Clinical trial results:
A Comparative, Open-Label, Randomized, Parallel Group Study to determine Intraperitoneal fluids, tissue, and serum concentrations of VML-0501 following five days of daily vaginal applications of single dose of VML-0501 (100 mg Danazol), in comparison to five days of Danazol treatment administered as an oral capsules (Danatrol) at a daily dose of 600 mg, in two groups of twelve each consisting of women with suspected or confirmed endometriosis and scheduled for laparoscopy.

Summary

EudraCT number	2017-000988-32
Trial protocol	IT
Global end of trial date	28 April 2020

Results information

Result version number	v1 (current)
This version publication date	03 June 2021
First version publication date	03 June 2021

Trial information

Trial identification

Sponsor protocol code	VML-0501-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03352076
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Viramal Ltd
Sponsor organisation address	106 New Bond Street, 3rd floor, London, United Kingdom, W1S 1DN
Public contact	Chief Medical Officer, Viramal Ltd 106 New Bond Street London United Kingdom W1S 1DN, 020 74953052, info@viramal.com
Scientific contact	Chief Medical Officer, Viramal Ltd 106 New Bond Street London United Kingdom W1S 1DN, 020 74953052, info@viramal.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	28 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2020
Global end of trial reached?	Yes
Global end of trial date	28 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the bioavailability of VML-0501 in comparison to oral Danazol in terms of:
- Concentrations in serum
- Concentrations in peritoneal fluid.

Protection of trial subjects:

The Study was covered with a clinical study insurance and a liability insurance, and received relevant Ethics approval.
Safety assessments included analysis of adverse events, physical examinations, vital signs, blood and urine tests to investigate the effects of the study drug on the clinical tolerability.
All the clinical activities were carried out under a controlled environment under the supervision of qualified medical staff.

Background therapy:

No background therapy was included

Evidence for comparator:

Danatrol capsule, therapeutic indication is symptomatic treatment of Endometriosis.

Actual start date of recruitment	30 October 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	Italy: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subject who fulfilled the inclusion and exclusion criteria were recruited in the study. Women aged 18 to 42 years, with suspected or confirmed endometriosis and scheduled for laparoscopy were screened and invited to participate in the study. Of 30 subjects enrolled 29 were randomized (16 to the VML-0501 group and 13 to the Danatrol group).

Pre-assignment

Screening details:

All subjects were screened for suspected or clinically diagnosed endometriosis. A number of assessments were performed during the Screening period to determine patient eligibility, e.g.physical examination, height and weight, blood pressure and heart rate, pregnancy test, routine blood and urine test.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	VML-0501

Arm description:

Subjects in the VML-0501 group were administered vaginally with 1.5 g of VML-0501 cream (containing 100 mg of Danazol)

Arm type	Experimental
Investigational medicinal product name	VML-0501
Investigational medicinal product code	VML-0501
Other name	Danazol Vaginal Cream
Pharmaceutical forms	Cream
Routes of administration	Vaginal use

Dosage and administration details:

Subjects in the VML-0501 group were administered with 1.5 g of VML-0501 cream (containing 100 mg of Danazol) deeply within the vagina using an internal applicator, followed by 30 minutes of lying on their back in a supine position. Subjects were dosed once daily every morning for 5 – 7 consecutive days until the date of their laparoscopy.

Arm title	Comparator

Arm description:

The Danatrol comparator was obtained from a local pharmacy and was not modified in any way. Danatrol was given in a dose of 200 mg three times daily for 5-7 consecutive days.

Arm type	Active comparator
Investigational medicinal product name	Danatrol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg three times daily for 5-7 days, to be taken orally with a glass of water.

Number of subjects in period 1[1]	VML-0501	Comparator
Started	16	13
Completed	15	11
Not completed	1	2
Consent withdrawn by subject	1	1
drop-out	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification:
on the VML-0501 arm one subject drop-out
on the the Comparator arm one subject drop-out and one subject withdrew consent.

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Women with suspected or confirmed Endometriosis scheduled for laparoscopy.

Reporting group values	Overall trial	Total	
Number of subjects	29	29	
Age categorical			
females 18-42 years of age			
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)	29	29	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Women with suspected or confirmed Endometriosis scheduled for laparoscopy.			
Units: Subjects			
Female	29	29	
Male	0	0	
Endometriosis			
Women with suspected or confirmed Endometriosis scheduled for laparoscopy.			
Units: Subjects			
suspected endometriosis	29	29	
Laparoscopy			
Women with suspected or confirmed Endometriosis scheduled for laparoscopy.			
Units: Subjects			
scheduled for laparoscopy	29	29	

Subject analysis sets

Subject analysis set title	Safety set
Subject analysis set type	Full analysis

Subject analysis set description:

This included all the subjects that enrolled in the study and received at least one dose of the investigational drug.

Subject analysis set title	Primary Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

These are subjects who have been selected, randomized and took at least one dose of the study medication.

Subject analysis set title	Secondary Population

Subject analysis set type	Per protocol

Subject analysis set description:

These are subjects who have completed the study and took at least 80% of the study medication.

Reporting group values	Safety set	Primary Population	Secondary Population
Number of subjects	30	29	26
Age categorical			
females 18-42 years of age			
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)	29	29	26
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Women with suspected or confirmed Endometriosis scheduled for laparoscopy.			
Units: Subjects			
Female	29	29	26
Male	0	0	0
Endometriosis			
Women with suspected or confirmed Endometriosis scheduled for laparoscopy.			
Units: Subjects			
suspected endometriosis	29	29	26
Laparoscopy			
Women with suspected or confirmed Endometriosis scheduled for laparoscopy.			
Units: Subjects			
scheduled for laparoscopy	29	29	26

End points

End points reporting groups

Reporting group title	VML-0501
Reporting group description:	
Subjects in the VML-0501 group were administered vaginally with 1.5 g of VML-0501 cream (containing 100 mg of Danazol)	
Reporting group title	Comparator
Reporting group description:	
The Danatrol comparator was obtained from a local pharmacy and was not modified in any way. Danatrol was given in a dose of 200 mg three times daily for 5-7 consecutive days.	

Subject analysis set title	Safety set
Subject analysis set type	Full analysis
Subject analysis set description:	
This included all the subjects that enrolled in the study and received at least one dose of the investigational drug.	
Subject analysis set title	Primary Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
These are subjects who have been selected, randomized and took at least one dose of the study medication.	
Subject analysis set title	Secondary Population
Subject analysis set type	Per protocol
Subject analysis set description:	
These are subjects who have completed the study and took at least 80% of the study medication.	

Primary: Concentration of Danazol in Serum

End point title	Concentration of Danazol in Serum
End point description:	
The primary efficacy endpoint analysis was pre-defined to be based on the comparison of the concentrations of danazol in the afore mentioned parameters within and between patients in both arms of the study (VML-0501 vs. Danatrol).	
End point type	Primary
End point timeframe:	
day 5 to day 14 of the treatment	

End point values	VML-0501	Comparator	Safety set	Primary Population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	16	13	29	29
Units: ng/ml				
number (not applicable)	16	13	29	29

End point values	Secondary Population			
Subject group type	Subject analysis set			
Number of subjects analysed	29			

Units: ng/ml				
number (not applicable)	26			

Statistical analyses

Statistical analysis title	SAS® System version 9.4
Comparison groups	Safety set v Primary Population v Secondary Population
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001 [2]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
Variability estimate	Standard deviation

Notes:

[1] - proof of concept

[2] - the concentration of Danazol in the serum

Primary: Concentration of Danazol in peritoneal fluid

End point title	Concentration of Danazol in peritoneal fluid

End point description:

End point type	Primary

End point timeframe:

day 5 to day 14

End point values	VML-0501	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: ng/ml				
number (not applicable)	16	13		

Statistical analyses

Statistical analysis title	SAS® System version 9.4

Statistical analysis description:

concentration of Danazol in Peritoneal fluid

Comparison groups	VML-0501 v Comparator

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.5
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
sides	2-sided
Variability estimate	Standard deviation

Notes:

[3] - Proof of Concept

Secondary: Concentration of Danazol measured in tissue

End point title	Concentration of Danazol measured in tissue

End point description:

Tissue samples (selected pelvic and peritoneal samples) were collected from subjects in both arms.

End point type	Secondary

End point timeframe:

At the time of the laparoscopy.

End point values	VML-0501	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: ng/g				
number (not applicable)				
secondary endpopint	6	11		

Statistical analyses

Statistical analysis title	SAS® System version 9.4

Statistical analysis description:

Concentration of Danazol in Tissue

Comparison groups	VML-0501 v Comparator
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0031
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[4] - Proof of Concept

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected for all patients from the time of the first dose to the day of final follow-up.	
Adverse event reporting additional description:	
Adverse events were collected regardless of causality.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	VML-0501
Reporting group description:	
This group received the Investigational Medicinal Product (IMP) VML-0501.	
Reporting group title	Comparator
Reporting group description:	
This group of subjects was randomized to receive the comparator drug-Danatrol.	

Serious adverse events	VML-0501	Comparator	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	VML-0501	Comparator	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	1 / 13 (7.69%)	
Surgical and medical procedures			
Phlebitis	Additional description: Phlebitis in the upper right limb, resolved and not related		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Social circumstances			
Road traffic accident	Additional description: not related and resolved		

subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchitis	Additional description: Subject presented with Bronchitis and Fever.Resolved and Not related.		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2018	(1) Change of PI (2) Planned number of patients increased from 24 to 34 (3) Addition of new exploratory endpoints to investigate the concentration of danazol in endometrium and myometrium tissue (if applicable)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes: