# 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<br>Units: Subjects | | | |
| 18-35 | 1314 | 1314 | |
| Gender categorical<br>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:<br>Study duration. | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |
| **Reporting groups** | |
| Reporting group title | Lisa Lang |
| Reporting group description:<br>Safety Population. | |
| Reporting group title | Lisa Kurz |
| Reporting group description:<br>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