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Medical Journal of Obstetrics and Gynecology

Short Communication

Saccharomyces cerevisiae CNCM I-3856 as a Natural Breakthrough for Vaginal Health: A Clinical Study

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Submitted: 28 September 2017

Accepted: 19 December 2017

Published: 21 December 2017

ISSN: 2333-6439

Keywords

• *Candida*; Vulvovaginitis; Treatment; Prevention; *Saccharomyces*; Relapse

Abstract

Vulvovaginal candidiasis (VVC) is a common and burdensome fungal infection in women. Although conventional therapies exert satisfactory results in curing acute VVC, prevention of relapse remains a concern. The objective of this double-blind, randomized, placebo-controlled pilot study was to evaluate the effect of oral administration of *S. cerevisiae* CNCM I-3856 in women conventionally treated for VVC. The women received a single conventional antifungal treatment and consumed a placebo or *S. cerevisiae* CNCM I-3856 once a day for 56 days. Vaginal *Candida* load was measured at each visit by a vaginal swab, and the proportion of relapses was assessed after 8 weeks (W8). Twenty-two (22) women with confirmed VVC were allocated to a verum (n=13) or a placebo group (n=9). Characteristics were similar at baseline except for vaginal *Candida* load. Compliance was excellent (98.8 ± 8.0%) and probiotic supplementation was well tolerated. In the verum group, *Candida* vaginal load significantly decreased from W0 to W4 ($p < 0.01$) and from W0 to W8 ($p < 0.01$) while remaining stable in the placebo group. At W8, 4/13 subjects (31%) relapsed in the verum group *vs* 6/9 subjects (67%) in the placebo group. *S. cerevisiae* strain CNCM I-3856 is efficient in the control of vaginal *Candida* proliferation and in preventing VVC recurrence. This probiotic yeast is well-tolerated and easy to use by oral administration.

ABBREVIATIONS

AE: Adverse Event; BV: Bacterial Vaginosis; CNCM: Collection Nationale De Cultures De Micro Organismes; CFU: Colony Forming Units; ITTS: Intent To Treat Set; M: Mean; Min: Minimum; Max: Maximum; OTC: Over the Counter; PPS: Per Protocol Set; RVVC: Recurrent Vulvovaginal Candidiasis SD: Standard Deviation; TEAE: Treatment Emergent Adverse Event; VVC: Vulvovaginal Candidiasis

INTRODUCTION

Vulvovaginal candidiasis (VVC) is a common infection that can be burdensome when recurrent. VVC is defined by the presence of pathogenic *Candida spp*. associated with vulvovaginal symptoms including pruritus, irritation, burning, erythema and vaginal discharge [1,2]. Experience of 4 or more episodes of VVC in the last 12 months is defined as recurrent VVC (RVVC) and is considered to be a complicated class of VVC [2,3].

The literature reports that 75% of women will experience at least one episode of VVC in their lifetime. About half of these women will have a second episode and 5-10% of all women will suffer from RVVC [2,3].

Candida albicans is the main causative agent of VVC although other non-*albicans Candida* such as *C. glabrata* can be involved. *C. albicans* may be naturally present in the vagina as part of the commensal microbiota. The alteration of the vaginal microflora and/or host immune system equilibrium can lead to its uncontrolled proliferation. Conventional therapy involves topical application of antifungals which are available over-the-counter (creams, lotions, vaginal ovules) or other drugs administered orally (fluconazole, itraconazole) [4,5]. These treatments are quite efficient in treating VVC but they can have side effects (*e.g.* skin irritation, redness, burning, gastro-intestinal disorders, and hepatotoxicity). RVVC requires treatment ranging from a few days to several months in the case of long-term suppressive therapy [3,6-8]. Although control of symptoms may be assured, a definitive microbiological cure cannot be guaranteed. Moreover, in the context of increasing antifungal resistance in *Candida*, alternative approaches are needed to better prevent VVC relapses.

Adjuvant therapies are commonly used by women to deal with recurrent vaginitis including RVVC, although no international guidelines support their use [9]. The use of probiotics as an approach for improving prevention and/or treatment of VVC has gained growing attention over the last years. Administered either orally or topically, probiotics classically contain lactic acid bacteria [10]. Less explored probiotics may be of help; for example, *Saccharomyces cerevisiae*, A non-pathogenic yeast with a long history of safe use in human nutrition and health. It has been recently demonstrated that *S. cerevisiae* CNCM I-3856 is able to positively influence the course of vaginal candidiasis in mice by accelerating the clearance of *C. albicans* [11]. However,

no study in women suffering from VVC has been performed with this strain to date.

The objective of this pilot clinical study was to evaluate the effect of oral administration of *S. cerevisiae* CNCM I-3856 in women suffering from VVC.

MATERIALS AND METHODS

A double-blind, randomized, placebo-controlled pilot study has been performed on female patients presenting symptoms of VVC with microbiological confirmation of *C. albicans*.

The study design was approved by the Individual Protection Committee South-Est II and III (Comité de Protection des Personnes - CPP) of Lyon (France) and was authorized by the French National Agency for Medicines and Health Products Safety (Agence Nationale de Sécurité du Médicamentet des produits de santé, France). The study is listed on ClinicalTrial.gov under the identifier NCT02345096.

Patients

Subjects with clinically diagnosed vulvovaginal candidiasis (VVC) were required to be premenopausal females 18 years of age or older, with normal menstrual cycles, normal gynaecological status, and without major gynaecological histories. Subjects were required to use effective contraceptive methods or to have undergone sterilization at least 3 months before entry. They gave a written informed consent prior to selection, and were covered by a Health Insurance System. Subjects were excluded if pregnant or breast feeding; had tumours of the genital tract or breast; were hypersensitive to the study product; had uterine or vaginal bleeding of unknown origin; used intravaginal antibiotics or antifungal agents within the previous 14 days or had concomitant medication with antifungal agents for other diagnoses. Patients with known sexually transmitted infections (HIV 1 or 2, *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Treponema pallidum*, *Herpes simplex*, *Trichomonas vaginalis*, human papillomavirus in active phase or under treatment) were excluded. Additionally, subjects were excluded if they were Immune- compromised, had a central venous catheter, or if they refused to stop the consumption of pre-/probiotic dietary supplements and food products enriched with pre-/probiotics.

Study design

Twenty-two (22) eligible subjects visited the same investigation centre (Grenoble, France) for 4 visits: pre-inclusion visit V0 (W0), inclusion visit V1 (7 ± 5 days after V0, W1), follow-up visit V2 (28 ± 5 days after V0, W4), end-of-study visit V3 (56 ± 5 days after V0, W8).

At V0, subjects meeting inclusion criteria were enrolled and randomized to orally consume either 1 capsule of 500 mg ($5x10^9$ CFU/g) of *S. cerevisiae* CNCM I-3856 or the placebo (500 mg maize starch), daily for 56 days (± 5 days). Clinical and gynaecological examinations were performed and a vaginal swab was taken and placed in transport liquid culture (Σ-Transwab®, MWE, UK). The physician assessed and rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe) the following symptoms: erythema, oedema, vagina redness, vulva redness, vagina ulceration, uterus ulceration. The subjects were asked to score the following symptoms using the same scale: smelly discharge, heavy vaginal discharge, itching/burning sensations, dyspareunia, dysuria, pain. A global symptom score was calculated by summing each symptom score. By the end of the visit, subjects were prescribed a conventional drug treatment including an antifungal vaginal ovule, to be administrated by each subject once in the evening at V0, and an external antifungal cream for one to two applications per day after showering, for a duration depending on the symptoms.

Inclusion was confirmed at V1 (W1) if *Candida* was detected on the V0 vaginal swab; otherwise, subjects were withdrawn from the study.

Included subjects were asked to return to the investigation centre for follow-up visits at V2 (W4) and V3 (W8). At each visit, the physician assessed and rated the presence of vulvovaginal symptoms, performed a vaginal swab and evaluated potential episodes of relapse at V3 (W8). Subjects scored their symptoms using the same scales. Compliance was monitored and adverse events that occurred since the previous visit were recorded.

Stool samples were collected from a limited number of patients at V0 (W0), V2 (W4) and V3 (W8) to assess the load of *Candida* in faeces.

Study products

Study products were contained in HPMC capsules, packaged in blisters. Verum and placebo products were similar in colour, form, flavour, size and weight. Subjects were instructed to orally consume one capsule of 500 mg per day, in the evening with a glass of water.

S. cerevisiae I-3856 is a proprietary and patented strain of Lesaffre Human Care (Lesaffre Group, France), registered in the French National Collection of Micro organisms (CNCM). This strain of *S. cerevisiae* has been characterized by using phenotypic (API® ID32C, Biomerieux SAS) and genotypic referenced methods (amplification and sequencing of 26S ribosomal DNA) [12,13]. Moreover, I-3856 has been defined by Inter delta typing using the Polymerase Chain Reaction (PCR) technique [14], and by other genetic methods (*e.g*., completes genome sequencing).

The conventional drug treatment administrated at V0 was composed of one ovule of Econazole® and the use of a topical cream (Econazole®). The ovule was administrated once, on the first evening after V0 and the cream, once to twice per day, as long as needed. If any relapse occurred, the investigator was free to prescribe another antifungal treatment and this was reported in the case report form as a concomitant treatment.

Microbiological Analysis

Cultures were centrally processed at Labazur laboratory (Crolles, France). The samples were suspended in saline and plated onto chrom ID™ Candida Agar (CAN2) medium for identification and quantification of *C. albicans* using the automated Previ Isola® system (BioMérieux, France). *C. albicans* identification was confirmed using the VITEK® 2 automated system (Biomérieux, France).

Study endpoints and statistical considerations

VVC was defined as the presence of *Candida* in vaginal swabs,

concomitantly with the presence of symptoms. VVC relapse was evaluated and reported by the investigator at W8 based on gynaecological examination, *Candida* quantification in vaginal swabs and symptoms questionnaires. The proportion of subjects who experienced at least one relapse at W8 was compared between groups using Fisher's exact test. The changes in *Candida* vaginal load (expressed in Log cfu/ml) were analysed in both the Intent-To-Treat Set (ITTS) and the Per-Protocol Set (PPS).

Results are expressed as mean ± standard deviation (m ± SD) or median [min; max] and numbers and percentages. Percentages were calculated on the number of non-missing data. The analysis was performed on an Intent-To-Treat basis and involved all patients having taken at least one unit of the study drug (ITTS). Results were confirmed in the per protocol population excluding any subjects with major protocol violation. Vaginal loads and changes from W0 were compared between groups at W1, W4 and W8 using Student's t-test after having checked homogeneity of variances. The same rules applied for *Candida* load in faeces (expressed in Log cfu/g faeces). Statistical evaluation was performed using the software package SAS release 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS AND DISCUSSION

The objective of this pilot study was to evaluate the effect of a 2-month oral administration of *S. cerevisiae* CNCM I-3856 on women conventionally treated for VVC. Among the 46 volunteers screened, 24 women were ineligible because no *Candida* was isolated from V0 vaginal samples. Twenty-two (22) subjects who were eligible for the study took at least one capsule of the study products and were involved in the ITTS (Figure 1). Nine (9) and 13 subjects were randomized in the placebo and verum group respectively (Table 1). At V0, the vulvovaginal symptoms score was 9.11 ± 3.02 for placebo and 10.77 ± 4.62 for verum. Vaginal *Candida* load was significantly higher in the verum group (5.31 ± 1.34 Log10 cfu/ml) than in the placebo group (4.06 ± 1.11 Log10 cfu/ml) ($p < 0.05$) (Table 2). Overall compliance from W0 to W8 was excellent ranging from 64.3% to 100% with a mean of 98.8 ± 8.0%.

In the ITTS population, *Candida* vaginal load was not different between placebo and verum groups at W1 (1.48 ± 2.95 Log10 cfu/ml and 2.52 ± 2.96 Log10 cfu/ml, respectively). At W4, the *Candida* load was lower in the verum group than in the placebo group (2.96 ± 2.90 vs 3.63 ± 2.92 Log10 cfu/ml) but the difference did not reach statistical significance. Similar results were found at W8 (2.31 ± 2.72 vs 2.72 ± 2.39 Log10 cfu/ml) (Figure 2). Interestingly, the change in *Candida* vaginal load from W0 to W1, W4 or W8 significantly differed between groups. In the placebo group, *Candida* vaginal load tended to decrease from W0 to W1 (-2.58 ± 3.42 Log10 cfu/ml; $p = 0.053$) and remained stable from W0 to W4 (-0.43 Log10 cfu/ml ± 3.04) and from W0 to W8 (-1.34 Log10 cfu/ml ± 2.71). Conversely, in the verum group, *Candida* vaginal load decreased significantly from W0 to W1 (-2.80 ± 2.72 Log10 cfu/ml; $p < 0.01$), from W0 to W4 (-2.35 ± 2.61 Log10 cfu/ml; $p < 0.01$) and from W0 to W8 (-3.00 ± 2.87 Log10 cfu/ml; $p < 0.01$). Similar results were observed in the PPS population (data not shown) (Table 3).

At W8, 6 out of 9 placebo subjects (67%) and 4 out of 13 verum subjects (31%) presented at least one VVC relapse symptom from the beginning of the study but the inter-group difference was not statistically significant. These results confirmed the probiotic's potential in enhancing the conventional treatment of VVC in infected women by accelerating the clearance of the pathogen and limiting the recurrence of infection. No serious adverse event was reported during the study thus validating the safety of I-3856 demonstrated in other clinical studies [15-17] (Table 4).

The therapeutic activity of *S. cerevisiae* CNCM I-3856 has been investigated in an experimental mouse model of vulvovaginal candidiasis [11,18]. These trials demonstrated that the probiotic was able to positively influence the course of vaginal candidiasis by accelerating the clearance of *C. albicans* from the vagina due to multiple interactions of *S. cerevisiae* with *C. albicans*. The probiotic yeast induced Co-aggregation with *Candida* consequently inhibiting its adherence to vaginal epithelial cells. In addition, it suppressed some major virulence factors of *C. albicans* (such as the ability to switch from the budding yeast to its mycelial form and its capacity to express several secreted Aspartyl proteases) [11]. Protection of Epithelial cells against damage caused by *C. albicans* was also observed. In addition, indirect mechanisms could be expected to modulate *Candida* infection, *e.g*., immunomodulation as described for other probiotics in the context of urogenital infections [19]. The capacity of *S. cerevisiae* CNCM I-3856 to modulate the vaginal inflammatory response of the host has been studied and demonstrated recently [20] .

The administration of probiotics to women suffering from vaginal infections can be either oral or topical. To date, no route has provided a clear superior effect to the other, as mixed results are documented with both, and no direct comparison of the mode of administration has been made [10,21,22]. Oral administration has the advantage being more convenient and confers the ability to act directly and/or indirectly with the intended target. Some data supports the ability of lactic acid bacteria to migrate from the gastro-intestinal tract to the vagina [23,24]. In previous studies, live *S. cerevisiae* strain CNCM I-3856 demonstrated a high survival rate after passage through a dynamic *in vitro* system simulating human gastrointestinal tract [25]. Now, further clinical experiments are necessary to determine if the probiotic yeast is able to migrate from the gut to the vagina.

Meanwhile, the mechanism of action of *S. cerevisiae* CNCM I-3856 observed in the vagina may be transferable to the gastrointestinal tract where *C. albicans* is also present and potentially pathogenic. There is a great interest in addressing one of the main sources of vaginal infections, which is the gut, with oral administration of the probiotic yeast *S. cerevisiae* CNCM I-3856. The notion of a *Candida* intestinal reservoir as source of reinfection has been described [2]. In our study, intestinal carriage of *C. albicans* tended to be similar between the groups. Interestingly, out of the 16 subjects analysed, the 2 subjects (1 in the placebo group and 1 in the verum group) in whom *Candida* was not detected in vaginal samples from W1 to W8, had *Candida*-free faecal samples over the entire study period.

In this pilot study only a limited number of subjects have been included. Firstly, with the availability of several over the counter (OTC) treatments, women are led to believe that they can diagnose themselves, but the accuracy of self-diagnosis remains

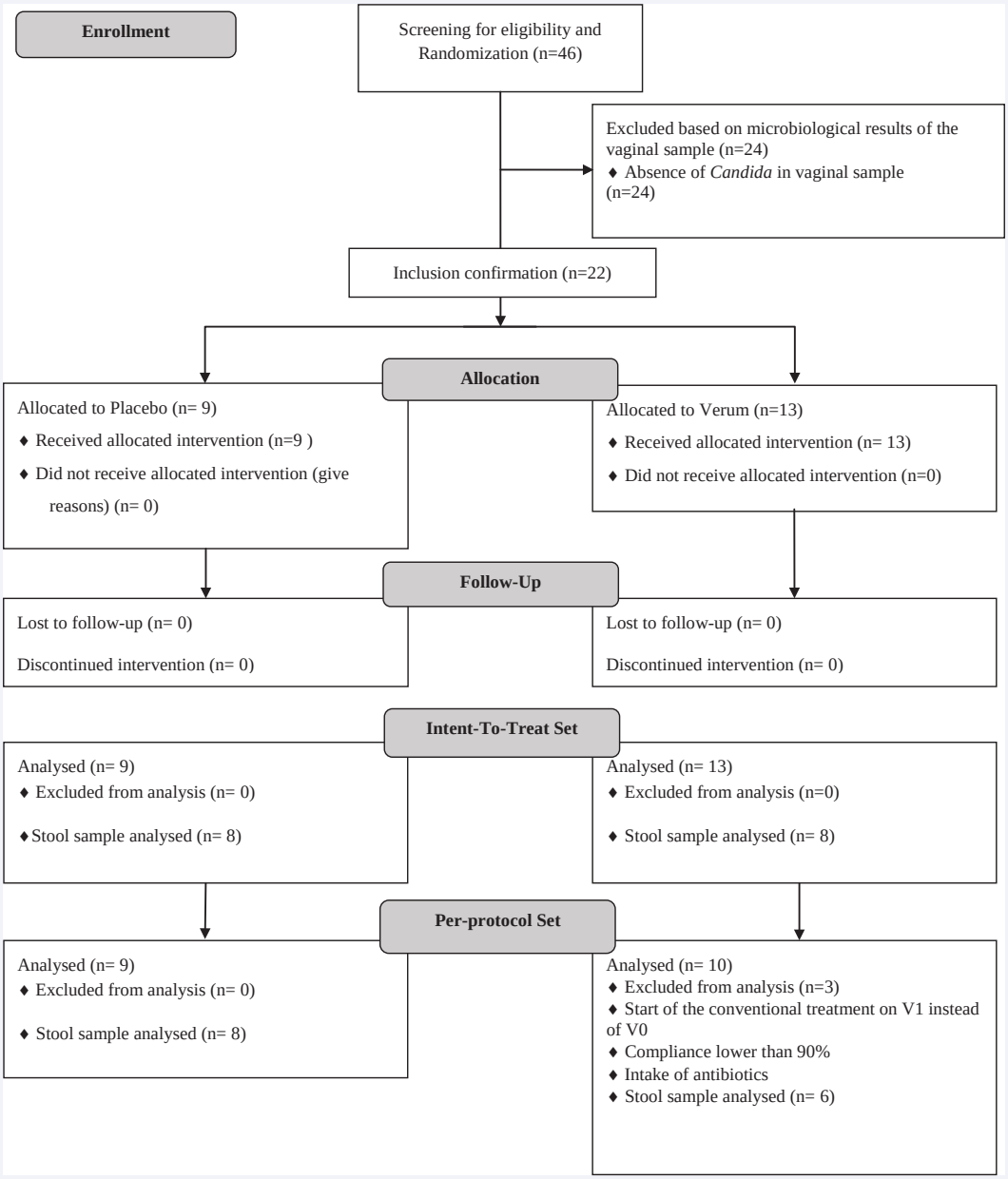

Figure 1 Study flow chart.

Table 1: Baseline population data.

ITTS	Statistics	Placebo (n=9)	Active product (n=13)	Overall (n=22)
Age (years)	N	9	13	22
	Mean ± SD	35.9 ± 7.9	34.5 ± 7.8	35.1 ± 7.7
Weight (kg)	N	9	13	22
	Mean ± SD	64.22 ± 12.85	59.50 ± 8.86	61.43 ± 10.65
Height (cm)	N	9	13	22
	Mean ± SD	165.3 ± 3.7	162.8 ± 4.8	163.9 ± 4.5
BMI (kg/m^2)	N	9	13	22
	Mean ± SD	23.41 ± 3.92	22.53 ± 3.84	22.89 ± 3.80

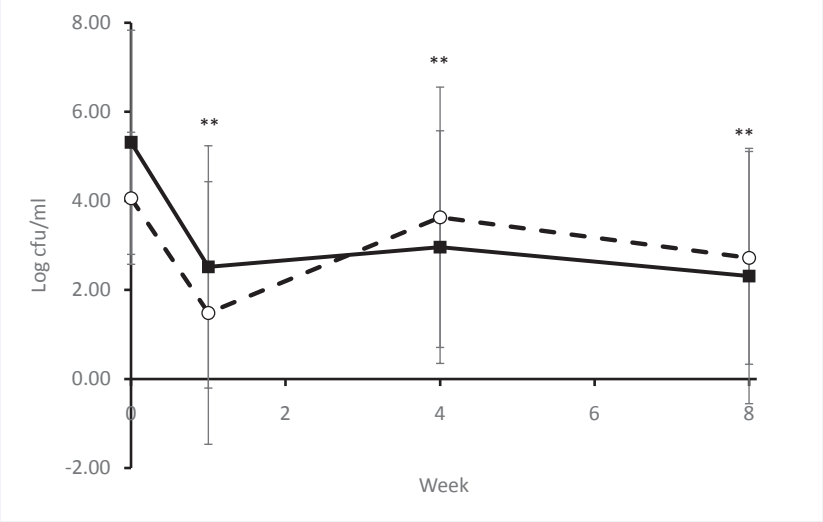

Figure 2 **Evolution of *Candida* vaginal colonization (ITTS).**
Candida vaginal loads in patients from the placebo group (0) and the verum group (■) are expressed as mean +/- SD. Change in *Candida* vaginal loads from W0 were compared using paired *t* test: **, p < 0.01 in the verum group only. Changes in the placebo groups were not significant. ITTS: Intention-to-treat set.

Table 2: Baseline vulvovaginal characteristics.

ITTS		**Placebo n=9**	**Verum n=13**	**p***
	n	9	13	
Symptom score	(m ± SD)	9.11 ± 3.02	10.77 ± 4.62	0.3572
	[min - max; med]	[5 - 14 ; 9]	[3 - 18 ; 12]	
Vaginal *Candida* load (Log_{10}cfu/ml)	n	9	13	
	(m ± SD)	4.06 ± 1.11	5.31 ± 1.34	0.0310
	[min - max; med]	[2 - 5.96 ; 4.45]	[2.90 - 7.41 ; 5.08]	

*means were compared using Student's t- test; ITTS: Intent-To-Treat set

Table 3: Change in *Candida* vaginal colonization.

ITTS	Log_{10}cfu/ml	**Placebo n=9**	**Verum n=13**	**p**
W1-W0	N	9	13	
	(m±SD)	-2.58 ± 3.42	-2.80 ± 2.72	0.8667 *(a)*
	[min - max; med]	[-5.96 - 3.26 ; -4.45]	[-6.65 - 1.50 ; -3.11]	
	p	0.0537*(b)*	0.0030*(b)*	
W4-W0	N	9	13	
	(m±SD)	-0.43 ± 3.04	-2.35 ± 2.61	0.1272 *(a)*
	[min - max; med]	[-4.48 - 3.15 ; 0.33]	[-6.65 - 0.74 ; -1.09]	
	p	0.6851*(b)*	0.0070*(b)*	
W8-W0	N	9	13	
	(m±SD)	-1.34 ± 2.71	-3.00 ± 2.87	0.1862 *(a)*
	[min - max; med]	[-4.46 - 2.37 ; -2.19]	[-7.41 - 0.84 ; -2.90]	
	p	0.1765*(b)*	0.0026*(b)*	

(a) Comparison performed using Student's t-test; (b) comparison performed using paired *t*-test; ITTS: Intent-To-Treat Set

Table 4: *Candida* faeces colonisation.

ITTS		Placebo N=8	Verum N=8
***Candida* detection**			
W0	n (%)	2 (25%)	4 (50%)
W4	n (%)	3 (37.5%)	4 (50%)
W8	n (%)	4 (50%)	4 (50%)
***Candida* quantification**			
W0	n	8	8
	(m±SD)	0.65 ± 1.25	1.83 ± 2.06
	[min - max; med]	[0 - 3.23 ; 0]	[0 - 4.76 ; 1.30]
W4	n	8	8
	(m±SD)	1.06 ± 1.46	1.30 ± 1.46
	[min - max; med]	[0 - 2.90 ; 0]	[0 - 3.43 ; 1]
W8	n	8	8
	(m±SD)	1.20 ± 1.31	1.28 ± 1.47
	[min - max; med]	[0 - 3 ; 1]	[0 - 3.73 ; 1]
W4-W0	n	8	8
	(m±SD)	0.40 ± 1	-0.53 ± 2.15
	[min - max; med]	[-0.39 - 2.70 ; 0]	[-4.25 - 3.43 ; -0.30]
W8-W0	n	8	8
	(m±SD)	0.55 ± 1.12	-0.55 ± 1.53
	[min - max; med]	[-0.93 - 2.30 ; 0]	[-3 - 2 ; -0.26]

ITTS: Intent-To-Treat Set

very poor. Secondly, women were selected on suspicion of VVC based on symptoms, but more than 50% (24/46) of the screened subjects could not be included because cultures for the presence of *Candida* were negative. In a prospective cohort of 95 women who had self-diagnosed VVC and were about to purchase an OTC antifungal, Ferris et al. [26], observed that 33.7% had VVC alone and 20.0% had VVC associated with other vaginal infections (mainly bacterial vaginosis (BV)). The remaining women had either no infection (13.7%) or infections other than VVC. Vaginal co-infections (*e.g.,* candidiasis and bacterial vaginosis) could be an interesting topic for future investigation.

Overall, our striking results show a positive effect of *S. cerevisiae* CNCM I-3856 on vaginal colonization by *Candida* and VVC relapse and encourage further research.

CONCLUSION

This pilot clinical study showed that oral administration of the probiotic yeast *S. cerevisiae* CNCM I-3856 as an adjuvant therapy in women suffering from VVC is easy-to-use and well tolerated. Furthermore, the probiotic yeast is efficient in controlling vaginal *Candida* proliferation after conventional treatment thus limiting VVC recurrence.

ACKNOWLEDGEMENTS

We thank Gunnard K. Jacobson from Lesaffre Yeast Corporation (Lesaffre Group, Milwaukee, United States) for proof-reading.

CONFLICT OF INTEREST

All authors are full-time employees of Lesaffre Group.

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Cite this article

Cayzeele-Decherf A, Pélerin F, Jüsten P (2017) Saccharomyces cerevisiae CNCM I-3856 as a Natural Breakthrough for Vaginal Health: A Clinical Study. Med J Obstet Gynecol 5(4): 1112.