

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 25 February 2019 | <p>Changes included the following:</p> <ul style="list-style-type: none">• 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