

**Clinical trial results:**

Therapeutic Equivalence (non-inferiority), Randomized, Observer-blind, two Parallel Group, Clinical Trial for Comparing the Efficacy and Tolerability of a Generic Formulation of Vaginal Ovule containing Clindamycin 100 mg/ovule versus Dalacin® 100 mg Vaginal Ovules (Pfizer©) in patients with Bacterial Vaginosis

Summary

EudraCT number	2016-004292-41
Trial protocol	GR
Global end of trial date	30 April 2018

Results information

Result version number	v1 (current)
This version publication date	22 September 2019
First version publication date	22 September 2019

Trial information**Trial identification**

Sponsor protocol code	BECRO/VF/FEMALE
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Verisfield (UK) Ltd, Greek Branch
Sponsor organisation address	8 Vironos str., Halandri, Greece, GR-15231
Public contact	Clinical Trials & Pharmacovigilance Department, Verisfield (UK) Ltd, Greek Branch, 0030 210 74 75 196, info@verisfield.gr
Scientific contact	CLINICAL TRIAL INFORMATION, BECRO Ltd, 0030 2106729037, trials@becro.gr

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	16 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2018
Global end of trial reached?	Yes
Global end of trial date	30 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To confirm the non-inferiority of a generic vaginal ovule formulation containing clindamycin (as phosphate) 100 mg/ovule (Test product) vs. Dalacin® 100 mg vaginal ovules/Pfizer (Reference product) in patients with bacterial vaginosis by examining the Amsel's clinical criteria (vaginal fluid amine odor, pH of vaginal fluid, vaginal discharge and clue cells on microscopy) at the Test of Cure visit (28 ± 7 days from the day of administrating the medicinal product).
- To estimate the bacteriological cure rate of Test product compared to Reference at the Test of Cure visit.
- To estimate the clinical cure rate of Test product compared to Reference at the Intermediate visit (14 ± 3 days).
- To estimate the bacteriological cure rate of Test product compared to Reference at the Intermediate visit.
- To demonstrate the safety and tolerability profile of Test product compared to Reference by assessing the occurrence of either topical or systemic AEs.

Protection of trial subjects:

The study conduct, including the clinical study protocol and the Informed Consent Form, was approved by the National (Hellenic) Ethics Committee (NEC) and the National (Hellenic) Organisation for Medicines (EOF). This trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. It was carried out in compliance with the clinical trial protocol and in accordance with BECRO's Standard Operating Procedures (SOPs). These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the following documents: World Medical Association Declaration of Helsinki, (Fortaleza, Brazil, October 2013); Note for Guidance on Good Clinical Practice [CPMP/ICH/135/95, July 1996; ICH Topic E6 (R2), November, 2016]; Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/97) (ICH Topic E8) March 1998; Commission Directives: 2001/20/EC, 2005/28/EC and 2003/94/EC; Clinical trials Regulation (EU) No 536/2014; Ministerial Decree ΔΥΓ3α/79602 (Modification of the common ministerial decree ΔΥΓ3α/89292/31-12-2003 on the harmonization of the Greek legislation to the corresponding Community one in compliance with Directive 2001/20/EC of 4 April 2001); Ministerial Decree Γ5α/59676A.

The investigators agreed, by signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP that it conforms to and to maintain subject's anonymity. Patients were identified on all study documentation by their identification numbers and initials and were not referred to by name. The log of patient's numbers, names and addresses and the signed Informed Consent Forms were maintained separated and were managed as strictly confidential. All volunteers participating in the study were covered by insurance on behalf of the sponsor. Adverse events and safety profile of both products were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2017
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	Greece: 292
Worldwide total number of subjects	292
EEA total number of subjects	292

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)	286
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female adult patients with clinical diagnosis of bacterial vaginosis (BV) who met the inclusion/exclusion criteria were selected to participate in the study after signing a consent form. Recruitment was conducted in six study centers in Greece from 22/Mar/2017 until 30/Apr/2018.

Pre-assignment

Screening details:

Female adult patients with clinical diagnosis of bacterial vaginosis (BV) who met the inclusion/exclusion criteria were selected to participate in the study after signing a consent form.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor ^[1]

Blinding implementation details:

The clinical trial was performed as open/observer-blind because of the differences in the packaging of both drugs. The clinical trial site had blind and non-blind clinical trial personnel. Blind personnel made all contacts with patients and performed all clinical trial related examinations, whereas non-blind personnel was responsible for clinical trial medication distribution and collection.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

The subjects were administered the experimental medicinal product.

Arm type	Experimental
Investigational medicinal product name	Clindamycin 100 mg vaginal ovules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pessary
Routes of administration	Vaginal use

Dosage and administration details:

One ovule containing clindamycin 100 mg/ovule for 3 consecutive days. The treatment was administered intravaginally at bedtime.

Arm title	Reference
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Arm description:

The subjects were administered the reference product.

Arm type	Active comparator
Investigational medicinal product name	Dalacin® 100 mg vaginal ovules/Pfizer
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pessary
Routes of administration	Vaginal use

Dosage and administration details:

One ovule of Dalacin® for 3 consecutive days. The treatment was administered intravaginally at bedtime.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The trial was performed as open/observer-blind because of the differences in packaging of

both drugs. The clinical trial site had blinded and non-blinded personnel. Blinded personnel made all contacts with patients and performed all clinical trial related examinations, whereas non-blinded personnel was responsible for trial medication distribution and collection. Patients and non-blinded personnel were cautioned not to reveal the clinical trial assignment to the blind evaluator.

Number of subjects in period 1	Test	Reference
Started	143	149
Completed	113	124
Not completed	30	25
Lost to follow-up	16	13
Protocol deviation	14	12

Baseline characteristics

Reporting groups

Reporting group title	Test
Reporting group description: The subjects were administered the experimental medicinal product.	
Reporting group title	Reference
Reporting group description: The subjects were administered the reference product.	

Reporting group values	Test	Reference	Total
Number of subjects	143	149	292
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	141	145	286
From 65-84 years	2	4	6
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	143	149	292
Male	0	0	0

End points

End points reporting groups

Reporting group title	Test
Reporting group description: The subjects were administered the experimental medicinal product.	
Reporting group title	Reference
Reporting group description: The subjects were administered the reference product.	
Subject analysis set title	Per Protocol Efficacy Data Set
Subject analysis set type	Per protocol
Subject analysis set description: To test the efficacy on the per protocol (PP) population. The per protocol (PP) population includes all those of the Intention To-Treat (ITT) population who had no major protocol violations, who completed clinical and laboratory examinations within the allowed time frames, who completed 3 days of treatment, and who did not take prohibited concurrent medication.	
Subject analysis set title	Intention-to-treat Efficacy Data Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: To test the efficacy on the intent-to-treat (ITT) population. ITT population includes all randomized patients who had at least one post baseline measurement of clinical and laboratory examinations as defined by Amsel's criteria and Nugent's score.	
Subject analysis set title	Safety Data Set
Subject analysis set type	Safety analysis
Subject analysis set description: To test the safety of IMPs. The safety population (SP) comprised all patients, who received at least 1 ovule of the Test or Reference product.	

Primary: Primary Efficacy Endpoint_Proportion of patients with clinical cure at the Test of Cure visit

End point title	Primary Efficacy Endpoint_Proportion of patients with clinical cure at the Test of Cure visit
End point description: The proportion of patients with clinical cure (i.e., resolution of clinical signs and symptoms, e.g., normal physiological vaginal discharge, whiff test negative for any amine "fishy" odor, saline wet mount negative for clue cells, and vaginal pH < 4.5) at the Test of Cure visit [28 ± 7 days from the day of administering the medicinal product, defined as visit 3 (V3)] in subjects treated with the test product as compared to subjects treated with the reference product.	
End point type	Primary
End point timeframe: From baseline to Test of Cure visit [28 ± 7 days from the day of administering the medicinal product, defined as visit 3 (V3)]	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	124		
Units: Proportion of patients	51	54		

Statistical analyses

Statistical analysis title	Per Protocol Primary efficacy analysis
Comparison groups	Test v Reference
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	-0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1543
upper limit	0.1002

Secondary: Secondary Efficacy Endpoint_Proportion of patients with bacteriological cure at the Test of Cure visit

End point title	Secondary Efficacy Endpoint_Proportion of patients with bacteriological cure at the Test of Cure visit
End point description:	The proportion of patients with bacteriological cure (i.e., Nugent score<4) at the Test of Cure visit.
End point type	Secondary
End point timeframe:	From baseline to Test of Cure visit [28 ± 7 days from the day of administering the medicinal product, defined as visit 3 (V3)]

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	124		
Units: Proportion of patients	81	84		

Statistical analyses

Statistical analysis title	Per Protocol Secondary Efficacy Analysis
Comparison groups	Test v Reference
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	-0.0245

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1212
upper limit	0.0721

Secondary: Secondary Efficacy Endpoint_Proportion of patients with both clinical and bacteriological cure at the Test of Cure visit

End point title	Secondary Efficacy Endpoint_Proportion of patients with both clinical and bacteriological cure at the Test of Cure visit
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End point description:

The proportion of patients with both clinical and bacteriological cure in patients with both clinical (Amsel's criteria) and microbiological diagnosis of BV (Nugent score ≥ 7) at the Test of Cure visit (V3)

End point type	Secondary
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End point timeframe:

From baseline to the Test of Cure visit [28 ± 7 days from the day of administrating the medicinal product, defined as visit 3 (V3)]

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	18		
Units: Proportion of patients	33	39		

Statistical analyses

Statistical analysis title	Per Protocol Secondary Efficacy Analysis
Comparison groups	Reference v Test
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	-0.0556
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4046
upper limit	0.1508

Secondary: Secondary Efficacy Endpoint_Proportion of patients with clinical cure at the Intermediate visit

End point title	Secondary Efficacy Endpoint_Proportion of patients with clinical cure at the Intermediate visit
End point description: Proportion of patients with clinical cure at the Intermediate visit [14 ± 3 days from the day of administrating the medicinal product, defined as visit 2 (V2)]	
End point type	Secondary
End point timeframe: From baseline to Intermediate visit [14 ± 3 days from the day of administrating the medicinal product, defined as visit 2 (V2)]	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	124		
Units: Proportion of patients	35	44		

Statistical analyses

Statistical analysis title	Per Protocol Secondary Efficacy Analysis
Comparison groups	Test v Reference
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Chi-squared corrected
Parameter estimate	Mean difference (net)
Point estimate	-0.0984
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2222
upper limit	0.0254

Secondary: Secondary Efficacy Endpoint_Proportion of patients with bacteriological cure at the Intermediate visit

End point title	Secondary Efficacy Endpoint_Proportion of patients with bacteriological cure at the Intermediate visit
End point description: Proportion of patients with bacteriological cure at the Intermediate visit [14 ± 3 days from the day of administrating the medicinal product, defined as visit 2 (V2)]	
End point type	Secondary
End point timeframe: from baseline to Intermediate visit [14 ± 3 days from the day of administrating the medicinal product, defined as visit 2 (V2)]	

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	124		
Units: Proportion of patients	89	88		

Statistical analyses

Statistical analysis title	Per Protocol Secondary Efficacy Analysis
Comparison groups	Test v Reference
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0763
upper limit	0.0881

Secondary: Secondary Efficacy Endpoint_Proportion of patients with treatment failure

End point title	Secondary Efficacy Endpoint_Proportion of patients with treatment failure
End point description:	The proportion of patients with treatment failure (i.e., subjects who needed bacterial vaginosis therapy, other than study product or had a Nugent score >3 at the Test of Cure visit).
End point type	Secondary
End point timeframe:	From baseline to Test of Cure visit [28 ± 7 days from the day of administering the medicinal product, defined as visit 3 (V3)]

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	124		
Units: Proportion of patients	19	16		

Statistical analyses

Statistical analysis title	Per Protocol Secondary Efficacy Analysis
Comparison groups	Test v Reference
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Mean difference (net)
Point estimate	0.0245
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0721
upper limit	0.1212

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the course of the clinical trial.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	Test
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Reporting group description: -

Reporting group title	Reference
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Reporting group description: -

Serious adverse events	Test	Reference	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 143 (1.40%)	1 / 149 (0.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Polypectomy			
subjects affected / exposed	1 / 143 (0.70%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laparoscopy removal ovarian vesicle			
subjects affected / exposed	0 / 143 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pelvic inflammatory disease			
subjects affected / exposed	1 / 143 (0.70%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Test	Reference	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 143 (0.70%)	5 / 149 (3.36%)	
Reproductive system and breast disorders			
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 143 (0.00%)	5 / 149 (3.36%)	
occurrences (all)	0	5	
Vulvovaginal pruritus			
subjects affected / exposed	0 / 143 (0.00%)	1 / 149 (0.67%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	1 / 143 (0.70%)	0 / 149 (0.00%)	
occurrences (all)	1	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