

**Clinical trial results:**

**A PHASE II PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED AND MULTI-CENTRE CLINICAL TRIAL TO ASSESS THE SAFETY OF 0.005 % ESTRIOL VAGINAL GEL IN HORMONE RECEPTOR-POSITIVE POSTMENOPAUSAL WOMEN WITH EARLY STAGE BREAST CANCER IN TREATMENT WITH AROMATASE INHIBITOR IN THE ADJUVANT SETTING.?BLISSAFE Study?**

**Summary**

EudraCT number	2014-004517-84
Trial protocol	ES SE
Global end of trial date	10 February 2017

**Results information**

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018
Summary attachment (see zip file)	Blissafe Results (SUMMARY OF THE RESULTS_ENG-v2resumidos.pdf)

**Trial information****Trial identification**

Sponsor protocol code	ITFE-2026-C10
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**Additional study identifiers**

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

Notes:

**Sponsors**

Sponsor organisation name	GEICAM
Sponsor organisation address	Av. de los Pirineos, 7, Madrid, Spain,
Public contact	GEICAM, GEICAM Spanish Breast Cancer Group, +34 916592870, geicam@geicam.org
Scientific contact	GEICAM, GEICAM Spanish Breast Cancer Group, +34 916592870, geicam@geicam.org
Sponsor organisation name	ITF Research Pharma S.L.U.
Sponsor organisation address	San Rafael 3, Madrid, Spain,
Public contact	ITF Research Pharma S.L.U., ITF Research Pharma S.L.U., 0034 916572323, italfarmaco@itfsp.com
Scientific contact	ITF Research Pharma S.L.U., ITF Research Pharma S.L.U., 0034 916572323,

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
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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	09 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 February 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the levels of FSH after treatment with 0.005% estriol vaginal gel in hormone receptor-positive postmenopausal women with early stage breast cancer in treatment with NSAIs in the adjuvant setting and symptoms of vaginal atrophy

Protection of trial subjects:

Not applicable, it was not necessary to applied extra measures for protection of the subjects out of the good clinical practice environment

Background therapy:

Patients were instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. Any medications including herbal supplements, vitamins, or treatment taken by the patient from 28 days prior to the start of study treatment and up to 30 days ( $\pm 5$  days) following the last dose of investigational product and the reason for their administration were recorded for analysis purposes.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), did not need to be recorded. Anaesthetics used for any surgical procedures performed during the patient's participation in the study was recorded as "unspecified anaesthesia".

The following treatments were prohibited throughout the duration of the active treatment phase:

- Anticancer agents: No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers or endocrine therapy (different than the NSAI: anastrozole or letrozole) were permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product insert were not permitted on study.
- Hormone replacement therapy with estrogens or progestins, tibolone, topical estrogens (different from the study drug/placebo), phytoestrogen, megestrol acetate and selective estrogen-receptor modulators (eg, raloxifene, tibolone) were prohibited during the active treatment phase.

Evidence for comparator:

Placebo Controlled Study

Actual start date of recruitment	26 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Sweden: 21
Worldwide total number of subjects	61
EEA total number of subjects	61

Notes:

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**Subjects enrolled per age group**

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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)	55
From 65 to 84 years	6
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

10 subjects were randomized for the initial safety phase in 2 sites in Spain;. 61 subjects were randomized for the study phase, 40 in Spain and 21 in Sweden

### Pre-assignment

Screening details:

61 patients were randomized in the study phase, 50 of them received the 0.005% estriol vaginal gel and 11 received placebo. A total of 52 patients completed the study treatment, 43 with the estriol vaginal gel and 9 with the placebo. 25 screened patients could not be randomized, 14 due to consent withdrawal and 11 due to not meet the inc/exc criteria

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Patients were randomized to receive 0.005% estriol vaginal gel or placebo vaginal gel, in a 4:1 proportion. The study drug, and its vehicle in gel (placebo vaginal gel) were of identical appearance and had the same aroma and the same texture in order to maintain the double blind.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	0.005% estriol vaginal gel

Arm description:

estriol vaginal gel

Arm type	Experimental
Investigational medicinal product name	estriol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

1 g of gel

Weeks 1-3: single daily application

Weeks 4-12: twice weekly administration

<b>Arm title</b>	placebo
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Arm description:

placebo vaginal gel

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

1 g of gel

Weeks 1-3: single daily application

Weeks 4-12: twice weekly administration

<b>Number of subjects in period 1</b>	0.005% estriol vaginal gel	placebo
Started	50	11
Completed	43	9
Not completed	7	2
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	-
patient decision	4	1
Protocol deviation	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	61	61	
Age categorical			
61			
Units: Subjects			
postmenopausal women	61	61	
Gender categorical			
Female			
Units: Subjects			
Female	61	61	
Male	0	0	

## End points

### End points reporting groups

Reporting group title	0.005% estriol vaginal gel
Reporting group description:	estriol vaginal gel
Reporting group title	placebo
Reporting group description:	placebo vaginal gel

### Primary: Variation in serum levels of FSH from baseline to 12 weeks of treatment

End point title	Variation in serum levels of FSH from baseline to 12 weeks of treatment
End point description:	
End point type	Primary
End point timeframe:	from baseline to 12 weeks of treatment

End point values	0.005% estriol vaginal gel	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	11		
Units: mUI/ml	50	11		

### Statistical analyses

Statistical analysis title	Mann-Whitney-Wilcoxon test
Statistical analysis description:	The variation of FSH levels was analysed using a non-parametric test (Mann-Whitney-Wilcoxon test) or an ANCOVA (if it must be adjusted by initial value)
Comparison groups	0.005% estriol vaginal gel v placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1
Method	Wilcoxon (Mann-Whitney)

### Secondary: Variation in serum levels of FSH at different time points compared to baseline

End point title	Variation in serum levels of FSH at different time points compared to baseline
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End point description:

End point type	Secondary
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End point timeframe:  
weeks 1, 3 and 8

<b>End point values</b>	0.005% estriol vaginal gel	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	11		
Units: mUI/ml	50	11		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Variation in serum levels of LH and plasma levels of estriol, estradiol and estrone

End point title	Variation in serum levels of LH and plasma levels of estriol, estradiol and estrone
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End point description:

End point type	Secondary
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End point timeframe:

at different time points compared to baseline (weeks 1, 3, 8 and 12).

<b>End point values</b>	0.005% estriol vaginal gel	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	11		
Units: mUI/ml	50	11		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in vaginal dryness and other symptoms and signs of vaginal atrophy

End point title	Changes in vaginal dryness and other symptoms and signs of vaginal atrophy
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End point description:

End point type	Secondary
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End point timeframe:  
at week 3 and week 12 vs baseline.

End point values	0.005% estriol vaginal gel	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	11		
Units: NA	50	11		

### Statistical analyses

No statistical analyses for this end point

### Secondary: changes in vaginal maturation value

End point title	changes in vaginal maturation value
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End point description:

End point type	Secondary
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End point timeframe:

at week 3 and week 12 vs baseline

End point values	0.005% estriol vaginal gel	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	11		
Units: NA	50	11		

### Statistical analyses

No statistical analyses for this end point

### Secondary: changes in vaginal pH

End point title	changes in vaginal pH
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End point description:

End point type	Secondary
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End point timeframe:

at week 3 and week 12 vs baseline

<b>End point values</b>	0.005% estriol vaginal gel	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	11		
Units: NA	50	11		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in sexual function measured by the Female Sexual Function Index

End point title	Changes in sexual function measured by the Female Sexual Function Index
End point description:	
End point type	Secondary
End point timeframe:	
at week 3 and week 12 vs baseline	

<b>End point values</b>	0.005% estriol vaginal gel	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	11		
Units: NA	50	11		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

baseline, week 1 (day 8 +/- 2 days), week 3 (day 22 +/- 3 days), week 8 (day 57 +/- 3 days), week 12 (day 85 +/- 3 days) and 4 weeks after the last study drug administration.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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### Reporting groups

Reporting group title	0.005% estriol vaginal gel
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Reporting group description: -	
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Reporting group title	placebo
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Reporting group description: -	
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Reporting group title	Total
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Reporting group description: -	
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Serious adverse events	0.005% estriol vaginal gel	placebo	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	0.005% estriol vaginal gel	placebo	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 50 (44.00%)	4 / 11 (36.36%)	26 / 61 (42.62%)
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
General disorders and administration			

site conditions			
Mucosal dryness			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Polyp			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Atrophic vulvovaginitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Breast tenderness			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Vaginal discharge			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Vulvovaginal inflammation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Vulvovaginal pruritus			
subjects affected / exposed	1 / 50 (2.00%)	0 / 11 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 50 (4.00%)	0 / 11 (0.00%)	2 / 61 (3.28%)
occurrences (all)	2	0	2
Vomiting			

subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 11 (0.00%) 0	1 / 61 (1.64%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 11 (0.00%) 0	1 / 61 (1.64%) 1
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Pain in extremity subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0  1 / 50 (2.00%) 1	1 / 11 (9.09%) 1  0 / 11 (0.00%) 0	1 / 61 (1.64%) 1  1 / 61 (1.64%) 1
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)  Gastroenteritis viral subjects affected / exposed occurrences (all)  Influenza subjects affected / exposed occurrences (all)  Pharyngitis subjects affected / exposed occurrences (all)  Urinary tract infection subjects affected / exposed occurrences (all)  Viral upper respiratory tract infection subjects affected / exposed occurrences (all)  Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0  1 / 50 (2.00%) 1  1 / 50 (2.00%) 1  1 / 50 (2.00%) 1  3 / 50 (6.00%) 3  1 / 50 (2.00%) 1  0 / 50 (0.00%) 0	1 / 11 (9.09%) 1  0 / 11 (0.00%) 0  0 / 11 (0.00%) 0  0 / 11 (0.00%) 0  1 / 11 (9.09%) 1  0 / 11 (0.00%) 0  1 / 11 (9.09%) 1	1 / 61 (1.64%) 1  1 / 61 (1.64%) 1  1 / 61 (1.64%) 1  1 / 61 (1.64%) 1  4 / 61 (6.56%) 4  1 / 61 (1.64%) 1  1 / 61 (1.64%) 1



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported