LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Slinda
(drospirenone)

SE/H/1809/01/DC

This module reflects the scientific discussion for the approval of Slinda. The procedure was finalised on 2019-09-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Exeltis healthcare S.L. has applied for a marketing authorisation for Slinda, 4 mg film-coated tablet. The active substance is drospirenone which belongs to a type of female sex hormone called progesterone. It is contraceptive based on the inhibition of ovulation, changes in the cervical mucus and effects on the endometrium, which becomes thinner.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

In accordance with article 7 of Regulation 1901/2006, as amended, the applicant has submitted a paediatric investigation plan EMEA-001495-PIP01-13-M01. The European Medicines Agency's decision P/0110/2014 was provided on 2014-05-05. A positive opinion of the paediatric committee on full compliance with the PIP was issued on 2018-03-23 (EMA/PDCO/78820).

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

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has 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 drospirenone are well known. As drospirenone is a widely used, well-known active substance, the applicant has not provided new or additional studies and further studies are not considered required. There are no objections to approval of Slinda 4mg from a non-clinical point of view.

III.1 Ecotoxicity/environmental risk assessment

The Applicant has performed an adequate ERA in accordance with relevant guidance. All studies submitted were performed in accordance with GLP. In the fish full life cycle study, no NOEC value could be determined as effects on general growth were noted already at the lowest concentration (0.87 µg/L). Using the SimpleTreat model described in EUSES, it was calculated that a NOEC/PNEC-safety factor of ~6700x ((0.87/10)/0.000013) was derived based on a ratio <1. While this approach was not considered ideal, it was acceptable given the very low likelihood that the real NOEC would be near a value that would give a RQ around 1. The overall conclusion of the ERA is that drospirenone is an EAS and may thus pose a risk to the environmental water compartment.

Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.26	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.26	not B
	BCF	Considered to be <2000 L/kg	not B
Persistence	DT50 or ready biodegradability	< 50 days water and total system	not P
Toxicity	NOEC or CMR	N/A	T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.00013	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			Endocrine disruptor
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =456 (sandy loam) K_{oc} =1100(sandy clay loam) K_{oc} =3100 (clay loam) K_{oc} =808 (sludge) K_{oc} =1170 (sludge)	No terrestrial studies triggered
Ready Biodegradability Test	OECD 301	Not conducted	Based on the

					structure of the molecule, it was not considered to be readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} total system =3.7 and 48 days % shifting to sediment 102 days) = 3.1% and 20.4 % (Drospirenone); 46.2 % and 53.6% (total radioactivity) Volatiles = 27.0% and 33.6 %			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	N/A	µg/L	Not conducted
Daphnia sp. Reproduction Test	OECD 211	NOEC	19.5	µg/L	
Fish, Full life cycle	OECD 210	LOEC	0.87	µg/L	NOEC <0.87
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	N/A	µg/L	Not determined
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	BCF considered to be <2000 L/kg	L/kg	Not B
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			Terrestrial studies not triggered
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	Terrestrial studies not triggered
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	Terrestrial studies not triggered
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	Terrestrial studies not triggered
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	Terrestrial studies not triggered
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

Drospirenone is a known active substance. The clinical pharmacology package consists of several study reports as well as bibliographical references.

Absorption

The relative bioavailability between different formulations with non-micronized and micronized drospirenone (*eg* Jasminelle® drospirenone/ EE 3 mg/20 µg) has been evaluated in a number of studies. Non-micronized drospirenone 3 mg resulted in comparable $AUC_{0\text{-}72h}$ but lower a C_{max} compared to micronized drospirenone. Further comparison of different batches with non-micronized drospirenone 4 mg was performed which concluded bioequivalence with respect to C_{max} and $AUC_{0\text{-}72h}$.

Co-administration with food and non-micronized drospirenone showed a slightly increase in exposure compared to fasted state, 1.1- and 1.3-fold higher for AUC_{0-72h} and C_{max}, respectively. This increase is not considered clinically relevant and drospirenone can be dosed without and with food.

The relative bioavailability (AUC_{0-72h}) after single dose of non-micronized drospirenone 4 mg was 1.2-fold compared to after Yaz®, (micronized drospirenone + EE) 3 mg/20 μg. The accumulation ratio at steady state was 1.9 and 2.8 following drospirenone 4mg and Yaz®, respectively. Thus, after repeated administration a lower total exposure, ca 0.75-fold, was seen after nonmicronized drospirenone compared to Yaz®. The total exposure of drospirenone following the non-micronized 4 mg dose was comparable after a single dose and at steady state (AUC_{τ}/AUC_{0-72h}=1) but following Yaz® od the ratio AUC_{τ}/AUC_{0-72h} was 1.7. C_{max} after 4 mg was approximately 0.7-fold compared to after Yaz® after both a single dose and at steady state.

Absorption of drospirenone is rapid and complete and the absolute bioavailability of drospirenone after oral administration to young, healthy women was on average 76%.

Distribution

Approximately 95 to 97 % of drospirenone is bound to serum protein. Drospirenone has been shown to interact with human serum albumin in vitro. Drospirenone does not bind to sex-hormone-binding globulin (SHBP) or corticosteroid-binding globulin (CBP) and does not attenuate the ethinyl estradiol induced increase in these proteins.

The distribution of drospirenone into breast milk, in lactating women dosed with non-micronized drospirenone 4 mg, showed a *ca* 0.2-fold exposure in the baby compared to in the mother. Assuming a daily intake of breast milk, by an infant, of 800 ml means that the daily dose of drospirenone in the baby is 3-30 μg drospirenone ie <1% of the maternal dose.

Elimination

Drospirenone is extensively metabolized in the liver. The major plasma metabolites are the acid form of drospirenone generated by the opening of the lactone ring and the 4,5-dihydro-drospirenone-3-sulfate. These metabolites are pharmacologically inactive, and they are generated independently of the cytochrome P450 (CYP) enzyme system. Drospirenone is also metabolized by CYP 3A4.

The metabolic clearance rate of drospirenone in serum is 1.5 ± 0.2 ml/min/kg. Excretion of DRSP is nearly complete after 10 days with trace amounts of drospirenone excreted unchanged in urine and faeces. At least 20 different metabolites are observed in urine and faeces. The faeces:urine excretion ratio is 1.2:1.4.

Dose proportionality

A dose-proportional increase in systemic exposure of drospirenone was seen after a single dose in the dose range 1-6 mg.

Time dependency

No time dependency in the PK of drospirenone was seen following repeated od with non-micronized drospirenone 4 mg.

Intra- and inter-individual variability
Inter-individual variability on F was 40%.

Pharmacokinetics in target population
Total systemic exposure of drospirenone, in target population, was estimated to about 450-830 ng/ml.

Special populations

Impaired renal function
Comparable exposure of drospirenone was seen in subjects with mild renal impairment (RI) and normal renal function. The exposure was slightly higher (ca 1.4-fold) in subjects with moderate RI

compared to normal function which is not deemed clinically relevant. There are no specific studies in patients with severe renal impairment.

Impaired hepatic function
Drospirenone is well tolerated in subjects with mild or moderate hepatic impairment (Child-Pugh B) while the use is contraindicated in patients with severe hepatic disease as long as liver function values have not returned to normal.

Race
No differences in exposure of drospirenone were seen between Caucasian and Japanese females following od administration of drospirenone/EE 3 mg/20 μg.

Weight
In the PopPK analysis BW was identified as a covariate on for CL/F, changing BW from the median 73 kg to the 5th percentile 51 kg or 95th percentile 118 kg causes a moderate change in exposure of 22% and -24%, respectively.

Interactions
The total systemic exposure of drospirenone and C_{max} at steady state increased 2.7-fold co-administered with ketoconazole, a strong CYP3A4 inhibitor.

In vitro, drospirenone is capable to inhibit weakly to moderately the cytochrome P450 enzymes CYP1A1, CYP2C9, CYP2C19 and CYP3A4.

Conclusions on pharmacokinetics

Initially the pharmacokinetic section of the Applicant's summary of Clinical Pharmacology was brief and basic ADME-data was missing. A few new literature references have been provided and the summary of Clinical Pharmacology updated. As drospirenone is a known active substance that has been used in combined oral contraceptives for almost 20 years the summary of Clinical Pharmacology with submitted references are now considered sufficient.

The pharmacokinetic properties of this product are sufficiently described to support approval.

IV.3 Pharmacodynamics

The mode of action for Slinda was supported by five pharmacodynamic studies, including the doses 2.8 mg and 4 mg drospirenone (DRSP). Thus, no formal dose-response studies covering a wide range of DRSP doses have been performed.

DRSP is a synthetic progestogen and an analogue to spironolactone with antimineralocorticoid and antiandrogenic activity. DRSP inhibits follicular growth and ovulation by suppressing luteinising hormone (LH). In addition, DRSP has a progestational effect on the cervical mucus and endometrium. The pharmacology studies 201A, 202, 203 and 204 focused on effects on ovulation.

Plasma concentrations of ovarian steroids (estradiol, progesterone), gonadotrophins (LH, FSH) and ultrasound of ovaries (follicle size) were assessed. Estradiol and progesterone together with the results of follicle size determinations were used to calculate the Hoogland score. In some instances the Landgren score was used, based on progesterone levels of >16 nmol/l sustained for at least 5 days. The Hoogland score, including more parameters, is considered a more reliable assessment of ovulation than the Landgren score, but both methods give an acceptably accurate assessment of ovulation. Endometrial thickness was measured by ultrasound and the Insler score of cervical mucus was assessed, which are acceptable methods. Data on bleeding were collected via diaries.

In pilot study 201A, ovulation inhibition during 2 treatment cycles as well as return to ovulation was demonstrated in a small population.

Study 202 investigated ovulation inhibition of DRSP 24/4 compared to Cerazette. The results indicated that the ovulation inhibition as measured by Hoogland score was comparable between the treatment groups. The Insler score was performed only in subjects with a follicular diameter >13mm. Although the difference between groups was little, there appeared to be more effects on cervical mucus in the DRSP 24/4 group, especially in the first cycle. Thus, the mechanism of action includes effects on cervical mucus. In both treatment groups, the return of ovulation by day 27 was documented for all but two subjects.

Study 203 investigated ovulation inhibition of DRSP 24/4 compared to DRSP 2.8 mg taken daily without a hormone free interval. Although two subjects ovulated according to Hoogland score in the DRSP 24/4 group and one in the DRSP 2.8 mg, the maximal progesterone level did not exceed 6.2 nmol/L in any subject, suggesting absence of ovulation according to the Landgren score. There were no statistically significant differences regarding Hoogland score assessments, progesterone levels, endometrial thickness, LH & FSH levels and other secondary parameters.

Study 204 investigated the effect of several 24h delayed pill intakes of DRSP 24/4 on ovulation inhibition in 127 women. Ovulation was defined by Landgren score and additional ultrasound examinations were performed. One single ovulation was detected and appears to have been detected between days 7 and 11 after delayed intake on days 3 and 6. The ovulation incidence in study 204 was in line with that previously reported for desogestrel 0,075 mg, which was 1% (95% CI of 0.02%-5.29%; Korver 2005).

From a mechanistic as well as pharmacokinetic perspective, the study protocol - with a short delay and a rapid “compensation” - is unlikely to seriously jeopardize ovulation inhibition. The real challenge would have been a prolongation of the hormone-free interval by 1 or 2 days, which could have allowed an ovulation to take place. This affected how the advice on “Management of missed tablets” in the SmPC section 4.2 could be phrased. While the study did not reveal signs of reduced efficacy despite the forgotten pills, firm conclusions could not be drawn based on the study design. In particular, the margins of efficacy around the tablet-free interval, should one or several tablets be omitted, have not been shown. Hence, the management of missed pills in the SmPC for Slinda does not mention a grace time of 7 days, as this has only been shown for combined oral contraceptives and not for a progestogen-only pill, nor for DRSP 24/4.

Overall conclusions on pharmacodynamics

The data available support the chosen dose of 4 mg. The choice of dosing regimen with the 4-day pill-free interval was not obvious, though. The pharmacodynamic studies on mechanism of contraceptive action demonstrated that DRSP 24/4 acts via inhibition of ovulation and with additional effects on cervical mucus as expected for a progestogen. The submitted studies did not demonstrate potential effects of missed pills around the hormone-free interval.

IV.4 Clinical efficacy

The clinical efficacy of Slinda is supported by three pivotal phase 3 studies, shown in the table below.

Table . Overview of clinical studies relevant for evaluating efficacy of LF111

Study ID	Design	Study Posology	Study objectives	Subjects/arm entered/completed	Duration of Treatment	Diagnosis incl. criteria
CF111/301 Phase III	Prospective, non-comparative, multicentre	LF111 coated tablets (DRSP 4 mg, 24 active followed by 4 placebo tablets), oral administration, once daily for 13 cycles	To evaluate contraceptive efficacy, tolerability and safety of LF111	700 planned Analysed (efficacy): 713 (7638 cycles), analysed (safety): 713 Completers: 515	13 cycles of 28 days	Healthy women of childbearing potential – 18-45y
CF111/302 Phase III	Prospective, comparative, randomised, double-blind, double-dummy, multicentre	LF111 coated tablets (DRSP 4 mg, 24 active followed by 4 placebo tablets), oral administration, once daily for 9 cycles *vs* Desogestrel 0.075 mg film-coated tablets (28 active tablets) Randomisation ratio 5 (LF111):2 (desogestrel)	To evaluate contraceptive efficacy, tolerability and safety of LF111	Planned: 1200 subjects (857 for LF111 and 343 for desogestrel 0.075 mg) Treated and analysed: 858 for LF111 and 332 for desogestrel Completers:	9 cycles of 28 days	Healthy women of childbearing potential – 18-45y
CF111/303 Phase III	Prospective, non-comparative, multicentre	LF111 coated tablets (DRSP 4mg, 24 active followed by 4 placebo tablets), oral administration, once daily for 13 cycles)	To demonstrate the contraceptive efficacy of LF111 and safety, tolerability and pharmacokinetics	Planned: 1000 subjects Analysed (efficacy): 1004 Analysed (safety): 1006	13 cycles of 28 days	Healthy women of childbearing potential – 15y- no upper age limit

The phase III clinical development program was conducted in several European countries (studies CF111/301, CF111/302, CF111/304) and in the US (CF111/303). Study CF111/301 and study CF111/303 were non-comparative studies of 13-month duration. Study CF111/302 was a randomised, double-blind 9-month study comparing LF111 with desogestrel while study CF111/304 was a non-comparative study of 13-month duration performed in adolescents (EMEA-001495-PIP01-13).

Design and conduct of clinical studies

Studies CF111/301 and CF111/302

Both the non-comparative study 301 and the randomised controlled study 302 were designed to comply with the EMA guideline and both were planned to be performed to contribute with at least half of the evaluable cycles needed to comply with the EMA precision requirement for overall Pearl Index.

The population included in studies 301/302 were healthy women at risk of pregnancy in the age range 18-45 years. Already pregnant women, as well as breastfeeding women were excluded. So were women with abnormal finding on pelvic, breast or ultrasound examinations and women with unexplained amenorrhoea, known polycystic ovary syndrome, or other conditions (e.g. hepatic or renal disease, psychiatric conditions). Regular concomitant use of barrier contraceptive methods, spermicides, IUDs or other contraceptive measures (excepting occasional use due to risk of infection) was not allowed. Study 302 had some additional exclusion criteria, mainly reflecting contraindications for Cerazette®. The population included is adequate and relevant for contraceptive studies.

Study 301 was non-comparative; hence, all women received the same treatment, i.e. one active tablet containing 4 mg DRSP per day for 24 days, followed by four days with intake of placebo tablets.

In study 302, an active comparator was used. Desogestrel 0.075 mg (in a regimen of 28 active pills, marketed as Cerazette®) was chosen, as it is more effective at preventing ovulation than other POPs and has been shown to inhibit ovulation in over 90% of cycles with a Pearl Index (PI) similar to the low-dose COCs.

The randomised study design of Study CF111/302 was primarily justified by the secondary objective, i.e. to demonstrate the safety and tolerability of LF111 in comparison to desogestrel 0.075 mg, especially regarding bleeding pattern. The objective was to show non-inferiority in the proportion of subjects with unscheduled bleeding/spotting during Cycles 2 to 6 assuming a failure rate of 24% in the control group and a non-inferiority margin of 9%. However, since scheduled bleeding days only occurred in the active treatment arm and the treatment regimens are different with regards to hormone free intervals, the relevance of comparing the amount of unscheduled bleeding between the two treatment arms are questioned (see further overall conclusions on bleeding). In fact, if all subject experience bleeding every day the used definition would declare superiority of the experimental treatment.

The primary efficacy variable in both studies was the **overall Pearl Index (PI)**, defined as:

Overall PI = number of pregnancies*1300/number of medication cycles

Secondary efficacy parameters were PI for method failures, PI after correction for back-up contraception and overall pregnancy ratio. The outcomes are adequate for an efficacy study for a contraceptive product.

For the estimation of overall PI, study 301 and study 302 was planned to contribute with at least half of the cycles needed to comply with the EMEA precision requirement for overall Pearl Index (EMEA/CPMP/EWP/519/98 Rev 1). The targeted number of cycles in each study was 6169 (i.e. 12337/2). In the end, the pooled overall PI was calculated based on a total of 14327 exposure cycles of which the Study 302 contributed with 46.7% (6691/14327).

Study CF111/303

Several inclusion and exclusion criteria were similar to those in Studies 301 and 302. However, this study did not have an upper age limit. Furthermore, female subjects between the ages of 15 and 17 at risk of pregnancy could be included in this study, as well as breastfeeding women, after a protocol amendment. Similar to Study CF11/301, this trial was non-comparative and all women received one active tablet containing 4 mg DRSP per day for 24 days, followed by four days with intake of placebo tablets, for 13 cycles.

The efficacy endpoints in this study were slightly different from those in studies 301/302, with the primary endpoint being Pearl index (PI) from evaluable cycles in non-breastfeeding women aged ≤ 35 years. The overall PI was a secondary endpoint. Data from breastfeeding women were excluded from the efficacy analyses. Only 11 breastfeeding women were actually included in the study.

Efficacy data and additional analyses

Conclusions on contraceptive efficacy

Studies CF111/301 and CF111/302

Both studies 301 and 302 included a population commonly seen in contraceptive trials; the majority of the women were aged 35 years or below (80%), Caucasian (close to 100%), non-smokers (around two thirds) with a BMI <30 kg/ m^2 (approximately 95%). In study 301, approximately 55% were 'switchers' (i.e. trial subjects who switched from another hormonal contraceptive without break), while 43% were 'starters' (subjects who had not used hormonal contraceptives prior to the trial or had at least one day break after the administration of another hormonal contraceptive). In study 302, the majority (73% of the Test and 78% of the Reference group subjects) were direct switchers. The following table shows baseline characteristics summarised for all three pivotal studies.

Table . Baseline subjects characteristics

		Study CF111/301	Study CF111/302		CF111/Study 303
	Statistic	LF111 N=713	LF111 (N = 858)	Desogestrel 0.075mg (N=332)	LF111 (N=1006)
Age (years)	Mean (SD)	28.7 (7.1)	28.9 (7.1)	28.9 (7.1)	27.5 (5.94)
Age group					
≤ 35 years	n (%)	569 (79.8%)	682 (79.5)	259 (78.0)	928 (92.2)
> 35 years	n (%)	144 (20.2%)	176 (20.5)	73 (22.0)	78 (7.8)
Ethnicity					
Caucasian	n (%)	710 (99.6%)	856 (99.8)	331 (99.7)	
Hispanic or Latino	n (%)				229 (22.8)
Not Hispanic or Latino	n (%)				777 (77.2)
BMI [kg/m^2]	Mean (SD)	23.0 (3.8)	22.96 (3.537)	22.82 (3.905)	28.61 (7.632)
	Min/Max	16/38	16.6/41.0	15.9/38.0	15.8/68.0
BMI group					
< 30 kg/m^2	n (%)	672 (94.2%)	828 (96.5)	316 (95.2)	652 (64.8)
≥ 30 kg/m^2	n (%)	41 (5.8%)	30 (3.5)	16 (4.8)	354 (35.2)
BP group					
SBP < 130 and DBP < 85 mmHg	n (%)	571 (80.1%)	727 (84.7)	290 (87.3)	887 (88.2)
SBP ≥ 130 and DBP ≥ 85 mmHg	n (%)	142 (19.9%)	131 (15.3)	42 (12.7)	119 (11.8)
Subject status					
Switcher	n (%)	391 (54.8%)			
Direct switcher	n (%)	-	628 (73.2)	259 (78.0)	264 (26.2)
Indirect Switcher	n (%)	-	39 (4.5)	14 (4.2)	70 (7.0)
Starter	n (%)	309 (43.3%)	191 (22.3)	59 (17.8)	672 (66.8)
Unknown	n (%)	13 (1.8%)	-	-	
VTE risk factor					
Presence of at least one risk factor	n (%)	110 (15.4%)	142 (16.5)	59 (17.8)	367 (36.5)
Previous delivery					
Yes	n (%)	305 (42.8%)	395 (46.0)	150 (45.2)	424 (42.1)
Regular menstrual bleeding during the last 6 cycles					
Yes	n (%)	680 (95.4%)	786 (91.6)	305 (91.9)	661 (99.0)
Prior treatment with sex hormones and modulators of the genital system					
Yes	n (%)	455 (63.8%)	469 (54.7)	195 (58.7)	267 (26.5)

The rate of premature discontinuation in study 301 was high (28%), with the main reason being adverse events (12%). The number of women completing the study was 515 and thereby was the target number achieved, i.e. at least 400 women having completed one year of treatment. In study 302, the discontinuation rate was nearly 20% for DRSP 4 mg and nearly 25% for Desogestrel 0.075 mg.

Protocol deviations were categorised according to their impact on the perfect medication cycle, which is reasonable for a contraceptive trial. In total, 24.5% of all cycles were excluded in study 301, most

commonly due to missed pills, but also due to no sexual activity or use of additional contraception. Similarly in Study 302, almost 30% of all cycles (30.6% for the Test and 27% for Reference) were excluded, with the most common reason being inadequate diary compliance with missed/not documented pill intake, or no sexual activity.

The reported mean compliance was higher than 100% (the median was 100%, though), presumably due to the way this figure was estimated and not due to intake of 'extra' pills.

In study **301**, a total of three in-treatment pregnancies occurred, all considered a result of method failure. The overall Pearl Index was **0.5106, 95% CI (0.1053; 1.4922)**. All three pregnancies were reported for the age subgroup ≤ 35 years and the overall PI (95% CI) for women ≤ 35 years was **0.6593 CI (0.1360; 1.9269)** (number of cycles: 5915). Thus, this can be considered a reasonably low PI with adequate precision, since the difference between the upper limit of the CI and the point estimate does not exceed 1, in agreement with the requirements in the CHMP guideline on steroid contraceptives. Pooling of studies CF111/301 and CF111/302 was however foreseen, as described above.

In study **302**, the overall Pearl Index for Slinda was higher compared with study 301, being close to 1 (**0.9715**) with a 95% CI of **0.3154; 2.2671**. Thus, the precision of this PI estimate was not within the limits required in the CHMP guideline of steroid contraceptives in this particular study. The overall PI for the comparator Desogestrel (Cerazette®) was lower (0.5227), but with a wide 95% CI, which is expected based on the lower number of cycles.

Thus, the point estimates for overall PI differed between study CF111/301 and study CF/111302 despite very similar study protocols and the study centres were mainly located in the same countries. As pre-specified, the overall PI was also calculated by pooling the data from the two studies. The Applicant discussed possible explanations for the difference in PI outcomes between study CF111/301 and study CF111/302. Having compared design and study features, subject baseline characteristics and treatment and study compliance for Study 301 and 302 the Applicant concluded that there is no documented justification that can explain the difference in terms of PI between the two studies. Two study/design features were however highlighted: the difference in the number of recruiting sites and the double-blind design in study 302. Given that no obvious difference between the studies was found that may have had an impact on the PI estimate and given similar baseline characteristics, the estimate of PI based on the pooled analysis of study 301 and 302 was accepted.

The overall PI and other efficacy outcomes (e.g. method failure PI) are shown in the table below, describing efficacy results from all three pivotal studies.

Table . Efficacy results of Overall Pearl Index in Study CF111/301, Study CF111/302, Study CF111/303 and Pooled analysis of Studies CF111/301 and CF111/302

		CF111/301	CF111/302		Pooled CF111/301/ CF111/302	CF111/303
	Statistic	LF111 (N = 713)	LF111 (N = 858)	Desogestrel 0.075mg (N=332)	LF111 Total (N = 1,571)	LF111 (N = 993)
Overall Pearl Index						
Total number of exposure cycles	n	7638	6691	2487	14329	6566
Pregnancy	n (%)	3 (0.4%)	5 (0.6%)	1 (0.3%)	8 (0.5%)	12 (1.2)
Overall Pearl Index	**%**	**0.5106**	**0.9715**	**0.5227**	**0.7258**	**2.3759**
95% CI	**Lower limit / Upper limit**	**0.1053 / 1.4922**	**0.3154/2.2671**	**0.0132/2.9124**	**0.3133/1.4301**	**1.2276/4.1502**
Overall Pearl Index After Correction for Additional Contraception and Sexual Activity Status						
Total number of cycles with sexual activity and without additional contraception	n	7191	5977	2224	13168	
Pregnancy	n (%)	3 (0.4%)	5 (0.6%)	1 (0.3%)	8 (0.5%)	
Overall Pearl Index After Correction for Additional Contraception and Sexual Activity Status	%	0.5423	1.0875	0.5845	0.7898	
95% CI	Lower limit / Upper limit	0.1118 / 1.5850	0.3531/2.5379	0.0148/3.2568	0.3410/1.5562	
Method Failure Pearl Index						
Total number of perfect medication cycles	n	6101	4641	1816	10742	3087
Pregnancy	n (%)	3 (0.4%)	5 (0.6%)	1 (0.3%)	8 (0.5%)	7 (0.70)
Method failure Pearl Index	%	0.6392	1.4006	0.7159	0.9682	2.9478
95% CI	Lower limit / Upper limit	0.1318 / 1.8681	0.4548/3.2684	0.0181/3.9885	0.4180/1.9077	1.1852/6.0737
Overall Pregnancy Ratio						
	%	0.50%	0.70%	0.34%	0.72%	1.77%
95% CI	Lower limit / Upper limit	0.00; 1.07%	0.09;1.31%	0.00; 1.01%	0.17;1.27%	0.31;3.22%

N: Number of subjects in FAS; n: Number of subjects/cycles with data available; %: Percentage based on N; CI: Confidence Interval

Study CF111/303

The majority of women were aged below 35 years of age. Even if adolescents were allowed for inclusion, none participated in the trial. Very few (n=11) breastfeeding women were included. The mean BMI was 28.6 kg/m^2, thus higher compared with the European studies with a mean BMI around 23. Around 60% were overweight or obese (BMI>25kg/m^2). This study included not only Caucasian women but also women with African-American or Hispanic or -Latino ethnicity. Most women were previous users of hormonal contraception or switchers.

Overall, only 35% of subjects completed this trial, while 65% prematurely terminated the trial. The most common primary reason for discontinuation were loss to follow-up (27%) and at subject's own request (withdrawal of consent; 15%).

For two study sites, there were serious non-compliance issues with FDA regulations and GCP. These sites were closed and data from these sites were excluded from statistical safety and efficacy analyses.

The Pearl index (PI) from evaluable cycles in non-breastfeeding women aged ≤ 35 years (primary endpoint) was **2.9** (**95% CI 1.5; 5.1**). The overall PI in all women was **2.4** (**95% CI 1.2; 4.2**). Thus, the Pearl index regardless of definition was overall higher in Study 303 compared with the EU studies. The Applicant has mainly focused on studies 301 and 302, being studies conducted in the EU. Upon request from the RMS, the Applicant outlined different possible reasons for the higher PI observed in the US study (303) compared with the European studies (301 & 302), e.g. demographic/socio-economic factors. Low income, Hispanic ethnicity, absence of higher formal education and obesity are factors that have been associated with low compliance in contraceptive trials. The RMS shared the Applicant´s view that PIs calculated using data from trials conducted in the US tend to be higher than those conducted in Europe. The results from the US study are described in section 5.1 of the SmPC.

Subgroup analyses

Subgroup analyses for efficacy were performed. However, it should be acknowledged that for an endpoint like Pearl index, based on relatively few outcomes (pregnancies), subgroup analyses may not be as informative as for another type of outcome.

With respect to age, the Overall PI in women ≤35 years in a pooled analysis of studies 301 and 302 was 0.9332 (95% CI 0.40/1.84).

Concerning BMI, analyses based on different BMI cut-offs were provided, i.e. both for BMI 25-30 and BMI ≥30. Reference was also made to some published studies for other contraceptives (both POPs and COCs) with somewhat variable results with respect to the effect of obesity on PK and PD parameters. Except for the emergency contraceptives, for which there are conflicting results, there is currently no common opinion/consensus that obese women generally achieve poorer efficacy of hormonal contraceptives. Obese women rather have a lower fertility, as well as other problems related to reproductive health, compared to normal-weight women according to several publications (Balen, 2007; Metwally, 2007, Brewer, 2010). Nevertheless, overweight or obesity often tends to affect the exposure to steroid hormones and for DRSP it was observed based on PK analyses of data from the US study 303 that changing body weight from the median value (73 kg) to the 5th percentile value (51 kg) or 95th percentile value (118 kg) caused changes in exposure of 22.2 % and -23.6 %, respectively.

For DRSP (Slinda), the pooled EU studies **301** and **302** included approximately 25 % of women with a weight equal or greater than 70 kg. A total of 8 pregnancies are reported in these studies; 4 in the baseline BMI group <25 kg/m^2, 4 in the group with baseline BMI 25-30 kg/m^2 and no pregnancy in the group with baseline BMI >30 kg/m^2. This resulted in PI values in the respective BMI groups of **0.48**, **1.90** and **0.0**, with acceptable precision only for the BMI <25 kg/m^2 group, as expected, since the other groups were relatively small and did not include a sufficient number of cycles.

In the US study **303**, a fairly large proportion of the women included were overweight or obese. Approximately 35% (352 out of 993 in the MFAS) had a BMI ≥ 30 kg/m^2. The overall PI values in the group with baseline BMI < 30 kg/m^2 and the group with BMI ≥ 30 kg/m^2 were similar, **2.4** (95% CI 1.0; 4.8) vs. **2.3** (95% CI 0.6; 5.8), respectively, neither of them with a precision in accordance with the CHMP guideline. In the group of overweight women (25 kg/m^2 ≦ BMI < 30 kg/m^2), one pregnancy occurred, resulting in a PI of 0.7. Based on median body weight, the overall PI (95% CI)

for women with a weight < median weight was **3.4** (1.4; 6.6) compared to **1.5** (0.4; 3.8) for women with a weight ≥ median weight. Thus, in this study there was no pattern suggesting a higher PI in overweight or obese women.

It was concluded that in the pooled EU studies (301 & 302) there seemed to be a higher PI in the overweight BMI category (with baseline BMI 25-30 kg/m^2). However, the number of pregnancies was not high and the resulting precision in the PI estimates was overall poor. In the US study, there was no tendency to higher PI values in the overweight or obese women, although the precision in the PI values was poor in this study as well. PK data have shown somewhat lower exposure to DRSP in women with higher body weight, but the effect is not dramatic. Taken together, available data do not suggest an obvious concern that overweight or obese women will have a lower contraceptive efficacy when using DRSP (Slinda). Also, there was not considered to be a need to describe the PI results or the PK results in relation to body weight or BMI.

Conclusions on bleeding

The rationale behind the DRSP 24/4 regimen, including 4 hormone-free days in each cycle, is the creation of a progestogen-only method, offering predictable withdrawal bleeds, otherwise not associated with progestogen-only contraception. However, for a withdrawal bleed to occur, there has to be some degree of oestrogen-induced proliferation of the endometrium. The main reason for the addition of oestrogen in a CHC is to provide proliferation of the endometrium to subsequently allow its shedding triggered by hormonal level decline. Therefore, a predictable bleeding pattern is not likely to occur during use of DRSP 24/4.

The bleeding/spotting data per cycle in the studies were presented as observed data only. The number of subjects with available data decreased from the first cycle to the last from about 90% in the first cycle to about 50% in the last cycle. Any conclusions on change in bleeding pattern over time are therefore doubtful.

In the comparative study, there was little difference in the number of bleeding/spotting days by 90-day-reference period between the continuous regimen (Cerazette) and DRSP 24/4, except possibly during the first reference period (cycles 2-4), when there were slightly more days of bleeding with Cerazette.

DRSP 24/4 has not convincingly been shown to fulfil the criteria for a predictable bleeding pattern, but the bleeding pattern is rather similar to that usually seen with progestogen-only methods that inhibit ovulation. As expected with a progestogen, the endometrial thickness was reduced after several cycles. The studies of the endometrium offer some explanation to the bleeding pattern and why the hormone-free interval often did not result in a withdrawal bleed. There has to be some degree of oestrogen-induced proliferation of the endometrium to allow its shedding following hormonal level decline.

The occurrence of a withdrawal bleeding (defined as a bleeding starting during the 4 hormone-free days, lasting for up to 8 consecutive days), was highest – occurring in less than 40% - during the first cycles and decreased with time. After 9 months of use, a withdrawal bleeding was recorded in less than 20% of users.

The objective of the comparison with desogestrel was to show non-inferiority in the proportion of subjects with unscheduled bleeding/spotting during cycles 2 to 6. However, since scheduled bleeding by definition only can occur in the DRSP 24/4 arm, the relevance of the comparison was questioned. Still, it was noted that the major part of the bleeding/spotting recorded with DRSP 24/4 in the various studies was classified as “unscheduled”. In the comparative study, the mean number of bleeding or

spotting days decreased from 13.1 days during cycles 2-4 to 9.7 days during cycles 7-9 in the DRSP group vs 16.9 to 10.8 days in the desogestrel group. Thus, the comparison between DRSP 24/4 and desogestrel demonstrates little difference between the study groups, except possibly during the first reference period (cycles 2-4), when there were slightly more days of bleeding with desogestrel.

In the comparative study, the proportion of subjects without any bleeding/spotting during the first reference period (cycles 2-4) was 20,1% for DRSP 24/4 and 13,5% for desogestrel. The proportion of subjects without any bleeding/spotting increased in the last reference period (cycles 7-9) to 26,7% for DRSP 24/4 and to 32,1% in the desogestrel group.

The number of subjects with prolonged bleeding, defined as a bleeding lasting >10 consecutive days, for DRSP 24/4 vs. desogestrel was 18,1% and 26,1 %, respectively, during cycles 2-4 and 9,1% and 16,7%, respectively, during cycles 7-9.

With no hormonal contraception, a woman is expected to experience around 15 days of bleeding over a 90-day period, corresponding to 3 consecutive pill cycles. The results suggest that most women did not exceed that number with either method studied. However, the variability was large as reflected by wide SDs and min/max. The withdrawal rate due to bleeding related adverse events was 3.3 % in the DRSP 24/4 group and 6.6 % in the desogestrel group, suggesting that women to a great extent accepted and tolerated the bleeding pattern.

It is important that prescribers are aware of the expected bleeding pattern for appropriate information to the women. A comprehensive bleeding pattern description was therefore included in section 5.1 of the SmPC.

IV.5 Clinical safety

The safety database for drospirenone is based on 5 short-term phase II studies (2 cycles), including 241 women, exposed to either 4 mg or 2.8 mg drospirenone, and 5 long-term studies (1 phase II and 4 phase III studies; 9 or 13 cycles), including 2700 women, of whom 102 were adolescents. For the analysis of clinical safety, data were pooled based on treatment duration, i.e. short-term and long-term studies. Overall, 2941 women have received at least one dose of drospirenone.

Extent of exposure

Table 7. Exposure for adults in long-term studies (Safety Set)

		Study						
		CF111/301 (N=713)	CF111/302 (N=858)	CF111/303 (N=1006)	CF111/304 (N=102)	CF111/205 (N=21)	All studies (N=2700)	Desogestrel
Exposure (days) [1]	n	713	858	1006	102	21	2700	332
	Mean (SD)	304.1 (107.93)	222.7 (65.79)	197.3 (144.43)	312.3 (99.71)	328.1 (48.2)	238.9 (121.46)	213.9 (72.14)
	Median	364.0	252.0	168.0	364.0	364.0	252.0	252.0
	Q1/Q3	280/364	252/252	57/364	317/364	363/364	138.0/364.0	242.5/252
	Min/Max	1/393	3/276	1/411	27/384	107/381	1/411	1/280
Cumulative exposure [n (%)] [1]	Any	713 (100.0)	858 (100.0)	1006 (100.0)	102 (100.0)	21 (100.0)	2700 (100.0)	333 (100.0)
	≥ 28 days	698 (97.9)	835 (97.3)	839 (83.4)	101 (99.0)	21 (100.0)	2494 (92.4)	327 (98.2)
	≥ 84 days	655 (91.9)	787 (91.7)	674 (67.0)	96 (94.1)	21 (100.0)	2233 (82.7)	292 (87.7)
	≥ 168 days	585 (82.0)	718 (83.7)	506 (50.3)	89 (87.3)	20 (95.2)	1918 (71.0)	263 (79.0)
	≥ 252 days	539 (75.6)	673 (78.4)	420 (41.7)	81 (79.4)	17 (81.0)	1730 (64.1)	244 (73.3)
	≥ 336 days	522 (73.2)	-	367 (36.5)	75 (73.5)	17 (81.0)	981 (36.3)	-

N: Number of subjects in specified treatment group; n: Number of subjects with data available; %: Percentage based on N; SD: standard deviation
Notes:
[1] Duration was defined as (the date of last IMP intake) – (the date of first IMP intake) + 1.
Source: ISS L15.1.1.7,

Median exposure in the short-term studies was 56 days, with most patients (94.2%) being exposed for

at least 56 days. Median exposure in the long-term studies was 252 days in study 302 (9 cycles) and 364 days in the remaining 4 studies (13 cycles). In total, 981 patients (36.3%) have been exposed for at least 336 days.

Adverse events

Summary of Adverse events – long-term studies (safety set)

	LF111 (N=2700) n (%)	Desogestrel (N= 333) n (%)
Subjects with at least one AE [n (%)]	1471 (54.5)	158 (47.4)
Number of AEs (#)	3838	319
Subjects with at least one TEAE [n (%)] [a]	1366 (50.6)	150 (45.0)
Number of TEAEs (#)	3434	289
Subjects with at least one OTAE [n (%)] [a]	1273 (47.1)	139 (41.7)
Number of OTAE (#)	3130	262
Subjects with at least one related TEAE [n (%)] [b]	588 (21.8)	62 (18.6)
Number of related TEAEs (#) [a]	994	103
Subjects with at least one related OTAE [n (%)] [b]	566 (21.0)	59 (17.7)
Number of related OTAE (#) [a]	946	99
Subjects with at least one severe TEAE [n (%)]	105 (3.9)	11 (3.3)
Number of severe TEAEs (#)	140	11
Subjects with at least one severe OTAE [n (%)]	99 (3.7)	9 (2.7)
Number of severe OTAE (#)	122	9

Cross-r

AE: Adverse Event. TEAE: Treatment Emergent Adverse Event. OTAE: On Treatment Adverse Event. SAE: Serious Adverse Event.

N: Number of subjects in specified treatment group and subgroup.

n: Number of subjects with adverse events. %: Percentage based on N. #: Number of events.

(Source: ISS, Table L.15.2.1.1.1)

SAEs were reported in 1.6% of subjects on LF111 and 1.8% of subjects on desogestrel; TEAEs leading to discontinuation were reported for 11% of subjects on LF111 and 13.3% of subjects on desogestrel. No relevant differences were observed between the LF111 and the desogestrel arm.

The most commonly reported TEAEs (≥2% of subjects) in the long-term studies (LF111 vs. desogestrel) concerned: nasopharyngitis (5.2% vs. 3.9%), headache (5.2% vs. 5.1%), acne (4.3% vs. 5.7%), metrorrhagia (2.9% vs. 2.1%), nausea (2.9% vs. 0.3%), breast pain (2.8% vs. 1.5%), weight increased (2.7% vs. 1.8%), dysmenorrhoea (2.6% vs. 0.6%) and cervical dysplasia (2.5% vs. 3.3%). Generally, TEAEs were balanced between LF111 and desogestrel treatment. The pattern of TEAEs reported in the short-term studies was generally similar to that in the long-term studies.

In both the short-term and long-term studies, the majority of the TEAEs were of mild or moderate severity. In the long-term studies, severe TEAEs were reported at similar frequency for LF111 and desogestrel: 3.9% and 3.3%, respectively. The most frequently reported severe TEAEs (≥0.2%) with LF111 across all long-term studies were dysmenorrhoea (n=10; 0.4%), breast pain (n=7; 0.3%), abdominal pain, abdominal pain upper and headache (0.2% each). In the short-term studies, the most frequently reported severe TEAE for LF111 was headache (n=3; 1.2%).

Related TEAEs/ADRs

Related TEAEs in ≥ 0.5% of subjects for long and short term studies

System Organ Class [a] Preferred Term	Relationship [c]	LF111 (N=2941) n (%)	Desogestrel (N= 364) n (%)	Norethisterone (N= 10) n (%)
Subjects with at least one TEAE [b]	Any	768 (26.1)	74 (20.3)	4 (40.0)
	Related	766 (26.0)	74 (20.3)	4 (40.0)
	Unknown	4 (0.1)	-	-
Reproductive System And Breast Disorders	Any	372 (12.6)	37 (10.2)	-
	Related	371 (12.6)	37 (10.2)	-
	Unknown	3 (0.1)	-	-
Metrorrhagia	Any	77 (2.6)	7 (1.9)	-
	Related	77 (2.6)	7 (1.9)	-
Dysmenorrhoea	Any	67 (2.3)	2 (0.5)	-
	Related	64 (2.2)	2 (0.5)	-
	Unknown	3 (0.1)	-	-
Breast Pain	Any	61 (2.1)	5 (1.4)	-
	Related	61 (2.1)	5 (1.4)	-
Vaginal Haemorrhage	Any	45 (1.5)	12 (3.3)	-
	Related	45 (1.5)	12 (3.3)	-
Breast Tenderness	Any	31 (1.1)	-	-
	Related	31 (1.1)	-	-
Menstruation Irregular	Any	30 (1.0)	6 (1.6)	-
	Related	30 (1.0)	6 (1.6)	-
Ovarian Cyst	Any	20 (0.7)	5 (1.4)	-
	Related	20 (0.7)	5 (1.4)	-
Menorrhagia	Any	18 (0.6)	1 (0.3)	-
	Related	18 (0.6)	1 (0.3)	-
Amenorrhoea	Any	15 (0.5)	-	-
	Related	15 (0.5)	-	-
Skin And Subcutaneous Tissue Disorders	Any	159 (5.4)	24 (6.6)	1 (10.0)
	Related	159 (5.4)	24 (6.6)	1 (10.0)
Acne	Any	124 (4.2)	21 (5.8)	1 (10.0)
	Related	124 (4.2)	21 (5.8)	1 (10.0)
Alopecia	Any	17 (0.6)	2 (0.5)	-
	Related	17 (0.6)	2 (0.5)	-
Nervous System Disorders	Any	141 (4.8)	7 (1.9)	-
	Related	141 (4.8)	7 (1.9)	-
Headache	Any	122 (4.1)	6 (1.6)	-
	Related	122 (4.1)	6 (1.6)	-
Gastrointestinal Disorders	Any	124 (4.2)	3 (0.8)	3 (30.0)
	Related	124 (4.2)	3 (0.8)	3 (30.0)

System Organ Class [a] Preferred Term	Relationship [c]	LF111 (N=2941) n (%)	Desogestrel (N= 364) n (%)	Norethisterone (N= 10) n (%)
Nausea	Any	53 (1.8)	-	1 (10.0)
	Related	53 (1.8)	-	1 (10.0)
Abdominal Pain Lower	Any	23 (0.8)	2 (0.5)	-
	Related	23 (0.8)	2 (0.5)	-
Abdominal Pain	Any	22 (0.7)	-	-
	Related	22 (0.7)	-	-
Psychiatric Disorders	Any	103 (3.5)	12 (3.3)	-
	Related	103 (3.5)	12 (3.3)	-
Libido Decreased	Any	34 (1.2)	5 (1.4)	-
	Related	34 (1.2)	5 (1.4)	-
Mood Swings	Any	17 (0.6)	-	-
	Related	17 (0.6)	-	-
Investigations	Any	99 (3.4)	8 (2.2)	-
	Related	99 (3.4)	8 (2.2)	-
Weight Increased	Any	55 (1.9)	6 (1.6)	-
	Related	55 (1.9)	6 (1.6)	-
General Disorders And Administration Site Conditions	Any	27 (0.9)	2 (0.5)	-
	Related	27 (0.9)	2 (0.5)	-
Fatigue	Any	16 (0.5)	-	-
	Related	16 (0.5)	-	-
Vascular Disorders	Any	18 (0.6)	2 (0.5)	-
	Related	18 (0.6)	2 (0.5)	-
Hot Flush	Any	15 (0.5)	1 (0.3)	-
	Related	15 (0.5)	1 (0.3)	-

The most commonly reported TEAEs assessed as related to LF111 were acne (4.2%), headache (4.1%), metrorrhagia (2.6%), dysmenorrhoea (2.2%) and breast pain (2.1%).

Hepatobiliary disorders
In the long-term studies, no relevant changes in mean or median values for the liver parameters (ALP, ASAT, ALAT, GGT, bilirubin direct and bilirubin total) were noted during treatment; mean and median levels for each of the liver parameters remained within the reference range.

In the long-term studies, increases in ALAT/ASAT ≥3x ULN or bilirubin ≥2x ULN have been reported. No subjects have been reported with an increase in both ALAT/ASAT ≥3x ULN and total bilirubin ≥2x ULN. Increased liver parameters have been included in section 4.8 of the SmPC.

Serious adverse events and deaths
No deaths were reported in either the short-term or the long-term studies. No SAEs were reported in the short-term studies. In the long-term studies the most frequently reported SAEs in the LF111 arm were: hyperkalaemia (n=5; 0.2%), appendicitis (n=4; 0.1%), fibroadenoma of the breast, cervical dysplasia, breast prosthesis implantation and cholelithiasis (n=2; 0.1%, each). Furthermore, 1 subject (<0.1%) on LF111 reported blood potassium increased as SAE. In the desogestrel arm none of the SAEs was reported in more than 1 subject.

Hyperkalaemia
SAEs of hyperkalaemia were observed in 7 subjects in studies 302 and 303. No trend regarding time to onset (or first occasion of increased blood potassium level) was noted; time to first increased blood potassium level ranged between 3 weeks (cycle 1) to 2.5 months after last dose of LF111. In 1 subject tachycardia was reported concomitantly with hyperkalaemia; the event of tachycardia was assessed by the investigator as not related to LF111. No clinical signs of hyperkalaemia were reported in the remaining subjects. No ECG abnormalities were reported in association with hyperkalaemia. Two of 7 subjects discontinued LF111 treatment due to hyperkalaemia.

Bone fractures
In the long-term studies, bone fracture has been reported with LF111 as follows: ankle fracture (n=2; 0.1%), hand fracture (n=3; 0.1%), lower limb fracture (n=1; <0.1%), skull fractured base (n=1; <0.1%), spinal fracture (n=1; <0.1%) and wrist fracture (n=3; 0.1%). No fractures have been reported with desogestrel. In the long-term clinical trials, bone fractures were reported in 9 subjects with LF111. Information on bone mineral density was not available in any of the cases. Given the relatively short time to onset in most cases and plausible other aetiology in some cases, these cases do not support causality between drospirenone and fracture.

Venous thromboembolism
A short summary of the recent literature on the risk of VTE with hormonal contraception, suggesting no increased risk in general in users of progestogen-only contraception, was provided. It is not possible to extrapolate conclusions from findings with combined hormonal contraceptives containing drospirenone or from other progestogens. As there are no studies so far on drospirenone as a POP, it is not known whether the low risk of VTE, reported for other POPs, also could be expected for drospirenone. The limited data on hemostatic parameters are encouraging but cannot really predict whether there is an increased risk or not.

There is a need for more data on the risk of VTE in users of progestogen-only contraception in general and in users of drospirenone-only in particular, in addition to routine pharmacovigilance and a targeted questionnaire. The Applicant has committed to perform a post-authorization safety study (PASS) to further monitor the risk of VTE in users of drospirenone-only contraception and compare the risk to that with an appropriate comparator, pending feasibility analysis (see RMP).

Discontinuation due to AEs

During the short-term studies, 1.2% of subjects in the LF111 arm discontinued due to TEAEs (affective disorder, depression and abdominal pain lower; 1 subject each). No subjects discontinued due to TEAEs in the desogestrel or norethisterone arm. In the long-term studies, TEAEs leading to discontinuation reported in more than 1% of subjects concerned (LF111 vs. desogestrel): vaginal haemorrhage (0.7% vs. 5.4%), metrorrhagia (1.4% vs. 0.3%) and acne (1.4% vs. 2.7%). In study 304 in adolescents, 11 subjects (10.8%) discontinued due to TEAEs with metrorrhagia (5 subjects; 4.9%) being reported most commonly.

Safety in special populations

Adolescents

In study 304, 102 subjects have been treated with at least 1 dose of LF111 for a median treatment duration of 364 days (mean treatment duration: 312 days); 68 subjects (66.7%) have been treated for at least 364 days.

TEAEs were reported in 65 subjects (63.7%) with the most commonly reported TEAEs being nasopharyngitis (n=13; 12.7%), acne and viral respiratory tract infection (n=7; 6.9%, each), followed by headache, abdominal pain, bronchitis and viral infection (six subjects each; 5.9%).

TEAEs considered at least possibly related to LF111 were reported in 23 subjects (22.5%) with the following TEAEs being reported most commonly: metrorrhagia (4.9%), acne (3.9%) and mood

altered, abdominal distension, headache and weight increased (2.9% each).

The majority of TEAEs were graded mild or moderate; severe TEAEs were reported in 11 subjects (10.8%). The following severe TEAEs (reported in 1 subject (1.0%) each) were considered at least possibly related to LF111: breast pain, hot flush, alopecia, dysmenorrhoea and mood swings. The TEAE of severe mood swings led to premature discontinuation from the study.

No deaths were reported. Two subjects (2.0%) reported an SAE during the extension phase: pharyngitis and joint dislocation (both assessed as not related to LF111).

Conclusion on clinical safety
The safety profile for drospirenone (Slinda) for the indication of oral contraception is generally consistent with progestogen and anti-mineralocorticoid activities.

IV.6 Risk Management Plans

The MAH has submitted an updated risk management plan version 0.3 (dated 25/09/2019), 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 Slinda (drospirenone 4 mg film-coated tablets).

Safety specification

The Applicant proposes the following summary of safety concerns:

Important Identified Risks	• Hyperkalemia
Important Potential Risks	• Venous Thromboembolism • Bone fracture/Decrease in bone mineral density • Disturbances of liver function • Benign and malignant liver tumours • Ectopic pregnancy • Breast cancer
Missing Information	• Not applicable

The proposed safety concerns are acceptable.

Pharmacovigilance Plan

Table Part III.3: Ongoing and planned additional pharmacovigilance activities

Study and status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities by the competent authorities				
• Post-authorisation safety study	To investigate the important potential risk of VTE with the use of drospirenone vs an active comparator	Important potential risk of VTE	- Feasibility report	Within 3 months of finalisation of the SE/H/1809/01/DC, SE/H/1810/01/DC, SE/H/1811/01/DC, SE/H/1868/01/DC, SE/H/1869/01/DC, and SE/H/1893/01/DC, procedures
			- Study protocol	Depending on the outcome of the feasibility analysis, due dates are to be determined.

The Applicant proposes routine PhV activities to monitor the important identified and potential risks. Targeted follow-up questionnaires are proposed for hyperkalaemia, venous thromboembolism and bone fracture/decrease in bone mineral density. For the risk of hyperkalaemia, questionnaires are not specifically requested as part of the RMP; if the Applicant intends to use questionnaires for hyperkalaemia, the Applicant may consider implementing a minimum level of serum potassium values for sending out a questionnaire in order to collect more detailed information on the moderate to severe cases of hyperkalaemia.

PASS

The Applicant has committed to perform a post-authorization safety study (PASS) to further monitor the risk of VTE in users of drospirenone-only contraception and compare the risk to that with an appropriate comparator. As such a PASS needs to very large and well designed in order to be scientifically sound, it is proposed that the Applicant, as a first step, presents a feasibility analysis for a PASS. Since a thorough evaluation and discussion of a feasibility analysis was not possible to perform within the scope of the procedure, this was included in the RMP.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The MAH has satisfactory responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 0.3 dated 25/09/2019, is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 PIL was Spanish.
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

Pharmacodynamic studies investigating the mechanism of contraceptive action demonstrated that Slinda acts via inhibition of ovulation and with additional effects on cervical mucus and the endometrium, as expected for a progestogen. The submitted studies did not demonstrate potential effects of missed pills around the hormone-free interval, however, this is handled via appropriate recommendations in the SmPC and PL.

The European pivotal efficacy studies showed adequate contraceptive efficacy of Slinda with a pooled PI below 1, with adequate precision. In the US study, the overall PI in all women was higher compared with that of the EU studies. Potential reasons for this difference (BMI, compliance, other factors) were adequately discussed and clarified and did not raise specific concerns as higher Pearl Index values are often seen in US vs. EU studies.

The safety profile for Slinda seems consistent with its progestogenic action and anti-mineralocorticoid activity; the EU long-term studies have shown an expected pattern of TEAEs.

A need for more data on the risk of VTE in users of progestogen-only contraception in general and in users of drospirenone-only in particular was identified. The Applicant has committed to perform a post-authorization safety study (PASS) to monitor the risk of VTE in users of drospirenone-only contraception and compare the risk to that with an appropriate comparator, following an initial feasibility analysis for a PASS.

Slinda was designed with 4 hormone-free days every cycle in order to trigger a withdrawal bleed, thereby creating a more predictable bleeding pattern than that usually seen with progestogen-only contraception that inhibits ovulation. As discussed above, the results do not support a reliable withdrawal bleed and the bleeding pattern cannot be regarded as predictable. The 4 hormone-free days may, on the other hand, represent an apparent risk for contraceptive failure, especially if the hormone free interval is unintentionally prolonged (due to missed pills or to delayed start of the next pack). In hindsight, this uncertainty could have been avoided if the progestogen in Slinda had been

given on a continuous basis. However, pharmacodynamic studies have shown adequate inhibition of ovulation and the pivotal (EU) studies showed an acceptable Pearl Index with the proposed 24+4 dosing regimen. The bleeding pattern is not likely to have been greatly improved by the use of a continuous regimen. The risks related to contraceptive failure due to missed pills in close proximity to the 4-day pill-free interval are handled via adequate (conservative) advice in the SmPC and PL.

The benefit/risk ratio is considered positive and Slinda, 4 mg film-coated tablet is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Slinda, 4 mg film-coated tablet was positively finalised on 2019-09-26.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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