Clinical trial results:
Controlled, prospective, multicentre, open, randomized study to investigate the contraceptive efficacy, bleeding patterns, metabolic effects, cycle-associated complaints, acceptance, and safety of an oral contraceptive containing 30 µg ethinylestradiol and 150 µg levonorgestrel, in two different regimens of intake (4 extended cycles of 91 days versus 13 conventional cycles of 28 days) in healthy women

Summary

EudraCT number	2012-004762-18
Trial protocol	DE
Global end of trial date	07 July 2016

Results information

Result version number	v1 (current)
This version publication date	22 July 2017
First version publication date	22 July 2017

Trial information

Trial identification

Sponsor protocol code	EL20T0.01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Madaus GmbH
Sponsor organisation address	Colonia Allee 15, Cologne, Germany, 51067
Public contact	Group Leader Study Manager, Meda Pharma GmbH & Co. KG, 0049 617288801, 42b@medapharma.de
Scientific contact	Head of Clinical Affairs Meda, Meda Pharma GmbH & Co. KG, 0049 617288801, 42b@medapharma.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2016
Global end of trial reached?	Yes
Global end of trial date	07 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the contraceptive efficacy of the EE30/LNG150 84+7 extended-cycle regimen according to the requirements of the EMA "Guideline on clinical investigation of steroid contraceptives in women" (EMEA/CPMP/EWP/519/98 Rev 1).

Protection of trial subjects:

No specific additional measures to minimise pain and distress were required. The subjects could withdraw from treatment at any time and for any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 1314
Worldwide total number of subjects	1314
EEA total number of subjects	1314

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1314
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study population consists of healthy eligible females aged 18-35. These subjects will be prospectively stratified into three strata with respect to previous COC use (Stratum A: new users, Stratum B: conventional-cycle users, and stratum C: extended-cycle users) and will be randomized to a treatment arm within strata.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lisa Lang

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ethinylestradiol and Levonorgestrel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets containing EE 30 µg, LNG 150 µg as active ingredients and 32.57 mg lactose monohydrate as an excipient. 1 tablet per day, taken orally, for 84 consecutive days, followed by
a 7-day tablet-free interval for 4 extended cycles.

Arm title	Lisa Kurz

Arm description: -

Arm type	Active comparator for secondary end-point.
Investigational medicinal product name	Ethinylestradiol and Levonorgestrel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets containing EE 30 µg, LNG 150 µg as active ingredients and 32.57 mg lactose monohydrate as an excipient. 1 tablet per day, taken orally, for 21 consecutive days, followed by
a 7-day tablet-free interval for 13 conventional cycles.

Number of subjects in period 1	Lisa Lang	Lisa Kurz
Started	1072	242
Completed	785	171
Not completed	287	71
Adverse event, serious fatal	1	-
Consent withdrawn by subject	80	14
Adverse event, non-fatal	70	28
Other	21	4
Not exposed	17	11
At the discretion of the Investigator	3	-
Lost to follow-up	36	6
Protocol deviation	59	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	1314	1314	
Age categorical Units: Subjects			
18-35	1314	1314	
Gender categorical Units: Subjects			
Female	1314	1314	
Male	0	0	

End points

End points reporting groups

Reporting group title	Lisa Lang
Reporting group description: -	
Reporting group title	Lisa Kurz
Reporting group description: -	

Primary: Overall (Unadjusted) Pearl Index

End point title	Overall (Unadjusted) Pearl Index[1][2]
End point description:	
End point type	Primary
End point timeframe:	
Study duration.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The unadjusted Pearl Index was calculated only for the extended-cycle group as planned in the clinical trial protocol.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The unadjusted Pearl Index was calculated only for the extended-cycle group as planned in the clinical trial protocol.

End point values	Lisa Lang			
Subject group type	Reporting group			
Number of subjects analysed	1053			
Units: Pregnancies / Women years * 100				
number (confidence interval 95%)	0.483 (0.132 to 1.237)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Study duration.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1
Reporting groups	
Reporting group title	Lisa Lang
Reporting group description: Safety Population.	
Reporting group title	Lisa Kurz
Reporting group description: Safety population.	

Serious adverse events	Lisa Lang	Lisa Kurz	
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 1055 (4.64%)	13 / 231 (5.63%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ovarian tumour			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma stage 0			
subjects affected / exposed	1 / 1055 (0.09%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 1055 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Lipoma excision			

subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy on oral contraceptive			
subjects affected / exposed	4 / 1055 (0.38%)	2 / 231 (0.87%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	16 / 1055 (1.52%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 16	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	2 / 1055 (0.19%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic adhesions			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 1055 (0.09%)	2 / 231 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychosomatic disease			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 1055 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 1055 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	2 / 1055 (0.19%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Thyroglossal cyst			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 1055 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	3 / 1055 (0.28%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 1055 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			

subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 1055 (0.09%)	2 / 231 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 1055 (0.09%)	0 / 231 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 1055 (0.00%)	1 / 231 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3.3 %

Non-serious adverse events	Lisa Lang	Lisa Kurz	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	666 / 1055 (63.13%)	136 / 231 (58.87%)	
Nervous system disorders			
Headache			
subjects affected / exposed	91 / 1055 (8.63%)	19 / 231 (8.23%)	
occurrences (all)	91	19	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	287 / 1055 (27.20%)	48 / 231 (20.78%)	
occurrences (all)	287	48	
Pelvic pain			
subjects affected / exposed	43 / 1055 (4.08%)	2 / 231 (0.87%)	
occurrences (all)	43	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	35 / 1055 (3.32%)	5 / 231 (2.16%)	
occurrences (all)	35	5	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	44 / 1055 (4.17%)	12 / 231 (5.19%)	
occurrences (all)	44	12	
Psychiatric disorders			
Mood swings			
subjects affected / exposed	50 / 1055 (4.74%)	6 / 231 (2.60%)	
occurrences (all)	50	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	42 / 1055 (3.98%)	6 / 231 (2.60%)	
occurrences (all)	42	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2014	Modifications based on update of the investigators brochure which in turn was harmonised with the current, approved SmPC for the meanwhile registered IMP. No impact on prior risk-benefit assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported