 (83.9%) subjects during Cycles 2-4 to 355 (74.7%) subjects during Cycles 11-13. A trend towards reduced numbers of subjects with scheduled bleeding days was over time.

Subgroup analysis

There were no dedicated studies in special populations. Both pivotal studies LPRI-424/301 and LPRI-424/302 evaluated the PI in subpopulations defined by age (whole population, women ≤ 35 years old and women ≥ 35 years old). The two confirmed on drug pregnancies reported in the study LPRI-424/302 in the DNG/EE 2 mg/20 μg treatment group occurred in women below 35 years old. The PIs for all categories (overall, evaluable cycles, perfect cycles) among women ≤ 35 years old ranged between 0.2 and 0.4 in pooled data, with varying upper limit of the 95% confidence interval. The PIs among all women ranged between 0.2 and 0.3 in the pooled analysis. When including all women, the precision of the PI was sufficient according to the guidelines, but since fertility declines with age, the PI for women ≤ 35 years old is the primary endpoint.

For efficacy, no subgroup analysis was made for BMI.

Tolerability and bleeding pattern was analysed in subgroups of non smokers, current smokers and former smokers. Results were similar across subgroups.

Analysis performed across trials

The primary efficacy outcome was to calculate the overall Pearl Index in women aged ≤ 35 years with pooled data from the studies LPRI-424/301 and LPRI-424/302.

Following the CHMP Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CPMP/EWP/519/98 Rev 1) the number of cycles collected should be at least large enough to give the overall PI with a 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1. The data from two studies (LPRI-424/301 and LPRI-424/302) were pooled for the calculation of the overall PI. In total, the analysed number of exposure cycles in both trials in women aged ≤ 35 years was 12 126 and in all women 14 597.

As there were no reported pregnancies in study LPRI-424/301, all pregnancies in the pooled analysis corresponded to the two confirmed on-drug pregnancies reported in the LPRI-424/302 trial, including one method failure pregnancy and one user failure pregnancy, both in subjects ≤ 35 years of age. A summary of the results regarding the primary and secondary efficacy endpoints of both studies obtained in the pooled population of subjects receiving at least one dose of Dienogest/Ethinylestradiol, 2 mg/0.02 mg, Prolonged-release tablet (LPRI-424) is presented in Table 15.

Table 15. Pearl Indices Based on Exposure Cycles, Evaluable Cycles, Perfect Cycles and Confirmed On-Drug Pregnancies in Pooled LPRI-424/301 and LPRI-424/302 Trials in All Women and Women Aged ≤ 35 Years

	LPRI-424	
	Women Aged ≤ 35 Years N = 1309	All Women N = 1576
Overall Pearl Index		
Total number of exposure cycles	12126	14597
Confirmed on-drug pregnancy		
Subjects with pregnancy (n [%])	2 (0.2)	2 (0.1)
Subjects without pregnancy (n [%])	1307 (99.8)	1574 (99.9)
Pearl Index (95% CI)	0.2 (0.03, 0.77)	0.2 (0.02, 0.64)
Pearl Index for evaluable cycles		
Total number of evaluable cycles	9624	11808
Confirmed on-drug pregnancy		
Subjects with pregnancy (n [%])	2 (0.2)	2 (0.1)
Subjects without pregnancy (n [%])	1307 (99.8)	1574 (99.9)
Pearl Index (95% CI)	0.3 (0.03, 0.98)	0.2 (0.03, 0.8)
Pearl Index for method failures		
Total number of perfect cycles	6415	8006
Confirmed on-drug pregnancy		
Subjects with pregnancy (n [%])	2 (0.2)	2 (0.1)
Subjects without pregnancy (n [%])	1307 (99.8)	1574 (99.9)
Pearl Index (95% CI)	0.4 (0.05, 1.46)	0.3 (0.04, 1.17)

N: Number of subjects in Full Analysis Set; n: Number of subjects with data available based on exposure cycles (overall PI), evaluable cycles (PI for evaluable cycles) or perfect cycles (PI for method failure);
%: Percentage based on N; CI: Confidence interval.
Source: Table 15.2.1.1.2, Table 15.2.2.1.3, Table 15.2.3.1.2, Table 15.2.1.2.2, Table 15.2.2.2.2 and Table 15.2.3.2.2 from LPRI-424/301 CRF

Considering the two confirmed on-drug pregnancies reported in study LPRI-424/302 for women aged ≤ 35 years, the PIs (95% CIs) calculated for pooled data were 0.2 (0.03, 0.77) for 12 126 exposure cycles (primary endpoint), 0.3 (0.03, 0.98) for 9 624 evaluable cycles and 0.4 (0.05, 1.46) for 6 415 perfect cycles. In the whole population of women, the PIs (95% CI) calculated for pooled data were 0.2 (0.02, 0.64) for 14 597 exposure cycles, 0.2 (0.03, 0.8) for 11 808 evaluable cycles and 0.3 (0.04, 1.17) for 8 006 perfect cycles.

Cumulative pregnancy rates calculated using Kaplan Meier estimates and 95% CIs for the pooled data from LPRI-424/301 and LPRI-424/302 trials considering women aged ≤ 35 years and all women are summarized in Table 16.

Table 16. Overall Life Table Analysis in Pooled LPRI-424/301 and LPRI-424/302 Trials (Confirmed On-Drug Pregnancies) in All Women and in Women Aged ≤ 35 Years

Exposure Cycles	LPRI-424			
	Women Aged ≤ 35 Years		All Women	
	Pregnancy Rate n/m (%)	Cumulative Pregnancy Rate and 95% CI %	Pregnancy Rate n/m (%)	Cumulative Pregnancy Rate and 95% CI %
Cycle 1	0/1269 (0.00)		0/1528 (0.00)	
Cycle 2	0/1222 (0.00)		0/1471 (0.00)	
Cycle 3	1/1180 (0.08)		1/1417 (0.07)	
Cycle 4	0/1144 (0.00)		0/1375 (0.00)	
Cycle 5	0/1125 (0.00)		0/1348 (0.00)	
Cycle 6	0/1096 (0.00)	0.08 (0.00, 0.25)	0/1315 (0.00)	0.07 (0.00, 0.21)
Cycle 7	0/1057 (0.00)		0/1268 (0.00)	
Cycle 8	1/1030 (0.10)		1/1232 (0.08)	
Cycle 9	0/988 (0.00)	0.18 (0.00, 0.43)	0/1188 (0.00)	0.15 (0.00, 0.36)
Cycle 10	0/530 (0.00)		0/641 (0.00)	
Cycle 11	0/514 (0.00)		0/626 (0.00)	
Cycle 12	0/499 (0.00)		0/609 (0.00)	
Cycle 13	0/472 (0.00)	0.18 (0.00, 0.43)	0/579 (0.00)	0.15 (0.00, 0.36)

n: Number of subjects with confirmed on-drug pregnancy in respective exposure cycle.; m: Number of subjects in respective exposure cycle; %: Percentage is based on the number of subjects in respective exposure cycle;
CI: Confidence interval.
Please note that trial LPRI-424/302 was performed only during 9 cycles.
Source: Table 15.2.4.1.2 and Table 15.2.4.2.2 from LPRI-424/302

The cumulative pregnancy rate (95% CI) based on exposure cycles in women aged ≤ 35 years increased from 0.08% (0.00%; 0.25%) (6-cycle rate) to 0.18% (0.00%; 0.43%) (9-cycle rate) and 0.18% (0.00%; 0.43%) (13-cycle rate).

The cumulative pregnancy rate (95% CI) based on exposure cycles (FAS) in all women increased from 0.07% (0.00%; 0.21%) (6-cycle rate) to 0.15% (0.00%; 0.36%) (9-cycle rate) and 0.15% (0.00%; 0.36%) (13-cycle rate).

I.1.5 Discussion of Clinical efficacy

Dienogest/Ethinylestradiol, 2 mg/0.02 mg, Prolonged-release tablet is a new combined oral contraceptive, containing the known active substances dienogest (DNG) 2 mg and ethinylestradiol (EE) 20 µg in a prolonged-release formulation. Immediate-release COCs containing the two substances in combination are previously available in some EU countries, with a higher EE dose (30 µg). The clinical experience with DNG and EE given either as monotherapy or in combination is considered extensive.

Design and conduct of clinical studies

The phase 3 studies had inclusion criteria that were adequate to capture sexually active women of fertile age. The exclusion criteria covered all general contraindications for combined hormonal contraception and are considered adequate. The listed prohibited concomitant therapies were acceptable. Planned regular concomitant use of barrier contraceptive methods or other contraceptive measures were not allowed, but occasional use was allowed (cycles not evaluable). The use of emergency contraception was not mentioned beyond this.

The LPRI-424/302 trial was a comparative study with a 5:2 randomisation. Included women received two blisters of tablets per cycle, either one blister containing DNG/EE (LPRI-424) active treatment (24+4) or corresponding placebo tablets and one blister containing DRSP/EE active treatment (24+4) or corresponding placebo tablets. The treatment duration was 9 consecutive cycles.

The LPRI-424/301 trial was non-comparative, all women received LPRI-424 active treatment consisting of one active tablet containing 2 mg DNG and 0.02 mg EE per day for 24 days, followed by four days with hormone-free tablets. The treatment duration was 13 consecutive cycles.

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

Study objectives of the pivotal studies are adequate for a study evaluating a new contraceptive. The primary and secondary efficacy endpoints are acceptable. The age limit ≤ 35 years for the primary efficacy endpoint is endorsed.

Statistical aspects

According to the "Guideline on clinical investigation of steroid contraceptives in women", a study evaluating contraceptive efficacy should be large enough to give the overall PI with a two-sided 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1 (pregnancies per 100 women years). Although this precision was not attained based on the study LPRI-424/302 alone, the results of the study LPRI-424/301 and the planned pooled primary analysis showed that the requirement was met.

In both pivotal studies, the primary analysis for women aged ≤35 years is calculation of overall Pearl Index and corresponding 95% CI using the equations from Gerlinger et al, based on confirmed on-drug pregnancies in exposure cycles, assuming that events of pregnancy have a Poisson distribution. Pregnancies following premature termination of IMP are excluded from the calculations if the estimated date of conception occurs later than seven days after the last tablet intake. This approach corresponds to while-on treatment strategy which is reasonable for the studied condition. The methods of statistical analysis in general are acceptable. No hypothesis testing between treatment groups was planned for the primary endpoint overall PI in the randomized study, which is acceptable. The "Guideline on clinical investigation of steroid contraceptives in women" does not generally request active comparator for efficacy purposes, although comparison to active control is recommended for certain safety and tolerability assessments. Comparison to active control was made for assessments of bleeding/spotting (in study LPRI-424/302).

In study LPRI-424/302, a non-inferiority 1-sided test at 2.5% level was performed to compare DNG/EE (LPRI-424) and DRSP/EE treatment in proportion of subjects with unscheduled bleeding/spotting in cycles 2 to 6, using an NI margin of 9 percentage points. The proportion of subjects with unscheduled bleeding/spotting in cycles 2 to 6 treated with DNG/EE (LPRI-424) was statistically significantly lower compared to the proportion of subjects treated with DRSP/EE. Thus, the non-inferiority of DNG/EE (LPRI-424) in this analysis was proved, and in addition, superiority of DNG/EE (LPRI-424) in terms of statistical significance could be concluded, as the confidence interval did not include zero.

In study LPRI-424/302, the most common reason for early discontinuation the DNG/EE (LPRI-424) group was adverse events (47%) followed by discontinuation at subject's own request (27%). Pregnancy during treatment as a reason for termination of study was reported in 2 cases. In the DRSP/EE group, the most common reason for early discontinuation was adverse events (52%) followed by discontinuation at subject's own request (34%). No discontinuations were due to pregnancy. In study LPRI-424/301, the most common reason for early discontinuation was adverse events (45%) followed by discontinuation at subject's own request (29%). No discontinuation was due to pregnancy.

Efficacy results

Study **LPRI-424/302** was performed in 54 enrolling sites in Europe, 1226 subjects were enrolled, whereof 198 subjects failed screening. Overall, 1028 subjects were randomised, and 1004 subjects received at least one dose of the IMP. There were 2 on-drug pregnancies and 3 not on-drug

pregnancies in study LPRI-424/302. One pregnancy was a method failure pregnancy, and one pregnancy was a user failure pregnancy. The rate of discontinuation was moderate, 23.9% up to cycle 9.

Study **LPRI-424/301** was performed in 53 enrolling sites in Europe, 1060 subjects were enrolled, whereof 200 subjects failed screening. Overall, 860 subjects received at least one dose of the IMP. One not-on-drug pregnancy was reported; a positive pregnancy test was reported before first IMP intake. No on-drug pregnancy was reported in the study. The rate of discontinuation was moderate, 29.2% up to cycle 13.

Pooled data results

The populations of the two main studies were similar regarding baseline demographic data, IMP compliance and tolerability. The design of the studies differed, with one single arm study and one randomised controlled study. The inclusion- and exclusion criteria were similar across studies, except for BMI where LPRI-424/301 included subjects with BMI <35 kg/m^2 and LPRI-424/302 <30 kg/m^2. Baseline data was comparable between the studies. Taken together, this supports the suitability of pooling the data.

The overall PI in women ≤35 years was 0.2 (95% CI 0.03, 0.77) and for evaluable cycles PI was 0.3 (95% CI 0.03, 0.98), which meets the EMA Guideline requirement on precision. The primary endpoint was PI for women 18-35 years, which adequate since fertility and the risk of pregnancy declines with age. When including all women (18-45 years of age), the PIs are lower with a narrower 95% CI.

For method failure in the pooled analysis the PI was 0.4 (95% CI 0.05, 1.46). Thus, the sample size was too small to show a reliable precision of the PI.

Tolerability and vaginal bleeding pattern

Tolerability and bleeding pattern were similar when data from both main studies was pooled. Subjects who received DNG/EE (LPRI-424) reported fewer bleeding days than the comparator group.

I.1.6 Clinical safety

Exposure

The safety database consists of data from six completed clinical trials, including two Phase 1 studies, two Phase 2 studies and two Phase 3 studies conducted in Europe. From a safety perspective, primarily the data from the Phase 2 and Phase 3 studies have been considered.

Within the six completed clinical trials that were submitted with the application (Table 6), a total of 1940 women received the combination DNG/EE, 18 subjects received one single dose and 1922 subjects received at least one dose in multiple doses studies. Studies no. 202, 301 and 302 had planned treatment duration of six, nine and thirteen 28-day cycles, respectively, and therefore provided long-term safety data. Study 201 had a planned treatment duration of four 28-day cycles. Altogether, 1400 subjects had a treatment duration of ≥168 days (six months), and 1192 subjects had a treatment duration of ≥ 252 days. Five of the six completed studies included only subjects ≥18 years of age, while Study LPRI-424/301 included also 15 adolescent patients (between 15 and 17 years). Across the 15 adolescent subjects in this study, the overall mean (SD) duration of treatment was 349.8 (58.42) days (range: 140 to 384 days per subject) and the majority of adolescents (93.3%) received treatment for at least 364 days, matching the scheduled duration of 13 medication cycles.

Common adverse events

In the two Phase 3 studies, treatment-emergent adverse events (TEAEs) were most frequently reported in the SOCs of reproductive system and breast disorders (23.3%), infections and infestations (22.6%), investigations (12.4%), nervous system disorders (9.0%), gastrointestinal disorders (9.0%) and psychiatric disorders (7.5%). Overall, the most common TEAEs by preferred term were metrorrhagia, headache, Corona virus infection and breast pain (5.3% of all subjects). All other TEAEs were

reported for less than 5% of subjects overall. The pattern of most common TEAEs was generally similar between the two Phase 3 studies.

The most frequently reported severe TEAEs in the Phase 3 studies were headache (8 subjects, 0.5%); dysmenorrhea (7 subjects, 0.4%), breast pain (6 subjects, 0.4%), abdominal pain (3 subjects, 0.2%) and mood swings (3 subjects, 0.2%). All other severe TEAEs were reported in ≤ 0.1% of subjects overall.

In the two Phase 3 studies, almost one-third of subjects (29.8%) had TEAEs considered related to study drug. Metrorrhagia was the most frequently reported related TEAE in both studies, followed by breast pain and weight increased in Study LPRI-424/301 and by headache and breast pain in Study LPRI-424/302. No other term was reported for more than 3% of subjects in any Phase 3 study.

Serious adverse events and deaths

Treatment-emergent serious adverse events (TESAEs) were reported for 1.5% of subjects in the two Phase 3 studies. Most SAEs were considered not related or unlikely to be related to study drug. Four subjects in Study LPRI-424/301 and 2 subjects in Study LPRI-424/302 reported a total of 8 TESAEs assessed to be at least possibly related to DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet.

In the Phase 2 studies in adults, one subject under treatment with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet at the selected DNG/EE dose of 2 mg/20 µg experienced a TESAE: cervix carcinoma stage 0. The SAE was judged to be not related to study drug.

Two deaths (due to myocardial ischemia or Corona virus infection, respectively) occurred during the clinical studies included in the submission. Both cases were considered unrelated to DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet.

Adverse events of special interest (AESIs)

Venous thromboembolism (VTE) and arterial thromboembolism (ATE) were considered AEs of special interest (AESIs). In the two Phase 3 studies, 4 subjects (0.3%) treated with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet experienced thromboembolic TEAEs: Two subjects experienced one TEAE of deep vein thrombosis, each, one subject had venous thrombosis, and one subject had a TEAE of pulmonary embolism. There were no thrombotic events in the control group (n=288) receiving DRSP/EE in study LPRI-424/302. None of the adolescents included in Study LPRI-424/301 experienced thromboembolic events.***Discontinuations due to Adverse events***

In the two Phase 3 studies included in the MAA, 11.7% of subjects overall had TEAEs leading to study discontinuation. Across all subjects in the Phase 3 studies, the most frequent TEAEs leading to study discontinuation were cervical dysplasia (1.7% of all subjects), metrorrhagia (1.1% of all subjects), headache (1.0% of all subjects), weight increased (0.9% of all subjects), nausea (0.6% of all subjects) as well as breast pain, libido decreased and mood swings (each 0.5% of all subjects). More than half of the TEAEs leading to study discontinuation were considered at least possibly related to study drug.

Only few TEAEs leading to discontinuation were of severe intensity.

Out of the adolescents in Study LPRI-424/301 (n=15), no subject reported any TEAE leading to discontinuation.

Across the Phase 2 studies, 7.2% of all subjects experienced TEAEs leading to discontinuation. Breast pain was the only TEAE leading to discontinuation that was reported for 2 subjects, all other cases were observed in no more than one subject. All TEAEs leading to discontinuation were assessed as being at least possibly related to study drug. Except abdominal pain in Study LPRI-421/201, all TEAEs were assessed as mild or moderate in severity.

Analysis of Quality of life – Libido changes and Mood swings

In the Phase 3 and Phase 2 studies, 2% of the subjects had at least one TEAE associated to libido changes: 1.5% of the subjects overall reported libido decreased and 0.4% of the subjects reported loss

of libido. In addition, one subject in Study LPRI- 424/301 discontinued prematurely due to the TEAE sexual aversion disorder.

In the Phase 3 and Phase 2 studies, 4.2% of the subjects overall had at least 1 TEAE associated to mood changes. The most frequently observed AEs were mood swings (1.4% of the subjects overall), followed by depressed mood, depression and mood altered in 0.8%, each.

Laboratory findings

Mean changes from baseline in each of *haematology parameters* were generally small, with changes less than the standard deviation (SD) of the measurement. Most frequent changes were observed for mean corpuscular haemoglobin count and haematocrit, followed by mean corpuscular volume (MCV) and lymphocytes. The incidence of haematology abnormalities reported as TEAEs was overall low (≤0.3%).

Mean changes from baseline in biochemistry parameters were generally small and less than the SD of the measurement. Most frequent changes were observed for lactate dehydrogenase and triglycerides. Only few biochemistry values showed potential clinical significance in the opinion of the investigators and the incidence of biochemical abnormalities reported as TEAEs was low (generally ≤0.3%). In Study LPRI-424/301, there were no biochemistry abnormalities reported as SAEs. A total of five biochemistry abnormalities leading to study discontinuation were reported in three subjects with two subjects experiencing one event each (fibrin D dimer increased and blood prolactin increased, respectively) and one subject with 3 events of increased liver enzyme values (aspartate aminotransferase increased, alanine aminotransferase increased and gamma-glutamyltransferase increased). In Study LPRI-424/302, one TEAE (Fibrin D dimer increased) in one subject was reported as SAE, which in addition was also reported as one of the few TEAEs leading to study discontinuation. This event has also been described under IV.5 Adverse events of special interest above. There was one additional subject in study LPRI-424/302 in which abnormal biochemistry led to study discontinuation. This subject experienced four events: blood creatine phosphokinase increased, aspartate aminotransferase increased, blood lactate dehydrogenase increased and alanine aminotransferase increased.

Special laboratory parameters

Special laboratory parameters were assessed in Study LPRI-424/302 in a subset of 51 randomised subjects per treatment group (DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet vs. an immediate-release COC with drospirenone (DRSP)/ethinylestradiol (EE)).

Additional blood samples were to be taken at baseline and after medication cycle 9 for the assessment of haemostatic variables, carbohydrate metabolism and bone biomarkers.

Investigated *haemostatic parameters* included clotting factor VIIc, clotting factor VIIIc, protein C activity, antithrombin III activity, D-dimer and resistance to activated protein C. Carbohydrate metabolism was analysed via assessment of fasting glucose, serum insulin and C-peptide. In addition, the bone biomarkers bone-specific alkaline phosphatase (BALP) and carboxy-terminal crosslinked telopeptide type 1 (CTX-1) were analysed. Overall, all special laboratory parameters remained stable over time during the study. Changes from baseline were generally small, with mean and median values remaining within the reference ranges at screening and at the end of treatment with the only exception of the haemostatic parameter clotting factor VIIc: For this parameter the median value at baseline and Visit 5b/EDV was above the reference range in both treatment groups. Differences in all special laboratory parameters between subjects receiving either LPRI-424 or DRSP/EE were small and no relevant differences between treatment groups were observed.

For evaluation of the insulin resistance index, fasting (or non-fasting) glucose, HOMA-I and insulin were assessed. Overall, the mean and median values of all parameters were within the reference ranges at screening and at the end of treatment, except the mean value for HOMA-I. No remarkable changes over time could be observed. None of the observed median changes from baseline were above 5% at the end of treatment.

Safety in Special populations

Overall, AEs, TEAEs, on treatment adverse events (OTAEs) and SAEs, including severe, related and those events leading to discontinuation, were comparable between subjects aged ≤ 35 years and subjects aged > 35 years.

Similarly, AEs, TEAEs and OTAEs, including severe cases and events leading to discontinuation, were comparable in both BMI subgroups. However, drug-related TEAEs and OTAEs were slightly more frequently observed in subjects with a BMI of < 25 kg/m^2 than in subjects with a BMI of ≥ 25 kg/m^2, while SAEs and drug- related SAEs were more frequently reported for subjects with a BMI of ≥ 25 kg/m^2. The most common TEAEs were similar across BMI subgroups.

AEs, TEAEs, TEAEs leading to discontinuation, SAEs and TESAEs, occurred at similar rates in subgroups of subjects based on blood pressure. The frequency of related TEAEs and related TESAEs was higher in the subgroup of subjects with normal blood pressure, while severe TEAEs were slightly more frequently reported in the group of subjects with high blood pressure values. Both deaths observed in the Phase 3 studies occurred in subjects with normal blood pressure.

Overall, AEs, TEAEs, treatment-related TEAEs and severe TEAEs were more common in current or former smokers than in non-smokers, with incidences in the group of current or former smokers being approximately 8-9% higher for AEs and TEAEs and approximately 3- 4% higher for related and severe TEAEs. The incidence of TEAEs leading to discontinuation was slightly higher in the subgroup of former smokers as compared to the subgroups of current smokers or non-smokers, while the incidence of SAEs, TESAEs and related TESAEs was similar between subgroups of subjects based on smoking status. The frequency of metrorrhagia was higher in the subgroups of current or former smoker as compared to non-smokers while the incidence of headache was lower in the subgroup of current smokers as compared to the other subgroups.

Adolescents

Due to the low proportion of adolescents (15 subjects out of 1573 subjects overall), no separate analysis with pooled data of adolescents was performed for the Phase 3 studies. Only a separate analysis of selected safety and tolerability data for the adolescent subgroup was performed.

For the subgroup of 15 adolescents in Study LPRI-424/301, the incidence and pattern of AEs were generally similar to those observed in the Phase 3 studies overall. TEAEs considered related to study drug were reported for two subjects (13.3%). The reported events were metrorrhagia (two events in the same subject) and uterine haemorrhage (SAE).

Renal and hepatic impairment

No studies examining the effects of DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet or other COCs containing a combination of DNG and EE in subjects with hepatic insufficiency or renal impairment were done.

The proposed SmPC contains the same contraindications and warnings regarding hepatic disease as for previously approved COCs.

Long-term safety data

The Applicant discussed long-term safety based on data from the two Phase 3 studies and the supportive Phase 2 studies, which ranged from 9 to 13 28-day cycles in duration in the Phase 3 studies and from approximately 4 to 6 months duration in the Phase 2 studies.

I.1.7 Discussion of Clinical safety

DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet is a new combined oral contraceptive (COC), containing the known active substances dienogest (DNG), 2 mg and ethinylestradiol (EE), 20 µg, in a prolonged-release formulation. Immediate-release COCs containing the two substances in combination are previously available in some EU countries, albeit with a higher EE dose (30 µg). The two

substances are also available as immediate-release COCs in other combinations, such as DNG/estradiol valerate (EV) or drospirenone (DRSP)/ethinylestradiol (EE).

Both active substances in DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet, thus, have a well-established use as oral contraceptives. The primary difference between DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet and previously approved COCs with DNG and EE is its prolonged-release and the lower dose of EE.

According to the Applicant the primary aim for the development of a prolonged-release formulation of the COC was improved cycle control. The basis was the improved cycle control observed with a vaginal ring, i.e. a non-oral prolonged-release combined contraceptive. Bleeding pattern data are described under Clinical Efficacy above. A better safety profile due to the lower EE dose in this prolonged-release formulation was also considered a possibility.

The safety database consists of data from six clinical trials, including two Phase 1 studies, two Phase 2 studies and two Phase 3 studies conducted in Europe. As the Phase 1 studies were performed with a single dose or 7 days of dosing only, from a safety perspective the data from the Phase 2 and Phase 3 studies are primarily considered. In the Phase 3 studies (LPRI-424/301 and LPRI-424/302) a total of 1573 subjects received at least one dose of DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet. These studies had a planned treatment duration of thirteen and nine 28-day cycles, respectively, and therefore provided long-term safety data. In these studies, only the intended dose of 2 mg DNG/20 µg EE was studied. Altogether, 1400 subjects had a treatment duration of ≥168 days (six months), and 1192 subjects had a treatment duration of ≥ 252 days. One of the Phase 3 studies included a control group (n=288) treated with an immediate-release COC containing 3 mg drospirenone (DRSP) and 20 µg EE. In addition, the Applicant presented data on venous thrombotic events observed in an ongoing Phase 3 study conducted in the US.

In general, the pattern of common adverse events (AEs), severe AEs, serious AEs (SAEs) or AEs leading to treatment discontinuation does not give raise to new concerns for LPRI-424 as compared with previously approved COCs.

As this is the first oral combined hormonal contraceptive (CHC) with a prolonged-release profile, the observed cases of VTEs in the two Phase 3 studies included in the marketing authorisation application and in the ongoing US Phase 3 study were thoroughly discussed during the assessment procedure.

In the two originally submitted Phase 3 studies (n=1573), four subjects (0.3%) receiving DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet experienced treatment emergent VTEs. There were no thrombotic events in the control group (n=288) receiving DRSP/EE in study LPRI-424/302.

An additional four cases of VTE from the ongoing Phase 3 study LPRI-424/303 in the US. Thus, there have been altogether eight (8) subjects experiencing VTEs that were considered related or possibly related to DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet among women during ongoing treatment with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet in Phase 3 studies (described in **Error! Reference source not found.** above). The total exposure in these three studies was 1465 woman.

The number of VTE events in the Phase 3 studies with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet appears somewhat high. It is noted, however, that at least three subjects with VTE events had a combination of risk factors that are listed in the SmPC section 4.4, which together would constitute a contraindication for COC use. These cases show the importance of adherence to risk minimisation measures as outlined in the SmPC.

Importantly, there is no plausible mechanistic explanation to why DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet should have an increased VTE risk compared with previously available immediate-release COCs. The VTE risk during use of a COC is usually considered associated with the oestrogen content. As DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet contains a lower dose of oestrogen than previous COC products with DNG/EE, the VTE risk would rather be expected to be lower for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet. Further, the combination DNG/EE is not new and the VTE risk for this combination has previously been accepted from a Benefit-Risk point of view. Moreover, non-oral contraceptives with prolonged release (PR) properties leading to low peak plasma concentrations and low fluctuations in plasma concentration over time, e.g. a vaginal ring, are

previously approved and have not been associated with a higher rate of VTE. The lower fluctuation in plasma concentrations *per se* does therefore not increase the VTE risk.

Pharmacokinetic data for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet show a relatively small mean delay in Tmax of about 2- hr for EE as compared with the immediate-release formulation (see Table 5 above). In study LPRI-424/302, there were no remarkable changes in coagulation parameters from baseline to treatment cycle 9, and similar relative changes from baseline were observed in both treatment groups (DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet versus the control immediate-release COC). There is, therefore, no indication that the slower first-pass over the liver affects coagulation parameters.

Further, due to the low frequency of VTEs, clinical studies are generally not considered sufficiently powered to quantify this effect (ref: CHMP assessment report for Article 31 referral EMA/739865/2013). A direct comparison of the VTE frequency in the studies with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet and that estimated from epidemiological data for immediate-release products, as described in the SmPC, should therefore be made with caution.

The Applicant noted that the DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet Phase 3 studies were all conducted during the peak of the Covid-19 pandemic, and suggested this could have added unknown risk factors for thrombotic events. However, none of the subjects experiencing treatment-emergent VTE events in the studies reported with the severe Covid-19 infection that has been associated with an increased risk for thrombosis, and it was considered unlikely that Covid-19 was the cause of any of the 8 treatment-emergent VTE cases in the studies with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet.

In conclusion, the pattern of common adverse events (AEs), severe AEs, serious AEs (SAEs) or AEs leading to treatment discontinuation does not give raise to new concerns for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet as compared with previously approved COCs, despite a relatively high number of VTEs in the studies with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet. It is mechanistically implausible that a lower EE dose should increase the VTE risk for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet compared with immediate-release COCs. Laboratory data do not suggest that the slower oral absorption from DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet as compared with immediate-release COCs affects coagulation parameters. Due to the size of the studies and the rarity of such events, the rate estimation is uncertain. Therefore, the seemingly high rate of VTEs in the studies with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet may be accepted as a chance finding, and may partly be due to inclusion of subjects for which COC use should have been contraindicated in the studies with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet. The VTE risk for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet will be closely monitored in PSURs, initially on a yearly basis.

Adolescents

The proposed indication for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet does not have a lower age limit, but should only be administered after menarche.

The previously approved COC products with the combination of DNG/EE in some EU countries (immediate-release products containing 2 mg DNG and 30 μg EE) also do not have an age restriction, other than after menarche. The same applies for COCs containing DNG in combination with another oestrogen (estradiol valerate; EV) or containing EE (20 μg or 30 μg) with another progestogen (drospirenone, DRSP).

The number of adolescents (15-17 years of age) included in the studies with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet is small, only 15 subjects. The current data do, however, not give raise to any specific concerns. The safety profile of DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet in post-pubertal subjects <18 years is not expected to differ more, or in other aspects, from the safety profile in adults than what is observed for other COCs approved in adolescents. The limited safety database for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet in women <18 years is therefore not considered on obstacle to approval of the proposed indication without age restriction.

SmPC

Based on the data from studies LPRI-424/301 and LPRI-424/302, the rate of thrombotic events indicated in the ADR table in section 4.8 of the SmPC is 'Uncommon', which is higher than the rate indicated in the SmPCs for most other COCs on the EU market, which is 'Rare'. However, as discussed above, due to the size of the studies and the rarity of such events, the rate estimation is uncertain. The SmPC for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet contains standard warnings and contraindications concerning the VTE/ATE risk.

I.1.8 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet.

Safety specification

Summary of Safety Concerns:

Important Identified Risks	- Venous Thromboembolism - Arterial Thromboembolism
Important Potential Risks	None
Missing Information	None

Pharmacovigilance Plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are proposed as follows:

> "A specific questionnaire, the form PVEX-F06 - Specific Follow-Up Questionnaire for Thromboembolic Events will be used for follow-up on received case reports on VTE or ATE in order to obtain further information.
>
> The questionnaire is divided in several parts asking information about the patient and the reporter, the suspected drug, the adverse drug reaction itself (symptoms, dates, severity...), the patient's medical history, past drug history, current concomitant medications, physical examinations, relevant laboratory and diagnostic tests, corrective treatment for the event and evolution.
>
> Form PVEX-F06 is attached in Annex 4"

There are no planned, ongoing or completed additional pharmacovigilance activities.

Risk minimisation measures

Routine risk minimisation is communicated in the SmPC and PIL.

The following additional risk minimisation measures are proposed for the important safety concerns, "Venous thromboembolism" and "Arterial thromboembolism".

1. Checklist for prescribers
2. Patient information card

Checklist for prescribers

Objectives:

Support proper indication of the product and delivery of information about risks and thrombosis signs/symptoms to the user.

The checklist is divided into some sections. The first section contains information concerning the risk of thromboembolism and the use of a COC. The second section provides information about prescribing or not this medicine, considering the clinical history of the patient and the possibility of developing thromboembolism when using COC. The third one is related to the education that the doctor should give to the patient on risks factors to develop thromboembolism by the patient.

Rationale for the additional risk minimisation activity:

Minimisation of occurrence of the risk in the target population is expected because check list for prescribers stands out the risk of VTE and encourages doctors to correct prescription and patient education.

Target audience and planned distribution path:

Target audience will be Healthcare Professionals prescribing contraceptives, mainly gynaecologists. The preferred distribution path will be publication at the Marketing authorisation holder (MAH) and NCA's websites, where it can be downloaded; distributed by sales representatives, and provided by MAHs under demand. The distribution plan will be agreed with the NCA.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, etc.

Criteria for judging the success of the risk minimisation measures are comparison of product information versus the individual case safety reports (ICSRs).

Assessment will be performed during medical review of case reports and during signal detection evaluation meetings. Results will be presented in PSURs following obligations stated in current EURD list.

Patient Information card

Objectives:

Patient education, patient awareness of symptoms of thromboembolism for early detection.

It's a document summarising the risks and risk factors related to thromboembolism for a patient, including instructions on risk detection and minimisation.

Rationale for the additional risk minimisation activity:

Minimisation of occurrence and severity of the risk in the target population is expected. Warning patients of symptoms of thromboembolism allows early detection and seek for medical attention.

Target audience and planned distribution path: Target audience are patients. The card will be provided by the prescriber. It will be available at the MAH's and NCA's websites, where it can be downloaded, and provided by the MAH under request. The distribution plan will be agreed with the NCA.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, etc. Criteria for judging the success of the risk minimisation measures are comparison of product information versus ICSR reports.

Assessment will be performed during medical review of case reports and during signal detection evaluation meeting. Results will be presented in PSURs following obligations stated in current EURD list.

Conclusion

It is well established that the risk of VTE is increased in users of COCs, and the risk for such events is handled by contra-indications and warnings in the SmPC for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet, in line with other COCs. Monitoring of VTE and ATE occurrence post-marketing and continuous reviewing of this risk in PSURs is in line with what is done for other COCs.

The use of a specific questionnaire for thromboembolic events, and a checklist for prescribers and a patient card with information on such events, is also in line with the measures outlined in RMPs for other COCs approved in the EU. The Applicant has, however, added a question on concomitant Covid-19 infection in the specific questionnaire for thromboembolic events for DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet.

Other class effects for COCs are well-characterised and are described in the SmPC. Thus, they are handled via routine risk minimisation.

No new risks have been identified in the studies with DNG/EE, 2 mg/0.02 mg, Prolonged-release tablet.

The submitted Risk Management Plan, version 0.2, signed 16/02/2024 is acceptable.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PlL was English.
The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product Kelzyn is found adequate. There are no objections to approval of Kelzyn, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Description	Due date
Submission of a new environmental risk assessment (ERA)	Within 2 years post-approval

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Kelzyn, 2 mg/0,02 mg, Prolonged-release tablet was positively finalised on 2024-02-28.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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