Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of VT-1161 Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis

Summary

EudraCT number	2018-001270-26
Trial protocol	CZ BE HU
Global end of trial date	13 October 2020

Results information

Result version number	v1 (current)
This version publication date	09 September 2021
First version publication date	09 September 2021

Trial information

Trial identification

Sponsor protocol code	VMT-VT-1161-CL-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03561701
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mycovia Pharmaceuticals, Inc.
Sponsor organisation address	4721 Emperor Blvd., Suite 220, Durham, United States, 27703
Public contact	Clinical Trial Administration, Mycovia Pharmaceuticals, Inc., +011 9194678539, adminops@mycovia.com
Scientific contact	Chief Development Officer, Mycovia Pharmaceuticals, Inc., +011 9194678539,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002392-PIP01-18
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	13 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of oral oteseconazole (VT-1161) in the treatment of recurrent vulvovaginal candidiasis (RVVC) through Week 48 of the study.

Protection of trial subjects:

The study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (GCP), all applicable subject privacy requirements, the guiding principles of the current version of the Declaration of Helsinki, and applicable country-specific regulatory requirements.

Background therapy:

Prior to randomization, subjects completed an Induction Phase where all subjects received 3 sequential 150 milligram (mg) doses of fluconazole that were administered 72 hours apart. After the Induction Phase, if subjects were still eligible for randomization, fluconazole was used as a rescue medication to treat an acute vulvovaginal candidiasis (VVC) infection during the remainder of the study.

Evidence for comparator: -

Actual start date of recruitment	04 October 2018
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	Belgium: 26
Country: Number of subjects enrolled	Czechia: 73
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Romania: 72
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	United States: 122
Worldwide total number of subjects	330
EEA total number of subjects	182

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)	329
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in generally healthy non-pregnant females aged ≥12 years (aged ≥18 years in Hungary, Romania, Ukraine and Czech Republic) with a history of RVVC and with a clinical diagnosis of symptomatic acute VVC. Subjects were randomized in a 2:1 ratio to receive either oteseconazole or a matching placebo regimen.

Pre-assignment

Screening details:

The study consisted of a 2-week Induction Phase (screening to Day 1 pre-randomization) and 48-week Maintenance Phase (comprising a 12-week treatment period and 36 weeks follow up). As a result of multiple GCP violations, a site was terminated from the study; 4 subjects enrolled at this site were excluded from the Intent-to-Treat (ITT) population.

Period 1

Period 1 title	Randomized
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Oteseconazole

Arm description:

Subjects received loading doses of 150 mg oteseconazole once daily on Days 1 to 7, followed by maintenance doses of 150 mg oteseconazole once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.

Arm type	Experimental
Investigational medicinal product name	Oteseconazole
Investigational medicinal product code	
Other name	VT-1161
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oteseconazole was administered as 150 mg oral capsules. Subjects were instructed to take the doses of investigational product (IP) within 30 minutes after ingestion of their main meal, at approximately the same time of the day consistently throughout the study.

Arm title	Placebo

Arm description:

Subjects received matching placebo regimen once daily on Days 1 to 7, followed by placebo once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.

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

Dosage and administration details:

Placebo was administered as oral capsules to match oteseconazole. Subjects were instructed to take the doses of IP within 30 minutes after ingestion of their main meal, at approximately the same time of the day consistently throughout the study.

Number of subjects in period 1	Oteseconazole	Placebo
Started	220	110
Completed	218	108
Not completed	2	2
Excluded from ITT population	2	2

Period 2

Period 2 title	Included in ITT Population
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Oteseconazole

Arm description:

Subjects received loading doses of 150 mg oteseconazole once daily on Days 1 to 7, followed by maintenance doses of 150 mg oteseconazole once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.

Arm type	Experimental
Investigational medicinal product name	Oteseconazole
Investigational medicinal product code	
Other name	VT-1161
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oteseconazole was administered as 150 mg oral capsules. Subjects were instructed to take the doses of IP within 30 minutes after ingestion of their main meal, at approximately the same time of the day consistently throughout the study.

Arm title	Placebo

Arm description:

Subjects received matching placebo regimen once daily on Days 1 to 7, followed by placebo once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.

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

Dosage and administration details:

Placebo was administered as oral capsules to match oteseconazole. Subjects were instructed to take the doses of IP within 30 minutes after ingestion of their main meal, at approximately the same time of the day consistently throughout the study.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 presents data for all subjects randomized and Period 2 presents data for all subjects included in the ITT population. 4 subjects were excluded from the ITT population due to GCP non-compliance at a site. The analysis population for baseline characteristics was the ITT population; Period 2 is therefore the baseline period.

Number of subjects in period 2[2]	Oteseconazole	Placebo
Started	218	108
Completed	190	91
Not completed	28	17
Consent withdrawn by subject	16	8
Physician decision	2	3
Adverse event, non-fatal	1	1
Sponsor request	1	-
Pregnancy	1	-
Non-compliance	-	2
Subject relocated	-	1
Lab assessment; clinically significant changes	1	-
Lost to follow-up	6	2

Notes:

[2] - 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: The analysis population for baseline characteristics was the ITT population which excluded 4 randomized subjects due to GCP non-compliance at a site.

Baseline characteristics

Reporting groups	
Reporting group title	Oteseconazole
Reporting group description:	
Subjects received loading doses of 150 mg oteseconazole once daily on Days 1 to 7, followed by maintenance doses of 150 mg oteseconazole once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo regimen once daily on Days 1 to 7, followed by placebo once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.	

Reporting group values	Oteseconazole	Placebo	Total
Number of subjects	218	108	326
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)	218	107	325
From 65-84 years	0	1	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	34	36	
standard deviation	± 9.4	± 10.8	-
Gender categorical			
Units: Subjects			
Female	218	108	326
Male	0	0	0
Race			
Units: Subjects			
White	193	96	289
Black or African American	23	8	31
Asian	0	3	3
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	2	1	3
Ethnicity			
Units: Subjects			
Hispanic or Latino	30	18	48
Not Hispanic or Latino	187	90	277
Unknown/Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Oteseconazole
Reporting group description:	
Subjects received loading doses of 150 mg oteseconazole once daily on Days 1 to 7, followed by maintenance doses of 150 mg oteseconazole once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo regimen once daily on Days 1 to 7, followed by placebo once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.	
Reporting group title	Oteseconazole
Reporting group description:	
Subjects received loading doses of 150 mg oteseconazole once daily on Days 1 to 7, followed by maintenance doses of 150 mg oteseconazole once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo regimen once daily on Days 1 to 7, followed by placebo once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.	

Primary: Percentage of Subjects with 1 or More Culture-verified Acute VVC Episodes during the Maintenance Phase

End point title	Percentage of Subjects with 1 or More Culture-verified Acute VVC Episodes during the Maintenance Phase
End point description:	
The primary efficacy outcome measure was the proportion of subjects with 1 or more culture-verified acute VVC episodes during the Maintenance Phase in the ITT population. The Maintenance Phase was defined as post-randomization through Week 48 of the study. An acute VVC episode during the Maintenance Phase (considered a recurrent episode) was defined as a positive culture for Candida species and a clinical signs and symptoms score of ≥3. Missing values were imputed with multiple imputation using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit. Analysis was performed on the ITT population which included all randomized subjects (except those specifically excluded from the analysis).	
End point type	Primary
End point timeframe:	
48 weeks	

End point values	Oteseconazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	108		
Units: percentage of subjects				
number (not applicable)	3.9	39.4		

Statistical analyses

Statistical analysis title	Comparison of oteseconazole to placebo
Comparison groups	Oteseconazole v Placebo
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

Secondary: Time to First Recurrence of a Culture-verified Acute VVC Episode during the Maintenance Phase

End point title	Time to First Recurrence of a Culture-verified Acute VVC Episode during the Maintenance Phase

End point description:

The Maintenance Phase was defined as post-randomization through Week 48 of the study. An acute VVC episode during the Maintenance Phase was defined as a positive culture for Candida species and a clinical signs and symptoms score of ≥3. Time to recurrence of acute VVC was estimated using the method of Kaplan-Meier and was calculated as:
Date of first culture-verified acute VVC episode – date of randomization+1
Subjects with no recurrence were censored at their last non-missing assessment. Analysis was performed on the ITT population which included all randomized subjects (except those specifically excluded from the analysis).

End point type	Secondary

End point timeframe:

48 weeks

End point values	Oteseconazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213[1]	107[2]		
Units: weeks				
median (confidence interval 95%)	999999 (999999 to 999999)	999999 (999999 to 999999)		

Notes:

[1] - 999999 denotes that the value was not estimable

[2] - 999999 denotes that the value was not estimable

Statistical analyses

Statistical analysis title	Comparison of oteseconazole to placebo

Statistical analysis description:

The Cox regression model included factors for treatment, region, baseline body mass index, baseline age, ethnicity and screening signs and symptoms score.

Comparison groups	Oteseconazole v Placebo

Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.17

Secondary: Percentage of Subjects with at Least 1 Positive Culture for Candida Species during the Maintenance Phase

End point title	Percentage of Subjects with at Least 1 Positive Culture for Candida Species during the Maintenance Phase

End point description:

The percentage of subjects with ≥1 positive culture for Candida species during the Maintenance Phase is reported. Missing values were imputed with multiple imputation using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit. Analysis was performed on the ITT population which included all randomized subjects (except those specifically excluded from the analysis).

End point type	Secondary

End point timeframe:

48 weeks

End point values	Oteseconazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	108		
Units: percentage of subjects				
number (not applicable)	27.6	84.0		

Statistical analyses

Statistical analysis title	Comparison of oteseconazole to placebo
Comparison groups	Oteseconazole v Placebo
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

Secondary: Percentage of Subjects with at Least 1 Culture-verified Acute VVC Episode through Week 24

End point title	Percentage of Subjects with at Least 1 Culture-verified Acute VVC Episode through Week 24

End point description:

The percentage of subjects with ≥1 positive culture for Candida species during post-randomization through Week 24 is reported. Missing values were imputed with multiple imputation using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit. Analysis was performed on the ITT population which included all randomized subjects (except those specifically excluded from the analysis).

End point type	Secondary

End point timeframe:

24 weeks

End point values	Oteseconazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	108		
Units: percentage of subjects				
number (not applicable)	2.8	31.9		

Statistical analyses

Statistical analysis title	Comparison of oteseconazole to placebo
Comparison groups	Oteseconazole v Placebo
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

Secondary: Change from Screening through Week 48 in the 36-item Short Form Survey (SF-36) Mental Component Score (MCS)

End point title	Change from Screening through Week 48 in the 36-item Short Form Survey (SF-36) Mental Component Score (MCS)

End point description:

The least squares (LS) mean change from Screening through Week 48 for SF-36 MCS is reported. The SF-36 questionnaire consists of 36 items which are used to calculate 8 scaled scores for the following domains: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health. Scores for the SF-36 scales range from 0 to 100, with higher scores denoting less disability. The MCS was derived as the average of the following 4 domain scores: vitality, social role functioning, emotional role functioning, and mental health. If 2 or more of the domain scores were missing, the MCS was missing. Missing values after applying the imputations according to the SF-36 scoring algorithm were imputed using last observation carried forward (LOCF). Analysis was performed on the ITT population which included all randomized subjects (except those specifically excluded from the analysis).

End point type	Secondary

End point timeframe:

48 weeks

End point values	Oteseconazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	101		
Units: scores on a scale				
least squares mean (confidence interval 95%)	14.19 (11.91 to 16.46)	11.69 (8.53 to 14.86)		

Statistical analyses

Statistical analysis title	Comparison of oteseconazole to placebo

Statistical analysis description:

The LS mean, 95% confidence interval (CI) for LS mean, difference in LS mean, 95% CI for the difference, and the p-value for the difference came from a repeated measures analysis of covariance (ANCOVA) model with a random effect for subject and fixed effects for treatment group, time point, treatment by time point interaction, and baseline value. A compound symmetry covariance structure was used.

Comparison groups	Oteseconazole v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	6.4

Secondary: Change from Screening through Week 48 in the SF-36 Total Score

End point title	Change from Screening through Week 48 in the SF-36 Total Score

End point description:

The LS mean change from Screening through Week 48 for SF-36 total score is reported. The SF-36 questionnaire consists of 36 items which are used to calculate 8 scaled scores for the following domains: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health. Scores for the SF-36 scales range between 0 and 100, with higher scores denoting less disability. The SF-36 total score was derived as the average of the 8 domain scores. If 3 or more of the domain scores were missing, the total score was missing. Missing values after applying the imputations according to the SF-36 scoring algorithm were imputed using LOCF. Analysis was performed on the ITT population which included all randomized subjects (except those specifically excluded from the analysis).

End point type	Secondary

End point timeframe:

48 weeks

End point values	Oteseconazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	101		
Units: scores on a scale				
least squares mean (confidence interval 95%)	13.69 (11.75 to 15.63)	11.45 (8.76 to 14.14)		

Statistical analyses

Statistical analysis title	Comparison of oteseconazole to placebo

Statistical analysis description:

The LS mean, 95% CI for LS mean, difference in LS mean, 95% CI for the difference, and the p-value for the difference came from a repeated measures ANCOVA model with a random effect for subject and fixed effects for treatment group, time point, treatment by time point interaction, and baseline value. A compound symmetry covariance structure was used.

Comparison groups	Oteseconazole v Placebo
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.186
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	5.56

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through Week 48 of the study.

Adverse event reporting additional description:

Treatment-emergent adverse events were defined as adverse events that occurred on or after the initiation of IP. The safety population was defined as all randomized subjects who received at least 1 dose of the IP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Oteseconazole

Reporting group description:

Subjects received loading doses of 150 mg oteseconazole once daily on Days 1 to 7, followed by maintenance doses of 150 mg oteseconazole once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo regimen once daily on Days 1 to 7, followed by placebo once weekly starting at Week 2 (7 days after the completion of daily dosing) through Week 12 of the study.

Serious adverse events	Oteseconazole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 217 (3.23%)	5 / 110 (4.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer female			
subjects affected / exposed	0 / 217 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocarditis			

subjects affected / exposed	0 / 217 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Motor dysfunction			
subjects affected / exposed	1 / 217 (0.46%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 217 (0.46%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 217 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 217 (0.46%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cholecystitis infective			
subjects affected / exposed	1 / 217 (0.46%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			

subjects affected / exposed	0 / 217 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe acute respiratory syndrome			
subjects affected / exposed	0 / 217 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 110 (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	Oteseconazole	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 217 (27.65%)	37 / 110 (33.64%)	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 217 (8.29%)	7 / 110 (6.36%)	
occurrences (all)	27	7	
Reproductive system and breast disorders			
Vulvovaginal pruritus			
subjects affected / exposed	4 / 217 (1.84%)	6 / 110 (5.45%)	
occurrences (all)	6	8	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 217 (2.76%)	2 / 110 (1.82%)	
occurrences (all)	6	2	
Vomiting			
subjects affected / exposed	6 / 217 (2.76%)	2 / 110 (1.82%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			

subjects affected / exposed	2 / 217 (0.92%)	3 / 110 (2.73%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 217 (1.84%)	3 / 110 (2.73%)	
occurrences (all)	4	3	
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	14 / 217 (6.45%)	6 / 110 (5.45%)	
occurrences (all)	23	7	
Nasopharyngitis			
subjects affected / exposed	11 / 217 (5.07%)	7 / 110 (6.36%)	
occurrences (all)	14	9	
Urinary tract infection			
subjects affected / exposed	12 / 217 (5.53%)	4 / 110 (3.64%)	
occurrences (all)	16	6	
Influenza			
subjects affected / exposed	6 / 217 (2.76%)	3 / 110 (2.73%)	
occurrences (all)	7	3	
Upper respiratory tract infection			
subjects affected / exposed	2 / 217 (0.92%)	7 / 110 (6.36%)	
occurrences (all)	2	7	
Cystitis			
subjects affected / exposed	5 / 217 (2.30%)	3 / 110 (2.73%)	
occurrences (all)	6	6	
Herpes simplex			
subjects affected / exposed	0 / 217 (0.00%)	3 / 110 (2.73%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2019	Changes included the following: • Expanded the description of Maintenance Phase dosing for IP to prevent confusion of the dosing regimens. • Updated details of collection of RVVC history for subjects in the United States only. • Clarified that the countries of Romania and Ukraine would not enroll subjects <18 years of age. • Added Romania and Ukraine to list of countries where subjects <18 years of age could not be enrolled. • Clarified subject population eligible for enrollment as post-menarcheal (this was previously assumed). • Established RVVC history to be based on locally approved testing, as outlined in the study design. • Improved clarity on timelines for Papanicolaou test requirement. • Clarified definition of abstinence and restricted contraceptive methods to only highly effective methods during repeat dosing of fluconazole. • Added a cross-reference to allowed treatment plan should a subject fail to respond to fluconazole treatment for an acute VVC episode. • Added collunarium/nasal to list of concomitant steroids permitted and to Exclusion Criterion #5. • Reduced potential confounding factors for efficacy assessments. • Improved clarity for which pregnancy testing (central serum or local urine) would be performed at each visit. • Implemented testing request to evaluate cholesterol and triglycerides across all subject populations. • Clarified Informed Consent Form and included assent for subjects aged 12 to 17 years. • Clarified which bacterial testing would be performed locally and centrally. • Provided clarification on capsule formulation of oteseconazole. • Clarified subjects can be eligible for re-screening once. • Modified the protocol deviation criterion for IP compliance. • Implemented changes made during European Union Voluntary Harmonisation Procedure review as they were beneficial to subject safety and data quality from a global perspective.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported