

**Clinical trial results:**

Phase III study to evaluate the efficacy of a novel antimycotic vaginal pessary combination (containing Benzydamine HCl 6 mg and Econazole nitrate 150 mg) in the Treatment of uncomplicated vulvovaginal candidosis (VVC) [BEtreat study]

Summary

EudraCT number	2016-002808-19
Trial protocol	BG PL IT
Global end of trial date	02 April 2018

Results information

Result version number	v1 (current)
This version publication date	17 April 2019
First version publication date	17 April 2019

Trial information**Trial identification**

Sponsor protocol code	030(4C)H016241
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Additional study identifiers

ISRCTN number	ISRCTN000000000
ClinicalTrials.gov id (NCT number)	NCT000000000
WHO universal trial number (UTN)	U0000-0000-0000

Notes:

Sponsors

Sponsor organisation name	Aziende Chimiche Riunite Angelini Francesco- A.C.R.A.F. S.p.A.
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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	02 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2018
Global end of trial reached?	Yes
Global end of trial date	02 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the microbiological and clinical efficacy, the safety and acceptability of the benzydamine HCl 6 mg and econazole nitrate 150 mg vaginal pessary, in comparison to Pevaryl® 150 mg vaginal pessary, in the treatment of uncomplicated VVC.

Protection of trial subjects:

No specific measures are provided. In case of ineffective treatment the Investigator can administer alternative drugs and the patients discontinue study.

Background therapy:

Not applicable

Evidence for comparator:

Pevaryl® 150 mg (Pevaryl®, Janssen Cilag S.p.A.), pessary was selected as Comparator because it represented the drug of choice authorized for the treatment of uncomplicated VVC. The dosage regimen of Pevaryl® 150 mg vaginal pessary to be administered to the patients was consistent with that reported in the relevant Summary of Product Characteristics (SmPC).

Actual start date of recruitment	06 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	Russian Federation: 183
Country: Number of subjects enrolled	Poland: 66
Country: Number of subjects enrolled	Bulgaria: 188
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	445
EEA total number of subjects	262

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)	445
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment of 440 (220 per treatment group) patients was planned. 445 (222 in benzydamine HCl / econazole group; 223 in Pevaryl® group) were randomised and received the study medication starting from 6 October 2017 to 2 April 2018.

Pre-assignment

Screening details:

456 patients were evaluated for eligibility. 11 patients were excluded and defined Screening Failures.

Period 1

Period 1 title	PERIOD 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The study was performed in double blind conditions, consequently, during the study, neither the Investigator nor the patient were aware of the treatment assigned. Despite the impossibility of masking the marketed Comparator due to reasons related to the manufacturing process, the double-blind condition was guaranteed introducing a second clinical staff member who acted as drug-administrator. Accordingly, the Investigator acted as assessor, blinded to the drug administered to the patient.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test: BNZ 6 mg / ECONAZOLE 150 mg

Arm description:

Benzydamine HCl 6 mg / Econazole nitrate 150 mg pessary, intravaginal.

Arm type	Experimental
Investigational medicinal product name	Benzydamine HCl 6 mg / econazole nitrate 150 mg
Investigational medicinal product code	030(C)
Other name	
Pharmaceutical forms	Pessary
Routes of administration	Vaginal use

Dosage and administration details:

1 pessary once daily for 3 consecutive days

Arm title	Reference: ECONAZOLE 150 mg
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Arm description:

Econazole 150 mg pessary (Pevaryl®, Janssen Cilag S.p.A.), intravaginal.

Arm type	Active comparator
Investigational medicinal product name	Econazole
Investigational medicinal product code	
Other name	Pevaryl®
Pharmaceutical forms	Pessary
Routes of administration	Vaginal use

Dosage and administration details:

1 pessary once daily for 3 consecutive days

Number of subjects in period 1	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg
Started	222	223
Completed	222	223

Baseline characteristics

Reporting groups

Reporting group title	Test: BNZ 6 mg / ECONAZOLE 150 mg
Reporting group description: Benzylamine HCl 6 mg / Econazole nitrate 150 mg pessary, intravaginal.	
Reporting group title	Reference: ECONAZOLE 150 mg
Reporting group description: Econazole 150 mg pessary (Pevaryl®, Janssen Cilag S.p.A.), intravaginal.	

Reporting group values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg	Total
Number of subjects	222	223	445
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)	222	223	445
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	222	223	445
Male	0	0	0

Subject analysis sets

Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population (SP) was defined as all randomized patients who took at least one dose of the study medication.	
Subject analysis set title	Modified Intention-to-Treat (m-ITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified Intention-to-Treat (m-ITT) population was defined as all randomized patients with signs score ≥ 1 and symptoms score ≥ 3 at Visit 0, who took at least one dose of the study medications and performed the microbiological evaluation at Visit 3 (if applicable), or at Visit 4 (TOC), or at ETV/ETTV, and having at least one-post baseline clinical evaluation of symptoms.	
Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol
Subject analysis set description: Per Protocol (PP) population: the patients from the m-ITT population with no major protocol violations.	

Reporting group values	Safety analysis	Modified Intention-to-Treat (m-ITT)	Per Protocol (PP) population
Number of subjects	445	443	420
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)	445	443	420
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	445	443	420
Male	0	0	0

End points

End points reporting groups

Reporting group title	Test: BNZ 6 mg / ECONAZOLE 150 mg
Reporting group description: Benzydamine HCl 6 mg / Econazole nitrate 150 mg pessary, intravaginal.	
Reporting group title	Reference: ECONAZOLE 150 mg
Reporting group description: Econazole 150 mg pessary (Pevaryl®, Janssen Cilag S.p.A.), intravaginal.	
Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population (SP) was defined as all randomized patients who took at least one dose of the study medication.	
Subject analysis set title	Modified Intention-to-Treat (m-ITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified Intention-to-Treat (m-ITT) population was defined as all randomized patients with signs score ≥ 1 and symptoms score ≥ 3 at Visit 0, who took at least one dose of the study medications and performed the microbiological evaluation at Visit 3 (if applicable), or at Visit 4 (TOC), or at ETV/ETTV, and having at least one-post baseline clinical evaluation of symptoms.	
Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol
Subject analysis set description: Per Protocol (PP) population: the patients from the m-ITT population with no major protocol violations.	

Primary: MYCOLOGICAL CURE (m-ITT)

End point title	MYCOLOGICAL CURE (m-ITT)
End point description: Since the clinical and microbiological endpoints are of equal importance for the overall judgement of efficacy of the Fixed Dose Combination (FDC) containing Benzydamine HCl 6 mg and Econazole nitrate 150 mg vaginal pessary in comparison to Pevaryl® 150 mg vaginal pessary, the clinical (time to first symptoms relief) and microbiological (mycological cure) endpoints have been regarded as co-primary. The first co-primary endpoint was the microbiological response, defined as the absence of Candida or other yeasts at microscopy (mycological cure), at Visit 3, or at Visit 4.	
End point type	Primary
End point timeframe: The time point was Visit 3 - 2 days (+2 days) after EOT (End Of Treatment) or Visit 4 - 7 days (+2 days) after EOT	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	223		
Units: percent				
number (confidence interval 95%)				

Absence of Candida (%)	94.6 (91.63 to 97.57)	92.8 (89.34 to 96.18)		
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Statistical analyses

Statistical analysis title	Confidence limits
Statistical analysis description:	
Benzydamine HCl 6 mg and Econazole nitrate 150 mg vaginal pessary would have been considered non-inferior to Pevaryl® 150 mg vaginal pessary if the lower limit of the two-sided 95% Confidence Interval (95% CI) of the difference between the study drugs in the mycological cure rates did not exceed the threshold of -10.0%.	
Comparison groups	Reference: ECONAZOLE 150 mg v Test: BNZ 6 mg / ECONAZOLE 150 mg
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (net)
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	6.36

Primary: CLINICAL RESPONSE (m-ITT)

End point title	CLINICAL RESPONSE (m-ITT)
End point description:	
clinical response: time to first relief of symptoms, defined as the earliest time when the sum of the scores for all symptoms declines by 1 point or more with respect to the sum of the scores at baseline	
End point type	Primary
End point timeframe:	
The time to first relief of symptoms was determined after the first IMP administration, using a specific 4-point scale: 0=absent, 1=mild, 2=moderate, 3=severe.	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	223		
Units: percent				
number (not applicable)	100	99.55		

Statistical analyses

Statistical analysis title	Survival analysis
Statistical analysis description: The time to first relief of symptoms was analyzed using the log-rank test, at a two-sided alpha level of 5%. A p-value less than 0.05 was considered statistically significant.	
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042
Method	Logrank

Primary: MICOLOGYCAL CURE (PP)

End point title	MICOLOGYCAL CURE (PP)
End point description: Since the clinical and microbiological endpoints are of equal importance for the overall judgement of efficacy of the Fixed Dose Combination (FDC) containing Benzydamine HCl 6 mg and Econazole nitrate 150 mg vaginal pessary in comparison to Pevaryl® 150 mg vaginal pessary, the clinical (time to first symptoms relief) and microbiological (mycological cure) endpoints have been regarded as co-primary. The first co-primary endpoint was the microbiological response, defined as the absence of Candida or other yeasts at microscopy (mycological cure), at Visit 3, or at Visit 4.	
End point type	Primary
End point timeframe: The time point was Visit 3 - 2 days (+2 days) after EOT (End Of Treatment) or Visit 4 - 7 days (+2 days) after EOT	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	221		
Units: percent				
number (confidence interval 95%)	95.2 (92.32 to 98.11)	93.4 (90.01 to 96.72)		

Statistical analyses

Statistical analysis title	Confidence limits
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (net)
Point estimate	1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.58
upper limit	6.28

Secondary: Time to total symptoms relief (m-ITT)

End point title	Time to total symptoms relief (m-ITT)
End point description:	The time to total symptoms relief, defined as the time when the sum of the scores for all symptoms becomes 0.
End point type	Secondary
End point timeframe:	The time to total symptoms relief was determined after the first IMP administration, using a specific 4-point scale: 0=absent, 1=mild, 2=moderate, 3=severe.

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	223		
Units: percent				
number (not applicable)	95.5	95.02		

Statistical analyses

Statistical analysis title	Survival analysis
Statistical analysis description:	The time to first relief of symptoms was analyzed using the log-rank test, at a two-sided alpha level of 5%. A p-value less than 0.05 was considered statistically significant.
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3942
Method	Logrank

Secondary: Area under the differences from baseline for local burning sensation (m-ITT)

End point title	Area under the differences from baseline for local burning sensation (m-ITT)
End point description: Changes from Screening/Baseline for local burning sensation of uncomplicated VVC, were assessed as the sum of the difference of the scores at each time point (AUC)	
End point type	Secondary
End point timeframe: From Screening/Baseline until 24 h after the first drug application.	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	223		
Units: AUC				
arithmetic mean (standard deviation)	42.7 (± 15.2)	40.2 (± 16.2)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072
Method	ANOVA

Secondary: Area under the differences from baseline for local pain (m-ITT)

End point title	Area under the differences from baseline for local pain (m-ITT)
End point description: Changes from Screening/Baseline for local pain of uncomplicated VVC, were assessed as the sum of the difference of the scores at each time point (AUC).	
End point type	Secondary
End point timeframe: From Screening/Baseline until 24 h after the first drug application.	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	223		
Units: AUC				
arithmetic mean (standard deviation)	31.2 (± 19.8)	27.7 (± 18.7)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067
Method	ANOVA

Secondary: Area under the differences from baseline for local pruritus (m-ITT)

End point title	Area under the differences from baseline for local pruritus (m-ITT)
End point description:	changes from Screening/Baseline for local pruritus of uncomplicated VVC, were assessed as the sum of the difference of the scores at each time point (AUC)
End point type	Secondary
End point timeframe:	From Screening/Baseline until 24 h after the first drug application.

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	223		
Units: AUC				
arithmetic mean (standard deviation)	47.3 (± 13.7)	43.8 (± 13.9)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg

Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	ANOVA

Secondary: Clinical evaluation (cure, improvement and failure) (m-ITT)

End point title	Clinical evaluation (cure, improvement and failure) (m-ITT)
End point description: Clinical cure, improvement and failure were evaluated on the basis of Investigator's and patient's assessment of the objective signs (presence and severity) and subjective symptoms (presence and severity) of uncomplicated VVC, respectively.	
End point type	Secondary
End point timeframe: The time point was at Visit 3 or at ETTV/ETV	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	223		
Units: Number				
CURE	132	125		
IMPROVEMENT	75	80		
FAILURE	2	6		

Statistical analyses

Statistical analysis title	Chi-squared
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Chi-squared

Secondary: Therapeutic cure (m-ITT)

End point title	Therapeutic cure (m-ITT)
End point description: The therapeutic cure, was defined combining mycological eradication (absence of Candida or other yeast at microscopy) and clinical cure (resolution of all signs and symptoms).	

End point type	Secondary
End point timeframe:	
The time point was at Visit 4 (TOC), or at ETTV/ETV.	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	221		
Units: Number				
CURE	166	166		
FAILURE	52	45		

Statistical analyses

Statistical analysis title	Chi-squared
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.532
Method	Chi-squared

Secondary: Recurrences

End point title	Recurrences
End point description:	
Recurrence was defined as the presence of Candida or other yeast at microscopy, at the Follow-up Visit in a patient judged as therapeutically cured at Visit 4 (TOC) who referred a reappearance of the symptomatic disease at the telephonic follow-up.	
End point type	Secondary
End point timeframe:	
The time point was at the Follow-up Visit .	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	166		
Units: Number				
SUCCESS	163	162		
RECURRENCE	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in the total score of symptoms (m-ITT)

End point title	Changes in the total score of symptoms (m-ITT)
End point description:	
Percent change in the total score of symptoms from the Screening/Baseline.	
End point type	Secondary
End point timeframe:	
This endpoint was evaluated at each time point after the first drug application.	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	221		
Units: percent				
arithmetic mean (standard error)				
15 min	11.55 (± 1.54)	10.72 (± 1.68)		
30 min	17.42 (± 1.91)	15.93 (± 1.90)		
45 min	23.72 (± 2.05)	22.60 (± 2.17)		
1 hour	31.82 (± 2.02)	27.70 (± 2.17)		
2 hours	29.14 (± 2.35)	26.45 (± 2.4)		
3 hours	34.68 (± 2.36)	29.96 (± 2.41)		
4 hours	41.96 (± 2.14)	37.02 (± 2.39)		
5 hours	48.51 (± 2.09)	39.61 (± 2.34)		
6 hours	53.13 (± 2.06)	43.33 (± 2.39)		
8 hours	57.83 (± 2.09)	49.99 (± 2.24)		
12 hours	64.98 (± 1.89)	55.94 (± 2.16)		
24 hours	64.95 (± 1.67)	57.29 (± 1.89)		
48 hours	81.45 (± 1.30)	76.74 (± 1.57)		
72 hours	90.58 (± 1.33)	88.45 (± 1.49)		
96 hours	94.91 (± 0.78)	92.39 (± 1.12)		
216 hours	97.21 (± 0.65)	97.85 (± 0.64)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: The number of subjects starting from 2 hours up to 216 hours differs from specified in the selected comparison groups because the evaluation was carried on observed cases.	
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 ^[1]
Method	ANOVA

Notes:

[1] - Significant differences were detected from 5 hours up to 48 hours.

Secondary: Acceptability (m-ITT)

End point title	Acceptability (m-ITT)
End point description: Individual acceptability of vaginal pessary comfortable was assessed through the completion of a questionnaire on the following items: sticky, greasy, stain after application, flowing out of the vagina, and easily to dissolve. Results on the use of vaginal pessary are reported while the results on other items are attached.	
End point type	Secondary
End point timeframe: Patient's acceptability of the drug treatment was assessed through the completion of a questionnaire, administered by the Investigator at Visit 2, or at ETTV.	

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	221		
Units: Comfortable				
number (not applicable)				
Comfortable use of the vaginal pessary	96.8	91.4		
Uncomfortable use of vaginal pessary	3.2	8.6		

Attachments (see zip file)	Acceptability BeTreat Tab.docx
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Statistical analyses

No statistical analyses for this end point

Post-hoc: Time to 50% reduction of total score symptoms (m-ITT)

End point title	Time to 50% reduction of total score symptoms (m-ITT)
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End point description:

A post-hoc analysis was carried out to evaluate the clinical response, in terms of the time to first relief of symptoms, defined as the earliest time when the sum of the scores for all symptoms is reduced by 50% or more with respect to the sum of the scores at Screening/Baseline.

End point type	Post-hoc
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End point timeframe:

The time to first relief of symptoms was determined after the first IMP administration, using a specific 4-point scale: 0=absent, 1=mild, 2=moderate, 3=severe.

End point values	Test: BNZ 6 mg / ECONAZOLE 150 mg	Reference: ECONAZOLE 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	223		
Units: percent				
number (not applicable)	99.55	98.64		

Statistical analyses

Statistical analysis title	Survival analysis
Comparison groups	Test: BNZ 6 mg / ECONAZOLE 150 mg v Reference: ECONAZOLE 150 mg
Number of subjects included in analysis	445
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0003
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The timeframe for reporting adverse events is from informed Consent signature up to the telephonic follow-up or Follow-up Visit.

Adverse event reporting additional description:

Separate evaluations were performed on pre-treatment AEs and on Treatment Emergent Adverse Events (TEAEs), if applicable. A TEAE is defined as any event started on or after the first study medication administration date and was not a pre-existing medical condition.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Patients who took BNZ 6 mg_ECONAZOLE 150 mg
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Reporting group description:

Patients receiving the Benzydamine HCl 6 mg and Econazole nitrate 150 mg vaginal pessary, 1 pessary (2.7 g) once daily for 3 consecutive days.

Reporting group title	Patients who took ECONAZOLE 150 mg
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Reporting group description:

Patients receiving ECONAZOLE 150 mg (Pevaryl®) pessary, 1 pessary (2.7 g) once daily for 3 consecutive days.

Serious adverse events	Patients who took BNZ 6 mg_ECONAZOLE 150 mg	Patients who took ECONAZOLE 150 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 222 (0.45%)	0 / 223 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain	Additional description: The event was of moderate intensity and relationship was judged as unlikely. The condition completely recovered after 24 hours.		
subjects affected / exposed	1 / 222 (0.45%)	0 / 223 (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: 5 %

Non-serious adverse events	Patients who took BNZ 6 mg_ECONAZOLE 150 mg	Patients who took ECONAZOLE 150 mg	
Total subjects affected by non-serious adverse events subjects affected / exposed	25 / 222 (11.26%)	22 / 223 (9.87%)	
Vascular disorders Hypertensive crisis subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 1	22 / 223 (9.87%) 0	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 1	22 / 223 (9.87%) 0	
Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all) Vulvovaginal burning sensation subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 1 25 / 222 (11.26%) 1	22 / 223 (9.87%) 0 22 / 223 (9.87%) 1	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0	22 / 223 (9.87%) 1	
Investigations ALT increased subjects affected / exposed occurrences (all) AST increased subjects affected / exposed occurrences (all) Blood glucose increased subjects affected / exposed occurrences (all) Blood pressure increased subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0 25 / 222 (11.26%) 0 25 / 222 (11.26%) 1 25 / 222 (11.26%) 1	22 / 223 (9.87%) 1 22 / 223 (9.87%) 1 22 / 223 (9.87%) 0 22 / 223 (9.87%) 1	

Blood triglycerides increased subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 1	22 / 223 (9.87%) 0	
Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 1	22 / 223 (9.87%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 4 25 / 222 (11.26%) 0	22 / 223 (9.87%) 3 22 / 223 (9.87%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 1	22 / 223 (9.87%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Haemorrhoids subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Oesophageal pain	25 / 222 (11.26%) 1 25 / 222 (11.26%) 0 25 / 222 (11.26%) 0 25 / 222 (11.26%) 0 25 / 222 (11.26%) 1	22 / 223 (9.87%) 0 22 / 223 (9.87%) 1 22 / 223 (9.87%) 1 22 / 223 (9.87%) 1	

subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 1	22 / 223 (9.87%) 0	
Toothache subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 2	22 / 223 (9.87%) 3	
Hepatobiliary disorders Cholecystitis chronic subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 1	22 / 223 (9.87%) 0	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0	22 / 223 (9.87%) 1	
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0	22 / 223 (9.87%) 1	
Hypertonic bladder subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0	22 / 223 (9.87%) 1	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0	22 / 223 (9.87%) 1	
Cystitis subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0	22 / 223 (9.87%) 1	
Influenza subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0	22 / 223 (9.87%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 3	22 / 223 (9.87%) 0	
Pharyngitis subjects affected / exposed occurrences (all)	25 / 222 (11.26%) 0	22 / 223 (9.87%) 2	
Pulpitis dental			

subjects affected / exposed	25 / 222 (11.26%)	22 / 223 (9.87%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	25 / 222 (11.26%)	22 / 223 (9.87%)	
occurrences (all)	2	0	
Respiratory tract infection viral			
subjects affected / exposed	25 / 222 (11.26%)	22 / 223 (9.87%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	25 / 222 (11.26%)	22 / 223 (9.87%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	25 / 222 (11.26%)	22 / 223 (9.87%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2017	The substantial Amendment no. 1 proposed changes addressed some requestes raised by the Italian Competent Authority (AIFA) during the review of the documentation submitted for the study approval. The changes regarded mainly inclusion/exclusion criteria and efficacy assessment. Some minor changes were performed to correct typing errors or better details the study procedures already described. This amendment was approved by National Ethics Committee and Competent Authority.
18 December 2017	The non-substantial Amendment no. 2 proposed an update of the Investigator's Brochure due to the availability of the final results from two Phase I clinical trials performed with the new combination containing 6 mg Benzydamine HCl and 150 mg Econazole nitrate (both as vaginal cream and pessary). In addition, changes regarding Sponsor Personnel involved in the study and a correction of an inaccuracy were also proposed. This amendments was approved by National Ethics Committee and Competent Authority when 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.

Not applicable

Notes: