Clinical trial results:
Multicenter, randomized, double-blind, comparative with reference product clinical trial to evaluate the efficacy and safety of treatment with Clindamycin vaginal suppositories 100 mg in patients with bacterial vaginosis

Summary

EudraCT number	2011-002386-38
Trial protocol	GR
Global end of trial date	19 October 2015

Results information

Result version number	v1 (current)
This version publication date	04 February 2017
First version publication date	04 February 2017

Trial information

Trial identification

Sponsor protocol code	CLVS100VER

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Verisfield (UK) Ltd
Sponsor organisation address	8 Vironos Street, Halandri/Athens, Greece,
Public contact	Clinical Research Scientist, Antonios Margaritis, VERISFIELD (UK) LTD, 0030 2107475196, info@verisfield.gr
Scientific contact	Clinical Trial Department, Verisfield (UK) Ltd, Greek Branch, VERISFIELD (UK) LTD, 0030 2107475196, info@verisfield.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	19 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2015
Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was the comparison of: (a) the efficiency, and (b) the safety of local treatment with clindamycin vaginal suppositories of Verisfield (UK) Ltd (Clindamycin/Verisfield, vaginal suppositories, 100 mg) and the therapeutic comparison with the reference product (Dalacin/Pfizer, vaginal suppositories, 100 mg), in women with bacterial vaginosis.

Protection of trial subjects:

This study was conducted in accordance with International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guidelines adopted by the European Medicines Agency (EMA). In accordance with local requirements, the study was submitted to the National Ethics Committee and the National Drug Organization for approval. The study begun only when Verisfield (UK) Ltd had received a copy of the written approval from the National Drug Organization. The conduct of the study was done in accordance with the relevant requirements of the National Drug Organization. Moreover, the involvement of patients in this study were reported to the Data Protection Authority in accordance with European Union Directive 95/46/EC and the Directives/laws of each country.Finally, the study has been designed according to the European Directives 2001/20/EC and 2005/28/EC and Directives ICH E1-E3 and E5-E11. Physical examination and an assessment of vital signs (blood pressure, pulse rate, temperature) were performed during the screening, as well as during all the study visits for all the participating volunteers. Moreover, adverse events (AEs) were observed during the entire study period and adequately handled and reported. Furthermore, a urine human chorionic gonadotropin (hCG) test was performed for all females of childbearing potential during all study Visits. Finally, all volunteers participating in this clinical study were covered by insurance on behalf of the sponsor.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	19 June 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	Greece: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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

Subject disposition

Recruitment

Recruitment details:

The participants were selected among adult premenopausal female patients with bacterial vaginosis, volunteers, aged 18-54 years (including the limits) that attended/visited the hospitals of the study sites

Pre-assignment

Screening details:

Adult premenopausal female patients with bacterial vaginosis, volunteers, aged 18-54 years (including the limits). Other inclusion and exclusion criteria applied.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

The subjects were administered with the experimental medicinal product.

Arm type	Experimental
Investigational medicinal product name	Clindamycin/Verisfield 100 mg vaginal suppositories
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suppository
Routes of administration	Vaginal use

Dosage and administration details:

The route of administration, dosage, dosage regimen and duration of treatment was in accordance with the summary of product characteristics of the original formulation (reference product). The dosage regimen was one suppository for three consecutive days, before bedtime.

Arm title	Reference

Arm description:

The subjects were administered with the reference product.

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

Dosage and administration details:

The dosage regimen was one suppository for three consecutive days, before bedtime.

Number of subjects in period 1	Test	Reference
Started	3	3
Completed	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	6	6	
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)	6	6	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	6	6	
Male	0	0	

End points

End points reporting groups

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

Primary: Efficacy -The cure of the patients defined as the absence of three or four criteria of Amsel (existence of one or none criterion) in the 2nd visit.

End point title	Efficacy -The cure of the patients defined as the absence of three or four criteria of Amsel (existence of one or none criterion) in the 2nd visit.[1]

End point description:

The Amsel criteria are the following four:
1. Homogeneous, white, attaching vaginal discharge (often with fishy smell).
2. Positive amine check (characteristic odor of fish by applying 10% KOH - whiff test).
3. pH> 4.5.
4. Presence of clue cells (epithelial cells covered by coccobacillary organisms) in wet mount of vaginal secretion.

End point type	Primary

End point timeframe:

The Amsel criteria for the primary endpoint were assessed in the 2nd visit (7-12 days after the beginning of the treatment)

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: In the context of the present study, 10 volunteers were screened, of which 6 who met the eligibility criteria, were enrolled in the study and received one of the IMPs. Since the number of the enrolled volunteers was very low, no statistical analysis could be performed.

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Confidence interval				

Notes:

[2] - Very low enrollment rate.No statistical analysis could be performed

[3] - Very low enrollment rate.No statistical analysis could be performed

Statistical analyses

No statistical analyses for this end point

Secondary: IGII (Patient Global Improvement Index)

End point title	IGII (Patient Global Improvement Index)

End point description:

Clinical evaluation of vaginitis based on the progression of symptoms by the investigator. The assessment is done using the following scale:
Serious deterioration (-2), Mild deterioration (-1), no change (0), mild improvement (1), moderate

improvement (2), significant improvement (3), complete improvement (4).

End point type	Secondary

End point timeframe:

The IGII (Patient Global Improvement Index) was assessed in the 2nd visit (7-12 days after the beginning of the treatment) and in the 3rd visit (21-30 days after the beginning of the treatment)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: IGII				
number (not applicable)				

Notes:

[4] - Very low enrollment rate. No statistical analysis could be performed.

[5] - Very low enrollment rate. No statistical analysis could be performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy_The cure of patients based to Amsel and Nugent criteria in the 2nd and 3rd visit

End point title	Efficacy_The cure of patients based to Amsel and Nugent criteria in the 2nd and 3rd visit

End point description:

The cure of patients was based on the absence of three or four Amsel criteria at Visit 3 and on the absence of three or four Amsel criteria and score <7 in Nugent scale in 2nd and 3rd visit.
The Amsel criteria are the following four:
1. Homogeneous, white, attaching vaginal discharge (often with fishy smell).
2. Positive amine check (characteristic odor of fish by applying 10% KOH - whiff test).
3. pH> 4.5.
4. Presence of clue cells (epithelial cells covered by coccobacillary organisms) in wet mount of vaginal secretion.

The Nugent method include:
1 loss of lactobacilli (score 0-4)
2 increase in the number of gram (+) and gram (-) coccobacillus (especially Gardnerella vaginalis, score 0-4)
3 Increase in the number of Mobi luncus spp (score 0-2)
These scores are added and based to their sum, the condition is assessed.
• The score of 0-3 is considered normal flora
• The score of 4-6 as intermediate

End point type	Secondary

End point timeframe:

The Amsel and Nugent criteria were assessed in the 2nd (7-12 days after the beginning of the treatment) and 3rd visit (21-30 days after the beginning of the treatment).

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Confidence Interval				

Notes:

[6] - Very low enrollment rate.No statistical analysis could be performed

[7] - Very low enrollment rate.No statistical analysis could be performed

Statistical analyses

No statistical analyses for this end point

Secondary: PGII (Patient Global Improvement Index)

End point title	PGII (Patient Global Improvement Index)

End point description:

Clinical evaluation of vaginitis by the patient, based on the progression of symptoms. The assessment is done using the following scale:
Serious deterioration (-2), Mild deterioration (-1), no change (0), mild improvement (1), moderate improvement (2), significant improvement (3), complete improvement (4).

End point type	Secondary

End point timeframe:

The PGII (Patient Global Improvement Index) was assessed in the 2nd visit (7-12 days after the beginning of the treatment) and in the 3rd visit (21-30 days after the beginning of the treatment)

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: PGII				
number (not applicable)				

Notes:

[8] - Very low enrollment rate. No statistical analysis could be performed.

[9] - Very low enrollment rate. No statistical analysis could be performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy -The cure of the patients defined as the absence of three or four criteria of Amsel (existence of one or none criterion) in the 3rd visit

End point title	Efficacy -The cure of the patients defined as the absence of three or four criteria of Amsel (existence of one or none criterion) in the 3rd visit

End point description:

The Amsel criteria are the following four:
1. Homogeneous, white, attaching vaginal discharge (often with fishy smell).
2. Positive amine check (characteristic odor of fish by applying 10% KOH - whiff test).
3. pH> 4.5.
4. Presence of clue cells (epithelial cells covered by coccobacillary organisms) in wet mount of vaginal secretion.

End point type	Secondary

End point timeframe:

The Amsel criteria were assessed in the 3rd visit (21-30 days after the beginning of the treatment).

End point values	Test	Reference		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Condifence interval				

Notes:

[10] - Very low enrollment rate. No statistical analysis could be performed.

[11] - Very low enrollment rate. No statistical analysis could be performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: The duration of the overall study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

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: None of the enrolled volunteers (6 in total) developed any adverse event during their participation in the study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2012	The modification was the addition of an extra visit 21-30 days after the start of the treatment (Visit 3), and the introduction of Nugent criteria on efficacy assessments in the 2nd and 3rd visit. This results in the addition of three additional secondary efficacy parameters: 1. The healing of patients under the Amsel criteria at Visit 3 2. The therapeutic effect based on the Amsel criteria and Nugent score at the second visit. 3. The therapeutic effect based on the Amsel criteria and Nugent score at the 3rd visit.
11 February 2014	This amendment included: 1. Amendment of the study protocol by 3rd Edition dated 08/03/2013 in 4th Edition dated 28/11/2013. 2. Modification of Informed Consent Form for volunteers participating in the study from 2nd Edition dated 14/03/2012 in 3rd Edition dated 28/11/2013. 3. Change of Principal Investigator in already existing Centre. More specifically, there was a replacement of the Principal Investigator of the already participating Centre (A Obstetrics-Gynecology Clinic, University of Athens, General Hospital of Athens "Alexandra") Professor Aristides Antsaklis by Associate Professor Alexandros Rodolakis. 4. Add of an additional center. More specifically, the study incorporated the VI Obstetrics-Gynecology Clinic Regional General Hospital-Maternity Hospital "Elena Venizelou" with Principal Investigator the obstetrician-gynecologist Mr. George Farmakides. 5. Extension of the study duration from 12 to 36 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

19 October 2015	In February 2014, a request for a substantial modification was made to the Greek National Authority of Medicines (EOF) and the National Ethics Committee (EED). The amendment was requested in order to prolong the duration of the study to the already participating center (1st Clinic of Obstetrics and Gynecology, Hospital "Alexandra") for one year and to add a second center in the study (6th Clinic of Obstetrics and Gynecology, Hospital "Elena Venizelou"). However, there were some delays during the approval procedure, mainly because of a change to the Board of Directors of the two involved hospitals and a consequent absence of meetings during that period (1st semester of 2014). As a consequence, the last approvals for this amendment were received in the last trimester of 2014; thus, the remaining time until the end of the requested extension (December 2014) was very limited. On the other hand, at the already participating center (1st Clinic of Obstetrics and Gynecology, Hospital "Alexandra"), a great difficulty in enrolling patients into the study was already noted. This resulted in a very low enrolment rate as well as in difficulty to be compliant with the recruitment timelines and to achieve the expected number of enrolled patients. Further to the above, in January 2015 it was decided to prematurely terminate the study in the first center of the study (1st Clinic of Obstetrics and Gynecology, Hospital "Alexandra"). The second center of the study (6th Clinic of Obstetrics and Gynecology, Hospital "Elena Venizelou") was not activated, since a further amendment was needed to extend the time duration of the study and because of the difficulty to find and enroll patients according to the protocol eligibility criteria that had been encountered in the first center of the study.	-

Notes:

Limitations and caveats

None reported