

**Clinical trial results:**

**An open, randomised, clinical trial parallel-controlled with Mycostatin oral suspension, evaluating the efficacy of Nystatin oral gel and Nystatin oral suspension in adult patients with oropharyngeal candidiasis.**

**Summary**

EudraCT number	2013-003784-56
Trial protocol	CZ
Global end of trial date	17 December 2014

**Results information**

Result version number	v1 (current)
This version publication date	16 June 2022
First version publication date	16 June 2022

**Trial information****Trial identification**

Sponsor protocol code	NV012013
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**Additional study identifiers**

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

Notes:

**Sponsors**

Sponsor organisation name	VUAB Pharma a.s.
Sponsor organisation address	Vltavská 53, Roztoky, Czechia, 25263
Public contact	Klára Kynčlová, VUAB Pharma a.s., +420 733 695 601, <a href="mailto:kkynclova@vuab.cz">kkynclova@vuab.cz</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	09 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2014
Global end of trial reached?	Yes
Global end of trial date	17 December 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Evaluation of the efficacy of Nystatin oral gel and Nystatin oral suspension compared to the reference medical product with the same active ingredient (nystatinum) in oral suspension form.

Note: This clinical trial was conducted as pilot one and its outcomes will be used for another clinical trial to confirm preliminary results of this trial.

Protection of trial subjects:

Oral administration did not require any specific measures to minimise pain and distress of trial subjects.

Background therapy:

None

Evidence for comparator:

The products Nystatin oral gel and Nystatin oral suspension are generic and their efficacy compliance with similar products containing the same active ingredient had to be demonstrated by a comparative study in accordance with article 10.3 of Directive 2001/83/ES.

As a reference medication (comparator), Mycostatin oral suspension (Bristol-Myers Squibb Pharmaceutical Limited, the holder of authorization) was chosen, which contains the nystatin as the active substance. No nystatin oral gel with suitable dossier was found in European Union countries. Therefore, Mycostatin oral suspension having suitable dossier confirmed by the Spain authority was chosen as the reference medication for both test investigational products (suspension and gel) in accordance with legislation.

Actual start date of recruitment	24 April 2014
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	Czechia: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	90
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects were approached for participation by investigators. Participation in the clinical trial was offered to all patients with oropharyngeal candidiasis visiting an otorhinolaryngology or allergology/immunology specialist. The recruitment was performed during study period (from April 2014 to November 2014) in the Czech republic.

### Pre-assignment

Screening details:

The investigator assessed clinical finding by physical examination – the count and extension of lesions as well as extension of erythema, thrush, and mucositis in mouth, including swab sample for laboratory confirmation.

### Pre-assignment period milestones

Number of subjects started	90
Number of subjects completed	90

### Period 1

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

Blinding implementation details:

None

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Nystatin suspension

Arm description:

The enrolled subjects used this test investigational product during 28 days of treatment.

Arm type	Experimental
Investigational medicinal product name	Nystatin 100,000 IU/ml oral suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oromucosal use, Buccal use, Oropharyngeal use

Dosage and administration details:

For study purposes, it was specified the dose of 5.0 ml of suspension at the concentration of 100.000 U/ml. It was required to apply one dose twice a day in interval of about 12 hours.

The subject was instructed to leave the investigational product in the affected area for at least 1 minute to achieve the desired effect. The subject was enabled to swallow both forms of investigational product. The investigational product had always to be applied after meals.

The suspension dose, which was shaken in the bottle before administration, had to be measured using a calibrated plastic syringe. The content of the syringe was administered in the mouth. The suspension was kept in the mouth for at least 1 minute before swallowing.

<b>Arm title</b>	Nystatin gel
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Arm description:

The enrolled subjects used this test investigational product during 28 days of treatment.

Arm type	Experimental
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Investigational medicinal product name	Nystatin 100,000 IU/ml oral gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral gel
Routes of administration	Buccal use, Oromucosal use, Oropharyngeal use

**Dosage and administration details:**

For study purposes, it was specified the dose of 5.0 ml of gel at the concentration of 100.000 U/g. It was required to apply one dose twice a day in interval of about 12 hours.

The subject was instructed to leave the investigational product in the affected area for at least 1 minute to achieve the desired effect. The subject was enabled to swallow both forms of investigational product. The investigational product had always to be applied after meals.

The gel dose had to be measured on the calibrated spoon, i.e., the study dose represented the amount of gel up to mark 5. The gel was applied with a finger from the spoon into the mouth. It was applied on the affected and surrounding areas. It had to be left to act for at least 1 minute and then swallowed.

<b>Arm title</b>	Mycostatin suspension
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**Arm description:**

The enrolled subjects used this reference product during 28 days of treatment.

Arm type	Active comparator
Investigational medicinal product name	MYCOSTATIN 100,000 IU/ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Buccal use, Oromucosal use, Oropharyngeal use

**Dosage and administration details:**

For study purposes, it was specified the dose of 5.0 ml of suspension at the concentration of 100.000 U/ml. It was required to apply one dose twice a day in interval of about 12 hours.

The subject was instructed to leave the investigational product in the affected area for at least 1 minute to achieve the desired effect. The subject was enabled to swallow both forms of investigational product. The investigational product had always to be applied after meals.

The suspension dose, which was shaken in the bottle before administration, had to be measured using a calibrated plastic syringe. The content of the syringe was administered in the mouth. The suspension was kept in the mouth for at least 1 minute before swallowing.

<b>Number of subjects in period 1</b>	Nystatin suspension	Nystatin gel	Mycostatin suspension
Started	30	30	30
Completed	30	30	30

## Baseline characteristics

### Reporting groups

Reporting group title	Nystatin suspension
Reporting group description: The enrolled subjects used this test investigational product during 28 days of treatment.	
Reporting group title	Nystatin gel
Reporting group description: The enrolled subjects used this test investigational product during 28 days of treatment.	
Reporting group title	Mycostatin suspension
Reporting group description: The enrolled subjects used this reference product during 28 days of treatment.	

Reporting group values	Nystatin suspension	Nystatin gel	Mycostatin suspension
Number of subjects	30	30	30
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)	30	30	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	48	42	44
full range (min-max)	21 to 60	19 to 59	25 to 58
Gender categorical Units: Subjects			
Female	22	18	15
Male	8	12	15

Reporting group values	Total		
Number of subjects	90		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	90		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean full range (min-max)			
Gender categorical Units: Subjects			
Female	55		
Male	35		

### Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

It represented all subjects regardless of Candida albicans load at treatment start or the study medication consumption.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS set (per protocol set) included of ITT set:

- subjects were not withdrawn from the study
- subjects with known laboratory result for each visit
- subjects with mycological score  $\geq 2$  at start of treatment

Reporting group values	ITT	PPS	
Number of subjects	90	61	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	90	61	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years arithmetic mean full range (min-max)	45 19 to 60	41 21 to 60	
Gender categorical Units: Subjects			
Female	55	42	
Male	35	19	

## End points

### End points reporting groups

Reporting group title	Nystatin suspension
Reporting group description:	The enrolled subjects used this test investigational product during 28 days of treatment.
Reporting group title	Nystatin gel
Reporting group description:	The enrolled subjects used this test investigational product during 28 days of treatment.
Reporting group title	Mycostatin suspension
Reporting group description:	The enrolled subjects used this reference product during 28 days of treatment.
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	It represented all subjects regardless of Candida albicans load at treatment start or the study medication consumption.
Subject analysis set title	PPS
Subject analysis set type	Per protocol
Subject analysis set description:	The PPS set (per protocol set) included of ITT set: <ul style="list-style-type: none"><li>• subjects were not withdrawn from the study</li><li>• subjects with known laboratory result for each visit</li><li>• subjects with mycological score <math>\geq 2</math> at start of treatment</li></ul>

### Primary: mycological cure rate (ITT)

End point title	mycological cure rate (ITT)
End point description:	
End point type	Primary
End point timeframe:	Treatment

End point values	Nystatin suspension	Nystatin gel	Mycostatin suspension	ITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	30	30	30	90
Units: Total	24	23	22	69

### Statistical analyses

Statistical analysis title	difference: Nystatin suspension - Mycostatin (ITT)
Statistical analysis description:	The two-sided confidence interval of difference between two proportions/rates was calculated as simple asymptotic.
Comparison groups	Mycostatin suspension v Nystatin suspension

Number of subjects included in analysis	60
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	> 0.05
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	28

<b>Statistical analysis title</b>	difference: Nystatin gel - Mycostatin (ITT)
Comparison groups	Nystatin gel v Mycostatin suspension
Number of subjects included in analysis	60
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	> 0.05
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.3
upper limit	12.3

### Secondary: mycological cure rate (PPS)

End point title	mycological cure rate (PPS)
End point description: The primary endpoint defined by the protocol was the mycological cure rate as a proportion of subjects who achieved mycological score <2 (i.e., mycological finding ≤5 CFU/swab) after study treatment.	
End point type	Secondary
End point timeframe: Treatment	

<b>End point values</b>	Nystatin suspension	Nystatin gel	Mycostatin suspension	PPS
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	21	20	20	61
Units: Total	17	13	16	46

## Statistical analyses

<b>Statistical analysis title</b>	difference: Nystatin suspension - Mycostatin (PPS)
Statistical analysis description: The two-sided confidence interval of difference between two proportions/rates was calculated as simple asymptotic.	
Comparison groups	Mycostatin suspension v Nystatin suspension
Number of subjects included in analysis	41
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	> 0.05
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.3
upper limit	25.2

<b>Statistical analysis title</b>	difference: Nystatin gel - Mycostatin (PPS)
Statistical analysis description: The two-sided confidence interval of difference between two proportions/rates was calculated as simple asymptotic.	
Comparison groups	Nystatin gel v Mycostatin suspension
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	> 0.05
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.3
upper limit	12.3

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events included close vigilance for reporting of reactions about 4-week treatment, as well as measurement of vital signs.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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### Reporting groups

Reporting group title	Nystatin suspension
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Reporting group description:

The enrolled subjects used this test investigational product during 28 days of treatment.

Reporting group title	Nystatin gel
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Reporting group description:

The enrolled subjects used this test investigational product during 28 days of treatment.

Reporting group title	Mycostatin suspension
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Reporting group description:

The enrolled subjects used this test investigational product during 28 days of treatment.

Serious adverse events	Nystatin suspension	Nystatin gel	Mycostatin suspension
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Nystatin suspension	Nystatin gel	Mycostatin suspension
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 30 (23.33%)	11 / 30 (36.67%)	4 / 30 (13.33%)
Social circumstances	-----		
Taste disorder	Additional description: unpleasant taste		
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	1 / 30 (3.33%)
occurrences (all)	1	2	1
Application site discomfort	Additional description: unsatisfactory application		
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	2	0

Gastrointestinal disorders Burning sensation subjects affected / exposed occurrences (all)	Additional description: mouth or gums burning		
	3 / 30 (10.00%)	4 / 30 (13.33%)	0 / 30 (0.00%)
	3	4	0
	Additional description: tongue tingling, tongue burning		
Tongue disorder subjects affected / exposed occurrences (all)	1 / 30 (3.33%)	1 / 30 (3.33%)	0 / 30 (0.00%)
	1	1	0
Nausea subjects affected / exposed occurrences (all)	1 / 30 (3.33%)	1 / 30 (3.33%)	1 / 30 (3.33%)
	1	1	1
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	Additional description: rash on the hands		
	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
	0	0	1
Infections and infestations Cough subjects affected / exposed occurrences (all)	1 / 30 (3.33%)	0 / 30 (0.00%)	1 / 30 (3.33%)
	1	0	1
	Additional description: unspecified virosis/cold		
Viral infection subjects affected / exposed occurrences (all)	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
	0	1	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

None
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Notes: