Clinical trial results:
Characterisation of ovulation inhibition and effects on metabolic parameters and haemostatic system of multiple administrations of a fixed-dose combination product containing 0.02 mg ethinylestradiol and 2 mg dienogest (24+4) in a multiple administration, comparative parallel-group trial vs. a marketed product containing 0.02 mg ethinylestradiol and 0.10 mg levonorgestrel with healthy females of childbearing potential

Summary

EudraCT number	2012-000041-12
Trial protocol	NL
Global end of trial date	05 March 2013

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	49/11/EDG/TP2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CRO SocraTec R&D study No.: 1259ed11ct

Notes:

Sponsors

Sponsor organisation name	Zentiva k.s.
Sponsor organisation address	U Kabelovny 130, Prague 10 Dolní Měcholupy, Czech Republic, 10237
Public contact	Tomáš Hauser, M.D., Zentiva k.s., 00420 267 243 451, tomas.hauser@sanofi.com
Scientific contact	Tomáš Hauser, M.D., Zentiva k.s., 00420 267 243 451, tomas.hauser@sanofi.com

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	31 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2013
Global end of trial reached?	Yes
Global end of trial date	05 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aims of this clinical trial are:
• descriptive characterisation of the influence of Test or Reference on ovarian activity determined by means of maximum follicular diameter and Hoogland score
• descriptive characterisation of the effect of Test or Reference on endometrial thickness, cervical mucus as well as on the pituitary and ovarian hormones the latter determined via follicle stimulating hormone (FSH), luteinising hormone (LH), estradiol (E2) and progesterone (P)
• descriptive characterisation of effect of Test or Reference on sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) levels, C-reactive protein, lipid profile as well as haemostatic and carbohydrate parameters
• descriptive characterisation of bleeding pattern
• descriptive characterisation of return of ovulation
• descriptive characterisation of overall safety and tolerability in the study population

Protection of trial subjects:

Subjects we advised to use barrier contraceptive methods.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	60
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

date of first enrolment: 2012-04-16
Clinical site: dinox b.v.
Hanzeplein 1, entrance 53
9713 GZ Groningen,
The Netherlands
Tel.: +31-50-361099-9
Fax: +31-50-361090-9

Pre-assignment

Screening details:

demographic data
medical, gynaecological and obstetric history (prior and concomitant medication,concomitant diseases)
physical examination
gynaecological and breast examination (incl. TVUS)
vital signs,BMI
clinical laboratory: blood analysis incl. haematology and serum chemistry
urine pregnancy test
PAP smear

Period 1

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

Blinding implementation details:

The study was performed in an open design.

Arms

Are arms mutually exclusive?	Yes
Arm title	TEST

Arm description:

Included subjects that entered the treatment phase and received Test treatment, stratified by time point of ovulation observed in the pre-treatment cycle.

Arm type	Experimental
Investigational medicinal product name	BONADEA PLUS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily administration of one tablet of Test containing 0.02 mg EE and 2 mg DNG over 24 days followed by 4 treatment-free days per cycle. Each treatment was administered over three treatment cycles of 28 days each.

Arm title	REFERENCE

Arm description:

Included subjects who entered the treatment phase and received Reference treatment stratified by time point of ovulation observed in the pre-treatment cycle.

Arm type	Active comparator

Investigational medicinal product name	Miranova®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily administration of one tablet of Reference containing 0.02 mg EE and 0.1 mg LNG over 21 days followed by 7 treatment-free days per cycle. Each treatment was administered over three treatment cycles of 28 days each.

Number of subjects in period 1[1]	TEST	REFERENCE
Started	29	30
Completed	27	26
Not completed	2	4
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1 subject not receiving medication:
Reason: drop out due to withdrawal of consent

Baseline characteristics

Reporting groups

Reporting group title	Treatment phase

Reporting group description: -

Reporting group values	Treatment phase	Total	
Number of subjects	59	59	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	59	59	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	24.63		
standard deviation	± 3.9	-	
Gender categorical Units: Subjects			
Female	59	59	
Male	0	0	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS was defined as all subjects of the SAS, who after randomisation, completed at least one treatment cycle of 28 days, or in whom ovulation and/or a Hoogland score >4 were observed in any cycle during randomised treatment.

Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects:
• who completely passed the pre-defined treatment regimen and
• whose relevant trial variables were available in all periods, and
• who finished the clinical trial without major protocol deviations.

Reporting group values	Full analysis set	Per protocol set	
Number of subjects	57	53	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	57	53	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	24.4	24.34	
standard deviation	± 3.7	± 3.7	
Gender categorical Units: Subjects			
Female	57	53	
Male	0	0	

End points

End points reporting groups

Reporting group title	TEST

Reporting group description:

Included subjects that entered the treatment phase and received Test treatment, stratified by time point of ovulation observed in the pre-treatment cycle.

Reporting group title	REFERENCE

Reporting group description:

Included subjects who entered the treatment phase and received Reference treatment stratified by time point of ovulation observed in the pre-treatment cycle.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS was defined as all subjects of the SAS, who after randomisation, completed at least one treatment cycle of 28 days, or in whom ovulation and/or a Hoogland score >4 were observed in any cycle during randomised treatment.

Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects:
• who completely passed the pre-defined treatment regimen and
• whose relevant trial variables were available in all periods, and
• who finished the clinical trial without major protocol deviations.

Primary: Maximum follicular diameter - Treatment cycle 1 (FAS)

End point title	Maximum follicular diameter - Treatment cycle 1 (FAS)

End point description:

End point type	Primary

End point timeframe:

Tretament cycle 1, 28 days

End point values	TEST	REFERENCE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: mm				
arithmetic mean (standard deviation)	7.14 (± 2.9)	6.92 (± 1.5)		

Statistical analyses

Statistical analysis title	Max.follicular diameter-treatment comparison (FAS)

Statistical analysis description:

The treatment groups were compared per treatment cycle (treatment cycles 1 and 3, only) using a 2-way analysis of variance models, in this case a linear mixed model with repeated measures, including the factors "treatment group", and "time (treatment cycle)" as well as an interaction factor between these two factors. The factor "treatment group" had two levels: Test and Reference. The factor "time" had two levels: treatment cycles 1 and 3.

Comparison groups	TEST v REFERENCE
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Mean difference (final values)
Point estimate	0.9732
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8419
upper limit	1.1249

Notes:

[1] - Several mixed models with different structures of the covariance matrix were calculated to find the best model. The model with best (=smallest) Akaike Information Criteria was to be taken. If more than one Akaike Information Criteria was smallest, the easiest structure of covariance matrix was to be taken; Easiest was compound symmetry, followed by unstructured, autoregressive and autoregressive moving average 1.1.

Primary: Maximum follicular diameter - Treatment cycle 3 (FAS)

End point title	Maximum follicular diameter - Treatment cycle 3 (FAS)

End point description:

End point type	Primary

End point timeframe:

Treatment cycle 3, 28 days

End point values	TEST	REFERENCE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	26		
Units: mm				
arithmetic mean (standard deviation)	7 (± 2.44)	9.1 (± 4.96)		

Statistical analyses

Statistical analysis title	Max.follicular diameter-treatment comparison (FAS)

Statistical analysis description:

The treatment groups were compared per treatment cycle (treatment cycles 1 and 3, only) using a 2-way analysis of variance models, in this case a linear mixed model with repeated measures, including the factors "treatment group", and "time (treatment cycle)" as well as an interaction factor between these two factors. The factor "treatment group" had two levels: Test and Reference. The factor "time" had two levels: treatment cycles 1 and 3.

Comparison groups	TEST v REFERENCE
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Mean difference (final values)
Point estimate	0.7479

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6023
upper limit	0.9287

Notes:

[2] - Several mixed models with different structures of the covariance matrix were calculated to find the best model. The model with best (=smallest) Akaike Information Criteria was to be taken. If more than one Akaike Information Criteria was smallest, the easiest structure of covariance matrix was to be taken; Easiest was compound symmetry, followed by unstructured, autoregressive and autoregressive moving average 1.1.

Primary: Hoogland and Skouby score - Treatment cycle 1 (FAS)

End point title	Hoogland and Skouby score - Treatment cycle 1 (FAS)

End point description:

End point type	Primary

End point timeframe:

Treatment cycle 1, 28 days

End point values	TEST	REFERENCE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: cumulative count	39	34		

Statistical analyses

Statistical analysis title	Hoogland/Skouby score-treatment comparison (FAS)

Statistical analysis description:

For the maximum Hoogland and Skouby score, the treatment groups will be compared per treatment cycle (treatment cycle 1 and 3) using the two-sided Mann-Whitney-U Test.

Comparison groups	REFERENCE v TEST
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Hoogland and Skouby score - Treatment cycle 3 (FAS)

End point title	Hoogland and Skouby score - Treatment cycle 3 (FAS)

End point description:

End point type	Primary

End point timeframe:

Treatment cycle 3, 28 days

End point values	TEST	REFERENCE		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	26		
Units: cumulative count	38	49		

Statistical analyses

Statistical analysis title	Hoogland/Skouby score-Treatment comparison (FAS)

Statistical analysis description:

For the maximum Hoogland and Skouby score, the treatment groups will be compared per treatment cycle (treatment cycle 1 and 3) using the two-sided Mann-Whitney-U Test.

Comparison groups	TEST v REFERENCE
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
125 study days - Treatment phase (3 Treatment cycles of 28 days) + Follow up phase	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	TEST
Reporting group description:	
Adverse events reported by subjects that received the Test treatment	
Reporting group title	REFERENCE
Reporting group description:	
Adverse events reported by subjects that received the Reference treatment	

Serious adverse events	TEST	REFERENCE	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	TEST	REFERENCE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 29 (96.55%)	29 / 30 (96.67%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Malaise			

subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Hangover			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Irritability			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Dysmenorrhoea			
subjects affected / exposed	5 / 29 (17.24%)	8 / 30 (26.67%)	
occurrences (all)	9	12	
Breast pain			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Vaginal discharge			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vulvovaginal pruritus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Coital bleeding			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Cough			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Libido decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Affect lability			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Traumatic haematoma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Contusion			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Concussion			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Eye injury			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 29 (41.38%)	17 / 30 (56.67%)	
occurrences (all)	28	24	

Migraine			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Amnesia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Migraine with aura			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 29 (10.34%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Abdominal pain lower			
subjects affected / exposed	7 / 29 (24.14%)	5 / 30 (16.67%)	
occurrences (all)	8	7	
Nausea			
subjects affected / exposed	5 / 29 (17.24%)	3 / 30 (10.00%)	
occurrences (all)	6	3	
Abdominal pain upper			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

Abdominal distension			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Abdominal discomfort			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Anorectal discomfort			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Lip swelling			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Dental discomfort			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Acne			
subjects affected / exposed	2 / 29 (6.90%)	4 / 30 (13.33%)	
occurrences (all)	2	4	
Eczema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 29 (10.34%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Arthralgia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 29 (34.48%)	15 / 30 (50.00%)	
occurrences (all)	10	19	
Gastroenteritis			
subjects affected / exposed	8 / 29 (27.59%)	2 / 30 (6.67%)	
occurrences (all)	8	2	
Oral herpes			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	2 / 29 (6.90%)	5 / 30 (16.67%)	
occurrences (all)	2	5	
Cystitis			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Furuncle			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Carbuncle			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			

Increased appetite subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 30 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported