Clinical trial results:
Effect of a progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia, srl) administered by oral route compared to an oral progesterone 200 mg capsule (Prometrium, Rottapharm SpA) on the endometrial thickness of post-menopausal women under hormone replacement therapy. A pilot, prospective, open-label, randomised, three arm, parallel-group, single centre, phase II clinical trial.

Summary

EudraCT number	2014-001185-10
Trial protocol	IT
Global end of trial date	28 December 2015

Results information

Result version number	v1 (current)
This version publication date	19 May 2017
First version publication date	19 May 2017

Trial information

Trial identification

Sponsor protocol code	14I/Prg02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	IBSA Institut Biochimique SA
Sponsor organisation address	Via del Piano 29, Pambio-Noranco, Switzerland, 6915
Public contact	Clinical Research Manager, IBSA Institut Biochimique SA, +41 583601000, claudia.scarsi@ibsa.ch
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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	21 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2015
Global end of trial reached?	Yes
Global end of trial date	28 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

to evaluate the protective effect of progesterone on the endometrium of post-menopausal women under HRT, assessed by measurement of endometrial thickness, upon administration of two dosing schemes (continuous sequential and combined continuous) of progesterone 25 mg solution administered by oral route, compared to an oral progesterone 200 mg capsule (Prometrium).

Protection of trial subjects:

The study population that has been selected (post-menopausal women) is the population that can benefit from HRT and for whom combined use of oestrogen and progesterone is indicated.
In an attempt to assure that the results of this study are applicable to the largest segment of the universe of patients undergoing HRT, exclusion criteria were limited primarily to those that reduce the risk of serious adverse events in the enrolled population, or that eliminate potential enrolees unlikely to benefit from treatment.

The study was conducted in accordance with the standard requirements and recommendations for HRT. Oestrogen was used according to its Summary of Product Characteristics (SPC). Progesterone was used according to the instructions given for the reference product (Prometrium) and to the current clinical practice. Considering the absorption profile of progesterone 25 mg solution, no additional safety concern was advised for this study with respect to standard HRT. Anyway, should the product prove ineffective or too much effective, the frequent checks (17 days, 1 and 3 months) and the short duration of treatment (3 months) minimized the risks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2014
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	Italy: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Post-menopausal women (defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml and since maximum 10 years, with intact uterus) were selected to comply with the protocol procedures. All of the subjects provided their written consent prior to the start of the screening visit.

Pre-assignment

Screening details:

the screening procedures included: demography; medical/surgical and medication history, general physical examination (including weight, height, blood pressure, heart rate, pelvic and breast examination); FSH. Transvaginal scan, mammography and/or a breast ultrasound and Pap test if not already available within the last 6 months.

Period 1

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

Blinding implementation details:

open label clinical trials

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A

Arm description:

Progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia srl, Italy) taken by oral route once-a-day at bedtime with a continuous sequential regimen.

Arm type	Experimental
Investigational medicinal product name	Progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia srl, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Oral use

Dosage and administration details:

Each vial (1.119 mL) contained 25 mg of progesterone (theoretical concentration 22.35 mg/mL).
Progesterone 25 mg solution had to be administered by oral route at the dosage of 25 mg (1 vial) once-a-day for 12 days/month (where a month is considered as 28 days) starting on day 17 (continuous sequential HRT).
It was recommended to take the medication far from meals and at bedtime.
The whole content of the ampule had to be drank altogether without prior dilution in water. Water could be drank after the solution was been swallowed, if the patient so desires.

Investigational medicinal product name	Progynova (estradiol valerate) 2 mg coated tablets (Bayer SpA, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Non-Investigational Medicinal Products:
The dosage was one tablet per day. The tablet had to be taken whole with some liquid and preferably always at the same time of the day.
Treatment could be started on any convenient day; this day had to be considered as day 1 of the study.
Progynova had to be taken continuously without a break between packs (continuous HRT).

If a dose was forgotten it could be taken as soon as possible. When more than 12 hours had elapsed, it was recommended to continue with the next dose without taking the forgotten tablet

Investigational medicinal product name	Dufaston (didrogesteron) 10 mg film-coated tablets (Abbott srl, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients displaying signs of hyperplasia at the histological assessment of the Final Visit had to receive didrogesteron (Dufaston) film-coated tablets (Abbott srl, Italy) 10 mg/day to be taken orally for 14 days. The dosage was one tablet per day. The tablet had to be taken whole with some liquid and preferably always at the same time of the day.

Arm title	Treatment B

Arm description:

Progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia srl, Italy) taken by oral route once-a-day at bedtime with a combined continuous regimen

Arm type	Experimental
Investigational medicinal product name	Progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia srl, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Oral use

Dosage and administration details:

Progesterone 25 mg solution (Pleyris 25 mg injectable solution, IBSA Farmaceutici Italia srl, Italy).
Each vial (1.119 mL) contained 25 mg of progesterone (theoretical concentration 22.35 mg/mL).
Progesterone 25 mg solution had to be administered by oral route at the dosage of 25 mg (1 vial) once-a-day without interruption for 3 months starting on day 1 (combined continuous HRT).
It was recommended to take the medication far from meals and at bedtime.
The whole content of the ampule had to be drank altogether without prior dilution in water. Water could be drank after the solution was been swallowed, if the patient so desires.

Investigational medicinal product name	Progynova (estradiol valerate) 2 mg coated tablets (Bayer SpA, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Non-Investigational Medicinal Products:
The dosage was one tablet per day. The tablet had to be taken whole with some liquid and preferably always at the same time of the day.
Treatment could be started on any convenient day; this day had to be considered as day 1 of the study.
Progynova had to be taken continuously without a break between packs (continuous HRT).
If a dose was forgotten it could be taken as soon as possible. When more than 12 hours had elapsed, it was recommended to continue with the next dose without taking the forgotten tablet

Investigational medicinal product name	Dufaston (didrogesteron) 10 mg film-coated tablets (Abbott srl, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients displaying signs of hyperplasia at the histological assessment of the Final Visit had to receive didrogesteron (Dufaston) film-coated tablets (Abbott srl, Italy) 10 mg/day to be taken orally for 14 days. The dosage was one tablet per day. The tablet had to be taken whole with some liquid and

preferably always at the same time of the day.

Arm title	Treatment C

Arm description:

Prometrium (micronized progesterone) 200 mg soft capsules for oral use (Rottapharm SpA, Italy) taken once-a-day at bedtime with a continuous sequential regimen.

Arm type	Active comparator
Investigational medicinal product name	Prometrium (micronized progesterone) 200 mg soft capsules for oral and vaginal use (Rottapharm SpA, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Prometrium had to be administered by oral route at the dosage of 200 mg (1 capsule) once-a-day for 12 days/month (where a month is considered as 28 days) starting from day 17.
It was recommended to take the medication far from meals and at bedtime.

Investigational medicinal product name	Progynova (estradiol valerate) 2 mg coated tablets (Bayer SpA, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Non-Investigational Medicinal Products:
The dosage was one tablet per day. The tablet had to be taken whole with some liquid and preferably always at the same time of the day.
Treatment could be started on any convenient day; this day had to be considered as day 1 of the study.
Progynova had to be taken continuously without a break between packs (continuous HRT).
If a dose was forgotten it could be taken as soon as possible. When more than 12 hours had elapsed, it was recommended to continue with the next dose without taking the forgotten tablet

Investigational medicinal product name	Dufaston (didrogesteron) 10 mg film-coated tablets (Abbott srl, Italy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients displaying signs of hyperplasia at the histological assessment of the Final Visit had to receive didrogesteron (Dufaston) film-coated tablets (Abbott srl, Italy) 10 mg/day to be taken orally for 14 days. The dosage was one tablet per day. The tablet had to be taken whole with some liquid and preferably always at the same time of the day.

Number of subjects in period 1	Treatment A	Treatment B	Treatment C
Started	2	2	4
Completed	2	2	4

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A
Reporting group description:	
Progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia srl, Italy) taken by oral route once-a-day at bedtime with a continuous sequential regimen.	
Reporting group title	Treatment B
Reporting group description:	
Progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia srl, Italy) taken by oral route once-a-day at bedtime with a combined continuous regimen	
Reporting group title	Treatment C
Reporting group description:	
Prometrium (micronized progesterone) 200 mg soft capsules for oral use (Rottapharm SpA, Italy) taken once-a-day at bedtime with a continuous sequential regimen.	

Reporting group values	Treatment A	Treatment B	Treatment C
Number of subjects	2	2	4
Age categorical Units: Subjects			
Adults (18-64 years)	2	2	4
Age continuous Units: years			
arithmetic mean	52	52.5	49.5
standard deviation	± 0	± 3.54	± 5.26
Gender categorical Units: Subjects			
Female	2	2	4

Reporting group values	Total		
Number of subjects	8		
Age categorical Units: Subjects			
Adults (18-64 years)	8		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	8		

End points

End points reporting groups

Reporting group title	Treatment A
Reporting group description:	
Progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia srl, Italy) taken by oral route once-a-day at bedtime with a continuous sequential regimen.	
Reporting group title	Treatment B
Reporting group description:	
Progesterone 25 mg solution (Pleyris, IBSA Farmaceutici Italia srl, Italy) taken by oral route once-a-day at bedtime with a combined continuous regimen	
Reporting group title	Treatment C
Reporting group description:	
Prometrium (micronized progesterone) 200 mg soft capsules for oral use (Rottapharm SpA, Italy) taken once-a-day at bedtime with a continuous sequential regimen.	

Primary: measurement of endometrial thickness at 3 (day 90) months

End point title	measurement of endometrial thickness at 3 (day 90) months[1]
End point description:	
The primary objective of this study was to evaluate the protective effect of progesterone on the endometrium of post-menopausal women under HRT, assessed by measurement of endometrial thickness, upon administration of two dosing schemes (continuous sequential and combined continuous) of progesterone 25 mg solution administered by oral route, compared to an oral progesterone 200 mg capsule (Prometrium).	
End point type	Primary
End point timeframe:	
Endometrial thickness has been measured by TVU at 3 (day 90) months of treatment with estrogen and progesterone.	

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: Due to the early interruption of the study and the resulting small number of patients randomised, it was not possible to use inferential statistics to make inference from our data: no statistical test was used, no p-value has been provided

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	4	
Units: mm				
arithmetic mean (standard deviation)	4.55 (± 2.19)	7.85 (± 6.01)	3.6 (± 0.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: vaginal bleeding month 1

End point title	vaginal bleeding month 1
End point description:	
Patients were asked to record in a daily diary the occurrence of vaginal bleeding by means of a pictorial	

blood loss assessment chart

End point type	Secondary

End point timeframe:

From that Day 1, the patients had to report on their diary drug consumption, and any episode of bleeding or spotting with relative pictorial scores.

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	4	
Units: subjects	1	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: endometrial thickness measured at day 17 of treatment

End point title	endometrial thickness measured at day 17 of treatment

End point description:

End point type	Secondary

End point timeframe:

The mean values of endometrial thickness measured by TVU at day 17 of treatment with estrogen and progesterone

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	2	4	
Units: mm				
arithmetic mean (standard deviation)	4.4 (± 0)	8.15 (± 4.88)	4 (± 1.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: endometrial thickness measured at day 34 of treatment

End point title	endometrial thickness measured at day 34 of treatment

End point description:

End point type	Secondary

End point timeframe:

The mean values of endometrial thickness measured by TVU at day 34 of treatment with estrogen and

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	4	
Units: mm				
arithmetic mean (standard deviation)	4.3 (± 1.13)	7.72 (± 4.69)	4.67 (± 2.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: vaginal bleeding month 2

End point title	vaginal bleeding month 2

End point description:

Patients were asked to record in a daily diary the occurrence of vaginal bleeding by means of a pictorial blood loss assessment chart

End point type	Secondary

End point timeframe:

From that Day 1, the patients had to report on their diary drug consumption, and any episode of bleeding or spotting with relative pictorial scores.

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	4	
Units: subjects	2	0	4	

Statistical analyses

No statistical analyses for this end point

Secondary: vaginal bleeding month 3

End point title	vaginal bleeding month 3

End point description:

Patients were asked to record in a daily diary the occurrence of vaginal bleeding by means of a pictorial blood loss assessment chart

End point type	Secondary

End point timeframe:

From that Day 1, the patients had to report on their diary drug consumption, and any episode of bleeding or spotting with relative pictorial scores.

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	4	
Units: subjects	2	0	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
Patients were asked about the occurrence of adverse events during each visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No untoward medical occurrences have been reported by the patients nor by the Investigator. Considering the very low number of patients included and limited duration of treatment, this is considered plausible.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	In the letter dated August 26, 2014 the AIFA raised the major objection that endometrial biopsies are performed in patients who do not present particular pathologies or conditions requiring such invasive assessment in clinical practice, resulting in a disadvantageous benefit/risk ratio for the study. Though the endometrial biopsy remains the best option for the assessment of the endometrium, the measurement of endometrial thickness by means of transvaginal ultrasonography has been demonstrated to have good diagnostic accuracy and allows to limit the hysteroscopy examination only to suspicious cases. For this reason, the protocol will be amended to exclude the endometrial biopsies and to limit the efficacy assessment to the non-invasive endoscopic evaluation of endometrial thickness, as well as to the assessment of bleeding. Hysteroscopy and endometrial biopsies will therefore only be performed in those patients who, at the end of the treatment period, display endometrial thickness > 4 mm or recurrent bleeding, in agreement with clinical practice standards. Inclusion at screening will be based on endometrial thickness ≤ 4 mm as well as on medical history. As a consequence, analysis of estrogen and progesterone receptors in bioptic tissues has been deleted. In addition to the above, time windows for screening visit and follow-up have been extended to allow availability of results of diagnostic procedures and a mistake in the numbering of the weeks in the Overall Study Schedule has been corrected.
21 January 2015	The inclusion criterion of menopause onset < 2 years appears to be too restrictive. In a reanalysis of data from the WHI study, age and time from last menses were significantly predictive of the occurrence of cardiovascular events and death. In the combined estrogen+progesterone arm, the odds ratio for coronary heart disease (CHD) was directly related to the time since menopause, with the hazard ratio for CHD in the hormone-treated versus placebo groups of 0.89 for <10 years, 1.22 for 10 to 19 years, and 1.71 for ≥20 years (Manson et al. 2003). In a further reanalysis by Rossouw et al for women with less than 10 years since menopause began, the hazard ratio for CHD (total mortality) was 0.76 (0.76), as compared to 1.10 (0.98) for 10 to 19 years, and 1.28 (1.14) for ≥20 years. International guidelines recognize that menopausal hormone therapy is the most effective treatment for vasomotor symptoms and other symptoms of the climacteric, with benefits more likely to outweigh risks for symptomatic women when therapy is started within 10 years after menopause onset. In consideration of the above, the study can be safely extended to women with menopause onset < 10 years, thus improving recruitment while maintaining the same benefit/risk ratio. In addition to the above, the study protocol foresees that a mammography is performed at screening if not already available within the last 6 months. As in the clinical practice, the availability of a breast ultrasound within 6 months is equally acceptable to the purpose of a safety assessment before starting the hormone replacement therapy. Due to some delay in the patients' recruitment, the study duration will be prolonged until December 2015.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 December 2015	The study was interrupted upon enrolment of 8 subjects, due to change in Sponsor's business strategy, not related with the safety of study drugs.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the low number of patients included in the study, it is not possible to draw conclusions on the efficacy and safety of the study treatments.

Notes: