A Pivotal, Multicenter, Double-Blind, Double-Dummy, Randomised Trial on the Contraceptive Efficacy, Tolerability and Safety of a novel oestrogen free contraceptive (Drospirenone 4mg 24+4) over 9 Cycles in Comparison with Desogestrel 75 µg

Dr Ali Kubba
Guy's and St. Thomas' NHS Foundation Trust UK
London Bridge Hospital, London

ESC 2018

DISCLOSURES

Dr Ali Kubba:

Consultations: Bayer, Merck, Gedeon Ritcher, Exeltis

Why a new product?.Oestrogen free contraception has a safer CV profile, but cycle control needs improvement

- Approximately 100 million women worldwide currently use an oral contraceptive containing an estrogen plus a progestin (COCs) [1]. COCs' use is associated with an increased risk of a venous thromboembolism (VTE) and cardiovascular disease [2,3].
- The World Health Organization has documented that oestrogen free contraceptives do not increase the risk of VTE, stroke and myocardial infarction [4]. This safety advantage should result in more women receiving this method
- Traditionally these pills, have been associated with poor cycle control, stringent missed-pill rules and with a suboptimal bleeding profile, a well recognized barrier to more widespread use. A novel drospirenone (DRSP)-only pill was developed to improve compliance and side effects.

1. Beller JP & McCartney CR 2013. Cardiovascular risk and combined oral contraceptives: clinical decisions in settings and uncertainty. Am J Obstet Gynecol 1: 39-41; 2 Collaborative Study Group. 1998, A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 μg/day or levonorgestrel 30 μg/day. Eur J Contracept Reprod Health Care 1998;3: 169-178 3 EMA/CHMP Guideline on Clinical Investigation of Steroid Contraceptives in Women. Committee for Medicinal Products for Human Use. 27 July 2005. EMEA/CPMP/EWP/519/98 Rev1. Accessed on 24th October 2014 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003349.pdf 4 Gerlinger C, Trussell J, Mellinger U, Merz M, Marr J, Bannemerschult R et al. 2014. Different Pearl Indices in studies of hormonal contraceptives in the United States: impact of study population. Contraception 90: 142-146

Objectives of the Study

- The primary objective of this prospective, multicenter, comparative Phase III study was to demonstrate the efficacy and safety of DRSP-only oral contraceptive (DRSP 4-mg tablets for 24 days+placebo for 4 days).
- A secondary objective of the study was to demonstrate the safety and tolerability of DRSP 4mg 24+4 in comparison to desogestrel 0.075 mg, especially regarding bleeding pattern. Also was to assess the efficacy of DRSP in a 24/4 regimen vs DSG in a continuous regimen

…Tolerability and Safety of a novel

Overview of Study

	Study 302
Objective	Contraceptive efficacy, tolerability, safety
Design	Prospective, comparative, randomized, double-blind, double-dummy, multicenter
Study Population	Healthy women of childbearing age, 18-45 yr; SBP <140 mm Hg and DBP <90 mm Hg
No. of subjects	Planned: 1200 subjects: 857, DRSP; 343, DSG Analyzed, efficacy: 858, DRSP; 332, DSG Completers: 688, DRSP; 250, DSG
Dosing	DRSP 4 mg (24/4) vs DSG 0.075 mg, 28 active tablets (28/0); once-daily oral administration, 9 cycles; randomization ratio 5:2 (DRSP:DSG)

…Tolerability and Safety of a novel

Baseline Characteristics

	302	
n (%)	DRSP (N=858)	DSG (N=332)
Age, mean (SD), yr	28.9 (7.1)	28.7 (7.1)
Age group		
≤35 yr	682(79.5)	259 (78.0)
>35 yr	176 (20.5)	73 (22.0)
BMI, mean (SD) (kg/m2)	23.0 (3.5)	22.8 (3.9)
BMI group		
<30	828 (96.5)	316 (95.2)
≥30	30 (3.5)	16 (4.8)
BP group (mm Hg)		
SBP <130, DBP <85	727 (84.7)	290 (87.3)
SBP ≥130, DBP ≥85	131 (15.3)	42 (12.7)
Presence of ≥1 VTE risk factor	142 (16.5)	59 (17.8)
Current smoker	237 (27.6)	103 (31.0)
Direct switchers	628 (73.2)	259 (78.0)

VTE=venous thromboembolism.

…Tolerability and Safety of a novel

DRSP 24+4 Efficacy

Pooled Analysis: Studies 301 and 302

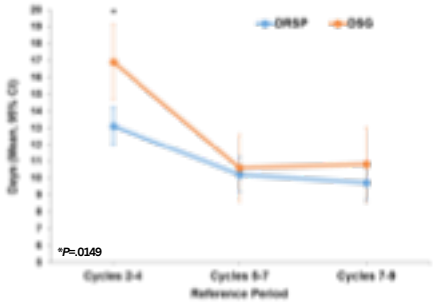
	Total (N=1571)		Subjects ≤35 yr (n=1251)	
	PI	95% CI	PI	95% CI
Overall PI	0.72	0.31-1.43	0.93	0.40-1.84
Corrected overall PIa	0.79	0.34-1.56	1.02	0.44-2.01

aCorrected for additional contraception and sexual activity.

- Study 301- Prospective, multicenter (41 EU sites and 753 participants), non-comparative Phase III study aimed to demonstrate the efficacy and safety of DRSP-only oral contraceptive (DRSP 4-mg tablets for 24 days+placebo for 4 days)

1. [illegible] Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and
2. [illegible] Efficacy, Tolerability and Safety of a

Fewer Total Bleeding and/or Spotting Days With DRSP



DRSP 4mg bleeding patterns

87% of women had a favorable experience with DRSP 4mg 24/4®

Cluster	% of women	Mean number of days of bleeding/spotting by cycle
1	45	1.24 +/- 0.11
2	14	3.59 +/- 0.17
3	28	4.63 +/- 0.21
4	13	9.33 +/- 0.30

87%

Source: D.Archer Predictors of Unscheduled Spotting and Bleeding in Women using Oral Drospirenone 4.0 mg 24/4 for Contraception- ESC 2018

Safety profile

Frequency >2.0% in Any Group

Preferred Term	DRSP (n=858)		DSG (n=332)	
	n	%	n	%
Vaginal hemorrhage	32	3.7	24	7.2
Headache	38	4.4	17	5.1
Acne	27	3.1	19	5.7
Nasopharyringitis	29	3.4	13	3.9
Cervical dysplasia	26	3.0	11	3.3
Weight increased	21	2.4	6	1.8
Influenza	6	0.7	7	2.1

The most common TEAEs leading to withdrawal

	DRSP n (%)	DSG n (%)
Vaginal hemorrhage	22 (2.6)	18 (5.4)
Acne	9 (1.0)	9 (2.7)
Weight increased	8 (0.9)	3 (0.9)
Uterine hemorrhage	5 (0.6)	3 (0.9)

Safety summary

1-No reports of venous thromboembolism during the clinical development program
2-No reports of arterial thromboembolism, myocardial infarction, stroke, or pulmonary embolism
3-No malignancies were reported
4-No clinically relevant changes in hemostatic parameters
5-Hyperkalemia
- Increased blood potassium was reported in 2 subjects with DRSP in study 302, but there were no clinical signs related to hyperkalemia; both increases resolved

[illegible] Efficacy, Tolerability and Safety of a novel
Poster #ESC230 - Drospirenone as estrogen-free pill and hemostasis: coagulatory study results comparing a novel 4 mg formulation in a 24+4 cycle with desogestrel 75 µg per day

Study Key Findings

- DRSP 4mg 24+4 is a novel oestrogen free oral contraceptive that provides clinical efficacy similar to that of the currently marketed combined oral contraceptive
- DRSP 4mg 24+4 has a good safety profile, with no reports of venous thromboembolism during the clinical development program, no reports of arterial thromboembolism, myocardial infarction, stroke, or pulmonary embolism and no clinically relevant changes in hemostatic parameters
- DRSP 4mg 24+4 has demonstrated and a better bleeding profile compared to desogestrel, which can lead to better tolerability and acceptance
- The 24 missing pill rule, similar as COCs, is also an important advantage for women and clinicians

[illegible] Efficacy, Tolerability and Safety of a novel

Thank you