Clinical trial results:
A phase IIa randomized, active-controlled, double-blind, dose-escalation study in patients with vulvovaginal candidiasis to evaluate clinical efficacy, safety and tolerability and dose response relationship of topically administered ProF-001

Summary

EudraCT number	2016-004268-21
Trial protocol	AT
Global end of trial date	30 July 2018

Results information

Result version number	v1 (current)
This version publication date	01 August 2020
First version publication date	01 August 2020
Summary attachment (see zip file)	Prof-001_Public disclosure synopsis_Version 1.1 (Prof-001_Public disclosure synopsis_Version 1.1.pdf)

Trial information

Trial identification

Sponsor protocol code	ProF-001_Phase_IIa

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03115073
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Profem GmbH
Sponsor organisation address	Riglergasse 4/I, Vienna, Austria, 1180
Public contact	Sponsor representative, Profem GmbH DDr. Marion Noe-Letschnig E-mail: marion.noe@profem.at , +43 676 7203070, office@profem.at
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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	20 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 July 2018
Global end of trial reached?	Yes
Global end of trial date	30 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the dose-response and the clinical efficacy of a cream containing a combination of clotrimazole and diclofenac sodium for the topical treatment of acute episodes of vulvovaginal candidiasis (VVC) after vaginal administration. Three different doses of diclofenac sodium in combination with clotrimazole were compared with clotrimazole alone as reference.

Protection of trial subjects:

Adverse event monitoring included subjective and objective symptom assessments applying an established symptom score as defined in the FDA guidance for treatment of VVC from 2016 and by Sobel and co-workers in 2001:

- Subjective symptoms: itching, burning pain and irritation/soreness classified as mild, moderate and severe,
- Objective symptoms: erythma, edema and excoriation as assessed by the gynecologist (classified as mild, moderate and severe).

Study subjects were asked to self-rate their physical condition and adverse reactions associated with the study medication at each visit. Subjective grading of local reactions has been documented by patients in the diary according to severity based on a visual analogue scale (VAS). The treating physician assessed the symptoms itching, burning pain and irritation/soreness according to the above mentioned symptom score (categorized into mild, moderate and severe) and objectively confirmed by gynecological examination.
Special attention of participating subjects has been drawn to document in the diary and to report the occurrence of local irritations such as erythema, peeling, itching or burning.

Background therapy:

not applicable

Evidence for comparator:

1% Clotrimazole for acute episode of VVC (015-072l_S2k_Vulvovaginalkandidose_2013-12; Pappas et al. US_clinical_practice_guideline_2016)

Actual start date of recruitment	09 May 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	Austria: 54
Country: Number of subjects enrolled	Poland: 32
Worldwide total number of subjects	86
EEA total number of subjects	86

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)	86
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was performed at secondary and tertiary care gynecology units in Austria (Vienna and Tyrolia) and Poland (City of Poznan).

Pre-assignment

Screening details:

Subject screening and entry examination included but was not limited to the grading of signs and symptoms by a gynaecologist and the performance of a vaginal smear (native, KOH) for budding yeasts and/or fungal (pseudo-)hyphae, normal (G I) or intermediate flora (G II) according to the Nugent criteria for the diagnosis of an acute episode of VVC.

Period 1

Period 1 title	Active treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

Central blinding of IMP was performed at manufacturing site - blinding was kept throughout the study until database lock

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Active controlled arm with Clotrimazole 1%

Arm type	Active comparator
Investigational medicinal product name	clotrimazole 1%
Investigational medicinal product code	comparator
Other name	
Pharmaceutical forms	Cream
Routes of administration	Vaginal use

Dosage and administration details:

cream containing 1% clotrimazole (Fungizid-ratiopharm® 1% Vaginalcreme) for intravaginal application (2.5 ml cream) and topical application (2 cm cream in the vulvar region)

Arm title	Candiplus 0.2%

Arm description:

Lowest dose group

Arm type	Experimental
Investigational medicinal product name	Candiplus 0.2%
Investigational medicinal product code	clotrimazole 1% + diclofenac 0.2%
Other name	ProF-001 0.2%
Pharmaceutical forms	Cream
Routes of administration	Topical use , Vaginal use

Dosage and administration details:

2.5 ml + 2 cm cream twice daily (days 1, 2 and 3) followed by 2.5 ml + 2 cm cream once daily (days 4, 5 and 6) to be administered as vaginal application (2.5 ml cream) and topical application (2 cm cream in the vulvar region)

Arm title	Candiplus 0.3%

Arm description:

Intermediate dose group

Arm type	Experimental
Investigational medicinal product name	Candiplus 0.3%
Investigational medicinal product code	clotrimazole 1% + diclofenac 0.3%
Other name	ProF-001 0.3%
Pharmaceutical forms	Cream
Routes of administration	Topical use , Vaginal use

Dosage and administration details:

2.5 ml + 2 cm cream twice daily (days 1, 2 and 3) followed by 2.5 ml + 2 cm cream once daily (days 4, 5 and 6) to be administered as vaginal application (2.5 ml cream) and topical application (2 cm cream in the vulvar region)

Arm title	Candiplus 0.4%

Arm description:

High dose group

Arm type	Experimental
Investigational medicinal product name	Candiplus 0.4%
Investigational medicinal product code	clotrimazole 1% + diclofenac 0.4%
Other name	ProF-001 0.4%
Pharmaceutical forms	Cream
Routes of administration	Vaginal use, Topical use

Dosage and administration details:

2.5 ml + 2 cm cream twice daily (days 1, 2 and 3) followed by 2.5 ml + 2 cm cream once daily (days 4, 5 and 6) to be administered as vaginal application (2.5 ml cream) and topical application (2 cm cream in the vulvar region)

Number of subjects in period 1	Control	Candiplus 0.2%	Candiplus 0.3%
Started	21	22	21
Completed	20	21	21
Not completed	1	1	0
Protocol deviation	1	1	-

Number of subjects in period 1	Candiplus 0.4%
Started	22
Completed	21
Not completed	1
Protocol deviation	1

Period 2

Period 2 title	Follow up period
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	Control

Arm description:

Active controlled arm with Clotrimazole 1%

Arm type	Active comparator
Investigational medicinal product name	clotrimazole 1%
Investigational medicinal product code	comparator
Other name	
Pharmaceutical forms	Cream
Routes of administration	Vaginal use

Dosage and administration details:

cream containing 1% clotrimazole (Fungizid-ratiopharm® 1% Vaginalcreme) for intravaginal application (2.5 ml cream) and topical application (2 cm cream in the vulvar region)

Arm title	Candiplus 0.2%

Arm description:

Lowest dose group

Arm type	Experimental
Investigational medicinal product name	Candiplus 0.2%
Investigational medicinal product code	clotrimazole 1% + diclofenac 0.2%
Other name	ProF-001 0.2%
Pharmaceutical forms	Cream
Routes of administration	Topical use , Vaginal use

Dosage and administration details:

2.5 ml + 2 cm cream twice daily (days 1, 2 and 3) followed by 2.5 ml + 2 cm cream once daily (days 4, 5 and 6) to be administered as vaginal application (2.5 ml cream) and topical application (2 cm cream in the vulvar region)

Arm title	Candiplus 0.3%

Arm description:

Intermediate dose group

Arm type	Experimental
Investigational medicinal product name	Candiplus 0.3%
Investigational medicinal product code	clotrimazole 1% + diclofenac 0.3%
Other name	ProF-001 0.3%
Pharmaceutical forms	Cream
Routes of administration	Topical use , Vaginal use

Dosage and administration details:

2.5 ml + 2 cm cream twice daily (days 1, 2 and 3) followed by 2.5 ml + 2 cm cream once daily (days 4, 5 and 6) to be administered as vaginal application (2.5 ml cream) and topical application (2 cm cream in the vulvar region)

Arm title	Candiplus 0.4%

Arm description:

High dose group

Arm type	Experimental
Investigational medicinal product name	Candiplus 0.4%
Investigational medicinal product code	clotrimazole 1% + diclofenac 0.4%
Other name	ProF-001 0.4%
Pharmaceutical forms	Cream
Routes of administration	Vaginal use, Topical use

Dosage and administration details:

2.5 ml + 2 cm cream twice daily (days 1, 2 and 3) followed by 2.5 ml + 2 cm cream once daily (days 4, 5 and 6) to be administered as vaginal application (2.5 ml cream) and topical application (2 cm cream in

the vulvar region)

Number of subjects in period 2	Control	Candiplus 0.2%	Candiplus 0.3%
Started	20	21	21
Completed	20	21	21

Number of subjects in period 2	Candiplus 0.4%
Started	21
Completed	21

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Active controlled arm with Clotrimazole 1%	
Reporting group title	Candiplus 0.2%
Reporting group description:	
Lowest dose group	
Reporting group title	Candiplus 0.3%
Reporting group description:	
Intermediate dose group	
Reporting group title	Candiplus 0.4%
Reporting group description:	
High dose group	

Reporting group values	Control	Candiplus 0.2%	Candiplus 0.3%
Number of subjects	21	22	21
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)	21	22	21
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	28	26	34
full range (min-max)	19 to 41	18 to 45	18 to 45
Gender categorical			
Units: Subjects			
Female	21	22	21
Male	0	0	0

Reporting group values	Candiplus 0.4%	Total	
Number of subjects	22	86	
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)	22	86	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	32		
full range (min-max)	18 to 48	-	
Gender categorical			
Units: Subjects			
Female	22	86	
Male	0	0	

Subject analysis sets

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

Subject analysis set description:

The full analysis set will comprise all randomized subjects who received at least six doses (3 days) of investigational product and who have sufficient data of the co-efficacy endpoint of: (i) Symptom relief within the first 60 minutes (after application of investigational product or active control, with reduction of the subjective symptom score ≥2) and (ii) clinical cure (absence of signs and symptoms of VVC) at the TOC visit (=day 7 ± 3). Analyses on the FAS will be performed according to the randomized dose group (intention to treat principle).

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population comprises all subjects who were randomized and received at least one dose of the IMP. Analyses based on the safety analyses were performed according to the actual dose the patients received.

Reporting group values	Full analysis set	Safety population	
Number of subjects	83	86	
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)	83	86	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	29	29	
full range (min-max)	18 to 48	18 to 48	
Gender categorical			
Units: Subjects			
Female			

Male			

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Active controlled arm with Clotrimazole 1%	
Reporting group title	Candiplus 0.2%
Reporting group description:	
Lowest dose group	
Reporting group title	Candiplus 0.3%
Reporting group description:	
Intermediate dose group	
Reporting group title	Candiplus 0.4%
Reporting group description:	
High dose group	
Reporting group title	Control
Reporting group description:	
Active controlled arm with Clotrimazole 1%	
Reporting group title	Candiplus 0.2%
Reporting group description:	
Lowest dose group	
Reporting group title	Candiplus 0.3%
Reporting group description:	
Intermediate dose group	
Reporting group title	Candiplus 0.4%
Reporting group description:	
High dose group	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set will comprise all randomized subjects who received at least six doses (3 days) of investigational product and who have sufficient data of the co-efficacy endpoint of: (i) Symptom relief within the first 60 minutes (after application of investigational product or active control, with reduction of the subjective symptom score ≥2) and (ii) clinical cure (absence of signs and symptoms of VVC) at the TOC visit (=day 7 ± 3). Analyses on the FAS will be performed according to the randomized dose group (intention to treat principle).

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population comprises all subjects who were randomized and received at least one dose of the IMP. Analyses based on the safety analyses were performed according to the actual dose the patients received.

Primary: Symptom relief after 60 minutes with clinical cure at day 7

End point title	Symptom relief after 60 minutes with clinical cure at day 7

End point description:

Composite primary endpoint combining two parameters:
1. Symptom relief within the first 60 minutes after application of the investigational medicinal product (IMP) defined as reduction of the subjective symptom score ≥2 in combination with
2. Clinical cure (absence of signs and symptoms of VVC) at the test of cure (TOC) visit at day 7 (±3 days)

End point type	Primary

End point timeframe:

Symptom assessment 60 minutes after application of IMP in combination with cure at the test of cure (TOC) visit at day 7 (±3 days)

End point values	Control	Candiplus 0.2%	Candiplus 0.3%	Candiplus 0.4%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	21	21	21
Units: numbers	7	12	7	6

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	83			
Units: numbers	33			

Statistical analyses

Statistical analysis title	logistic regression

Statistical analysis description:

The logistic regression was performed to test effects of dose-concentration on the primary endpoint. Results indicated that the model did not provide a statistically significant effect (p=0.39). The Nagelkerke R2 indicated that model accounted for 1.3% of the total variance. The correct prediction rate was about 66.2%. The wald test showed that the predictor did not significantly predict the primary endpoint.

Comparison groups	Control v Candiplus 0.2% v Candiplus 0.3% v Candiplus 0.4% v Full analysis set
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	regression coefficient
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day of randomization until end of follow-up period (day 60 ± 5 days after randomization)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	Control
Reporting group description: Active controlled arm with Clotrimazole 1%	
Reporting group title	Candiplus 0.2%
Reporting group description: Lowest dose group	
Reporting group title	Candiplus 0.3%
Reporting group description: Intermediate dose group	
Reporting group title	Candiplus 0.4%
Reporting group description: High dose group	

Serious adverse events	Control	Candiplus 0.2%	Candiplus 0.3%
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Candiplus 0.4%		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Control	Candiplus 0.2%	Candiplus 0.3%
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 21 (57.14%)	12 / 22 (54.55%)	15 / 21 (71.43%)
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	0 / 21 (0.00%)
occurrences (all)	0	9	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 21 (4.76%)	1 / 22 (4.55%)	3 / 21 (14.29%)
occurrences (all)	3	1	6
Reproductive system and breast disorders			
Vulvovaginal burning sensation			
subjects affected / exposed	9 / 21 (42.86%)	7 / 22 (31.82%)	10 / 21 (47.62%)
occurrences (all)	23	26	49
Vulvovaginal disorder			
subjects affected / exposed	0 / 21 (0.00%)	3 / 22 (13.64%)	1 / 21 (4.76%)
occurrences (all)	0	6	1
Vulvovaginal pruritus			
subjects affected / exposed	4 / 21 (19.05%)	2 / 22 (9.09%)	2 / 21 (9.52%)
occurrences (all)	4	2	4
Genital burning sensation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	9
Pruritus genital			
subjects affected / exposed	0 / 21 (0.00%)	0 / 22 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	9

Non-serious adverse events	Candiplus 0.4%		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 22 (68.18%)		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Vulvovaginal burning sensation			
subjects affected / exposed	14 / 22 (63.64%)		
occurrences (all)	74		
Vulvovaginal disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Vulvovaginal pruritus			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	13		
Genital burning sensation			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Pruritus genital			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2018	Follow-up period of the last cohort amended to complete the end of trial information: The study was considered completed when the TOC visit of the last randomized patient is reached (last randomized subject completes test of cure visit) or the study is terminated early based on recommendation of the Independent Safety Monitoring Committee. Those patients who have entered the follow-up period before approval of protocol amendment V4.0 dated March 5, 2018, were to be followed up to the second telephone visit. All other patients were to be followed until the TOC visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported