# 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 |

**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/59676Α.
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 |

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<br>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<br>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 administrating 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 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 | 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 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 | 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 |

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 |

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 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 | 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 |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 21 |
| **Reporting groups** | |
| Reporting group title | Test |
| Reporting group description: - | |
| Reporting group title | Reference |
| 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 | |
| Laparascopy 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