Experiences of Women with Bacterial Vaginosis and Expectations for a *Lactobacillus* Product

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Abstract

Background: Bacterial vaginosis (BV) is the most prevalent vaginal infection among women of reproductive age and is associated with significant physical and psychosocial discomfort as well as several important adverse reproductive health outcomes. There is limited research on women's experiences of BV and what factors would be important to women using a probiotic intervention.

Objectives: To identify how prior experiences with BV treatment, the psychosocial impact of BV, and expectations for a *Lactobacillus* product vary among women screened for the Lactin-V Phase 2b clinical trial to treat recurrent bacterial vaginosis.

Methods: Women between the ages of 18-45 who were not currently pregnant or breastfeeding were recruited for screening for the Lactin-V Phase 2b clinical trial at Zuckerberg San Francisco General Hospital, where study staff collected demographic information, gynecologic and sexual history, and biological specimens for each participant. Prior experiences with BV, the psychosocial impact of BV, and expectations for a *lactobacillus* product were assessed by a self-administered questionnaire. While the complete clinical study report of this multisite study will include the analysis of all 228 women enrolled in the study, only women who were not further enrolled in the Lactin-V trial (considered "screen fails") were included in this analysis.

Results: Though 104 screening visits that resulted in a screen failure were conducted, these visits yielded only 74 completed Baseline Acceptability Questionnaires since some participants screened out too early in the visit to complete the questionnaire. Of these, 98% had some experience with BV and 32.7% had experienced five or more episodes of BV. About half of the sample reported that BV has had a major or severe impact on their life, and this perceived impact increased with number of BV episodes. Though 31.9%, agreed that their treatment in the past had been effective, 87.7% were interested in using a probiotic product in the future and a wide variety of alternative therapies already in use were reported. It was most important to women that such a product was effective at treating BV and improved their vaginal health, and few women were concerned with their partner's approval of using such a product.

Conclusions: BV is having a significant impact emotionally, physically, and sexually, and this impact increases as the number of lifetime BV episodes increases. Participants overwhelming expressed interest in an effective *lactobacillus* product. Further analysis of Lactin-V users will yield valuable information on product accessibility and it is important that we continue to assess the social and cultural norms that shape women's experiences with BV and impact the success of potential probiotic intervention.

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1. Introduction

1.1 Background of Bacterial Vaginosis

Bacterial vaginosis (BV) is the most prevalent vaginal infection among women of reproductive age and is associated with significant physical and psychosocial discomfort as well as several important adverse reproductive health outcomes. BV is characterized by a deficit in the normal, lactic acid producing bacteria in the vaginal microbiome and an overgrowth of the other, predominantly anaerobic, pathogenic species including *G. vaginalis*, *ureaplasma*, and *mycoplasma* [22]. Prevalence of BV is consistently high worldwide, but can vary by geographic location, socio-demographic factors, and health behaviors. A meta-analysis conducted in 2019 that included data from 122 publications reported that worldwide prevalence in the general population of women age 14-49 is about 23-29% across regions [19]. Studies show that rates tend to be highest in sub-Saharan Africa and lowest in East Asia and Western Europe, though these comparisons are of limited usefulness due to the significant variation within regions and inconsistencies in the type population measured [12].

In the United States, stark ethnic disparities in the prevalence of BV are readily documented. The National Health and Nutrition Examination Survey of 2001-2004 found a general prevalence of 29.2% for BV, but prevalence was highest among non-Hispanic blacks at 51.4%, measure at 31.9% among Mexican-Americans, and lowest among non-Hispanic whites 23.2% [1,13]. It is unclear how much of this ethnic variation can be attributed other risk factors and behaviors. Earlier sexual debut, increased sexual partners,

douching and use other intra-vaginal hygiene products, smoking status, pregnancy, and high BMI have consistently been reported as risk factors associated with BV acquisition [2,8,13]. The role of contraceptive use in BV is also not entirely elucidated, but there is some evidence that condom use and oral contraceptive use are protective against BV while use of intra-uterine devices may be at higher risk of acquired BV due to the IUD's disruption of the vaginal micro-biome or increased irregular vaginal bleeding [15,20].

The symptoms of BV are characterized by a thin, homogeneous discharge and a strong vaginal odor, along with itching and irritation around and in the vagina and pain with urination or sex. Though many remain asymptomatic or unaware of their condition, BV research is of particular importance because of its association with other serious adverse reproductive health outcomes. BV has been consistently associated with, pelvic inflammatory disease and increased acquisition and transmission of HIV and STDs such as chlamydia and gonorrhea, as well as increased risk of adverse pregnancy outcomes including preterm birth, early miscarriage, and intrauterine infection [10, 16, 23]. Therefore, it is important to further examine burden of BV on people's lives and that social and cultural factors that may shape people's willingness to seek treatment.

1.2 Probiotic Treatment

The only treatment for BV currently approved by the FDA is antibiotics; the CDC recommends oral or vaginal Metronidazole and Clindamycin [22]. While these antibiotics are generally effective short-term with 80-90% cure rates at one week after treatment, these treatments are ineffective for many in the long run [21]. Though long-term follow-up studies are limited, it is estimated that one third of patients will have a second episode

within three months and 50% of patients will experience recurrence within 12 months [4,6].

Though the cause of the transition in microbiome from protective, lactic acid producing species to pathogenic species is still unknown, there has recent effort to work towards alternative therapies that recolonize the vagina with protective microorganism, largely lactobacilli. Interest in probiotic treatments has been widely expressed among those who suffer from BV, for example, one study found that over half of respondents were interested in using a probiotic to treat vaginal infections and close to half had already used a natural or home remedy to treat a gynecologic health issue [5]. A 2014 meta-analysis of 1,304 participants in 12 clinical trials using probiotic treatments for BV showed that probiotic supplementation can significantly increase the cure rates for adults with BV. The researchers emphasized, however, though the results are promising, data is limited and more large-scale studies on side effects and effectiveness (over efficacy) are needed [11].

A challenge that has arisen in clinical trials is the divergence of reported use of such probiotic study products and actual use of the products. For example, in the previous Lactin-V Phase 2a trial, although 88% of the participants reported using all of the applicators as directed, confirmatory staining of the applicators indicated that only 50% of the participants had used all of the applicators as directed [9]. Therefore, assessing acceptability, user's priorities for such a product, and beliefs and social constructs surrounding BV is key to determining effectiveness and marketing strategies for such a product.

1.3 Psychosocial Impact of BV

Two other studies examining the psycho-social impact of BV were identified, both indicating that BV is associated with shame, embarrassment, and self-consciousness that can have a moderate to severe impact on sufferer's lives. Frustration with recurrence, lack of understating about the cause of episodes, and continued need for medical attention also emerged as a common theme in both studies. Bilaradi et al. found that participants felt the biggest burden on the sexual behaviors and intimacy with partners, while Payne et al. was most alarmed that 60% of the participants reported vaginal odor negatively impacting their work attendance, job performance and productivity, and relationships with coworkers [3,17]. These qualitative studies, however, both had limited sample sizes (n=20 and n=35), so further assessment of the psychosocial impact of B.V and its relationship with acceptability and product use is needed.

1.4 Hypothesis and Objectives

In order to test our hypothesis that recurrent BV is having a significant impact on people's lives due to high recurrent rates and stigma surrounding BV symptoms and, as such, there is wide interest in a *lactobacillus* product, we sought to explore participants' prior experiences with BV and assess participants' expectations for such a product.

2. Methods:

2.1 Study Design

Lactin-V Phase 2b Trial was conducted at four sites across the United States between June 2016 and February 2019. Interested participants were reached briefly on the phone to determine if they had some knowledge of BV and to inform them of the basic eligibility criteria for the study (ages 18-45 and not pregnant or breastfeeding). Participants were invited to schedule a screening visit at ZSFGH, where study staff consented participants and collected survey and biological specimens for each participant. To qualify for enrollment in the study, participants needed to have untreated BV on the day of screening, no other urogenital infections, and no use of an antibiotic in the last 21 days, along with other criteria. Full eligibility criteria (inclusion and exclusion requirements) can be found in Appendix 1.

Eligible participants were expected to complete a five day course of MetroGel® before returning for an enrollment visit, where they were consented for enrollment and randomized to receive either the Lactin-V study product (a powder formulation containing *L. crispatus* CTV-05 at a potency of 2 x 109cfu/dose in a pre-filled, tampon-like applicator) or the placebo (same powder formulation without *L. crispatus* CTV-05) at a 2:1 ratio. Participants took their first Lactin-V dose at the enrollment visit and were instructed to take the subsequent doses for the next four days consecutively then twice a week for the following ten weeks. Participants were followed for a total of sixth months, during which time they attended four more in-person visits, two phone visits, and were asked to fill out a log tracking their symptoms.

This analysis includes only women who were screened to participate in the Lactin-V trail and completed the Baseline Acceptability Questionnaire assessing prior experiences with BV and product expectations, but were not eligible to receive the intervention for a variety of reasons to be discussed (referred to as "screen fails"). Additionally, this pilot analysis includes only the UCSF site of the trial, which was conducted at Zuckerberg San Francisco General Hospital (ZSFGH) Clinical Research Center.

If a participant was screened for participation in the Lactin-V Trial more than once, the same consenting and protocol was followed but only the data from the first screening visit was included in this analysis.

2.2 IRB Approval

This analysis of product expectations and prior experiences with BV at baseline is part of the larger, multi-site Lactin-V Phase 2b trial, approved by the Committee on Human Research at UCSF, IRB #15-18143, and sponsored by DMID grant, protocol #14-0029.

2.3 Study Recruitment

Participants were recruited through paper (flyers, posters, letters, etc.), online media, and direct referrals from local clinics in the San Francisco Bay Area. More specifically, study staff reached out to local clinics with a high volume of potential participants to encourage them to refer patients who presented with BV to the Lactin-V Study. Using internal UCSF patient recruitment services, letters were sent to patients formerly diagnosed with BV within a 5-mile radius of Zuckerberg San Francisco General Hospital. In addition, physical ads were placed in ZSFGH and nearby laundromats, cafes, yoga studios in the surrounding neighborhood, at SFSU and USF Women's Resource Center, and at UC Berkeley, Touro University, UCSF hallways and women's restrooms. Electronic

ads were posted on Facebook, the Indeed job searching site, MyChart, Craigslist, and Google Ads, though these online efforts recruiting general population were reduced later in the trial.

2.4 Study Measures

Urine dipstick and urine analysis to screen for urinary tract infection, pregnancy test and Amsel criteria measurement (Appendix 2) were conducted by study staff on site. If a participant met all other eligibility criteria to participate in the study, samples for Nugent scoring and STI testing were sent to Magee Women's Research Institute in Pittsburgh, PA and Quest Diagnostics respectively. If a participant failed to reach eligibility requirements, all bio-specimens were discarded.

Demographic information, eligibility criteria, gynecological and sexual history, medical history, birth control, and concomitant medications were collected by interview with study staff.

2.5 Acceptability Questionnaire

The main study measure in this analysis was the Baseline Acceptability Questionnaire (Appendix 3), self-administered during the screening visit to assess prior experiences with BV and product expectations. Questions assessing product expectations were modeled of previous iterations of Lactin-V trial in phase 1 and 2a [8]. The added psychosocial measures were modeled off a number of validated measures and themes from previous studies [3, 15]. A keyword search using various permutations of wellness and quality of life questionnaire and urogenital syndromes was conducted, and three main questionnaires were identified (SF-36, PCO Syndrome Questionnaire, and Menorrhagia Impact Questionnaire) [7,18, 14].

Measures on the Acceptability Questionnaire included visual analog scales (VAS), Likert scales, and space for open-ended responses. The first seven items assessed number of previous BV episodes, prior treatments used, and the psychosocial impact of BV. The following five items, a set of visual analog scales, examined how bothersome participants found the different symptoms of BV. Finally, participants interest in using *a lactobacillus* product (Likert Scale) was assessed, as well as potential positive (eight items) and negative (six items) product characteristics were examined with visual analog scales.

2.6 Data Analysis

Data were transposed by hand from study documents (paper case report forms) into an Excel spreadsheet, which was imported into STATA/IC 15.1 for analysis. Unless otherwise noted, all tests for statistical significance were two-sided and used $p < 0.05$ as the level of significance. Comparisons of categorical proportions were conducted using Chi^2 tests, and analysis of continuous VAS measures were conducted using two sample t-tests.

3. Results

3.1 Screened Population Characteristics

In total, 104 screening visits that resulted in a screening failure were conducted. Six of these visits were repeat screens, leaving 98 unique participants. Of these 98 participants, all of whom identified as female, a large proportion reported having experience with BV: only 2% of them reported not having experienced any prior episodes of BV in their lifetime, 21.4% reported one or two prior BV episodes, 22.4% reported three of four BV episodes, 32.7% reported five or more episodes, and 21.5% had an unknown number of prior BV episodes or did not report. The basic population characteristics of those who had experienced fewer lifetime BV episodes (1-2) versus those who had experienced three or more lifetime BV episodes were not significantly different for any of the characteristics examined (Table 1). It is of note that all participants who declined or did not report their race identified as ethnically Hispanic or Latino.

Table 1. Basic Population Characteristics

Characteristic	n(%) 1-2 BV Episodes	n(%) 3+ BV Episodes	p-value
Total	21(100%)	54(100%)	
Race			0.922
American Indian or Alaskan Native	0 (0.0)	1 (1.9)	
Asian	3 (14.3)	7 (13.0)	
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	
Black or African American	5 (23.8)	15(27.8)	
White	9(42.9)	23(42.6)	
Mixed	1(4.8)	4(7.4)	
Refused/Not-Reported	3(14.3)	4 (7.4)	
Ethnicity			0.092
Hispanic or Latino	7 (33.3)	8 (14.8)	
Non-Hispanic or Non-Latino	13(61.9)	45 (83.3)	

Not reported	0 (0.0)	1 (1.9)	
Unknown	1 (4.8)	0 (0.0)	
Age at Screen			0.532
mean years (std)	31.2 (8.2)	30.2(6.0)	
Relationship Status			0.096
Single	4 (19.0)	10 (18.5)	
Married	0 (0.0)	4 (7.4)	
Widowed	0(0.0)	0 (0.0)	
Steady partner, cohabitating	1 (4.8)	7 (13.0)	
Steady partner, not cohabitating	10 (47.6)	12 (22.2)	
Casual partner	2 (9.5)	8 (14.8)	
Not reported	4 (19.0)	4 (7.4)	
Number of Pregnancies			0.442
None	10 (47.6)	30 (55.6)	
1-4	5(23.8)	17 (31.5)	
4 or more	3 (14.3)	4 (7.4)	
Not reported	3 (14.3)	3 (5.6)	
Current form of birth control			0.359
Condoms alone	7 (33.3)	20 (37.0)	
Intrauterine device, hormonal	4 (19.0)	10 (18.5)	
Intrauterine device, non-hormonal	2 (9.5)	3 (5.6)	
Hormonal implant	2 (9.5)	0 (0.0)	
Oral contraceptive	1 (4.8)	8 (14.8)	
Hormonal injections	0 (0.0)	2 (3.7)	
Same-sex relationship	1 (4.8)	2 (3.7)	
Abstinence	1 (4.8)	5 (9.3)	
Not reported	3 (14.3)	4 (7.4)	

3.2 Exclusion from Lactin-V Intervention Arm

Out of all 104 screen-fail visits, 67 of them were excluded from enrolling in the Lactin-V 2b trial because they did not have untreated BV (symptomatic or asymptomatic) during the screening visit (Table 2). Three of these participants were diagnosed with BV via saline wet mount using Amsel criteria (greater than or equal to three) at the screening visit, but the secondary gram stain using Nugent Scoring (scores of greater than or equal to four) did not confirm the BV diagnosis. Other common reasons for exclusion from enrollment

included 12 incidences of urogenital infection at screening recorded. These incidences, however, likely underestimate the prevalence of urogenital infections in this sample because participants who were not diagnosed with BV via saline wetmount at the screening visit or who failed to meet some other eligibility requirement earlier in the screening visit were not tested for STIs. The second most common reason for exclusion was recent use of vaginal or systemic antibiotic or antifungal therapy (other than the MetroGel® given as part of study procedures after screening) within 21 days before screening or within 30 days before enrollment, but this was a much less common reason for exclusion at just n=4. One participant met all eligibility criteria but did not want to enroll due to concern about potential risks.

Table 2. Primary reason for exclusion

Exclusion criteria	n
No untreated BV at screening	67
Other urogenital infection at screening	12
Trichomonas vaginalis, n = 4	
Chlamydia trachomatis, n=3	
UTI, n=3	
Vaginal candidiasis, n=2	
Use of antibiotic within 21 days of screening	4
Social, medical, or psychiatric condition that would make it unlikely for the participant to comply	3
Two or more outbreaks of *N. gonorrhoeae, C. trachomatis, T. pallidum, T. vaginalis,* or herpes simplex virus (*Herpes genitalis*) within six months	2
Known allergy to Lactin-V, MetroGel®, or latex condoms	2
Above age 45	2
Within 2 months of pregnancy or breastfeeding	2
No predictable menstrual cycle	1
Not willing to abstain from intercourse during required durations	1
Uterine procedure within 2 months of screening (IUD, surgery, etc.)	1

3.3 Psychosocial Impact of BV

The psychosocial impact of BV was measured using the self-administered Baseline Acceptability Questionnaire. When results were stratified by number of lifetime BV episodes, three of the four measures were significantly associated with the number of lifetime BV episodes via chi^2 testing (Table 3). Close to half of the sample reported that BV has had a major or severe impact on their life (47%), and perceived impact on life increased with the number of lifetime BV episodes a woman had experienced. Among participants who had experienced fewer episodes (1-2), 30% believed that BV had had a major or severe impact on their life, while 45% among participants with three or four episodes, and 59.4% among participants with five or more episodes stated a major or severe impact of BV on their life. A vast majority (81.1%) of the overall sample reported that they "agree" or "strongly agree" that BV has had a negative impact on their sex life, and that proportion increased as number of BV episodes increased, reaching 90.7% among participants with five or more episodes of BV. Similarly, 82.4% of the overall sample reported that they "agree" or "strongly agree" that BV makes them feel self-conscious or embarrassed, and again, this effect increased as number of experienced lifetime BV episodes increased.

Table 3. Psychosocial Impact of BV

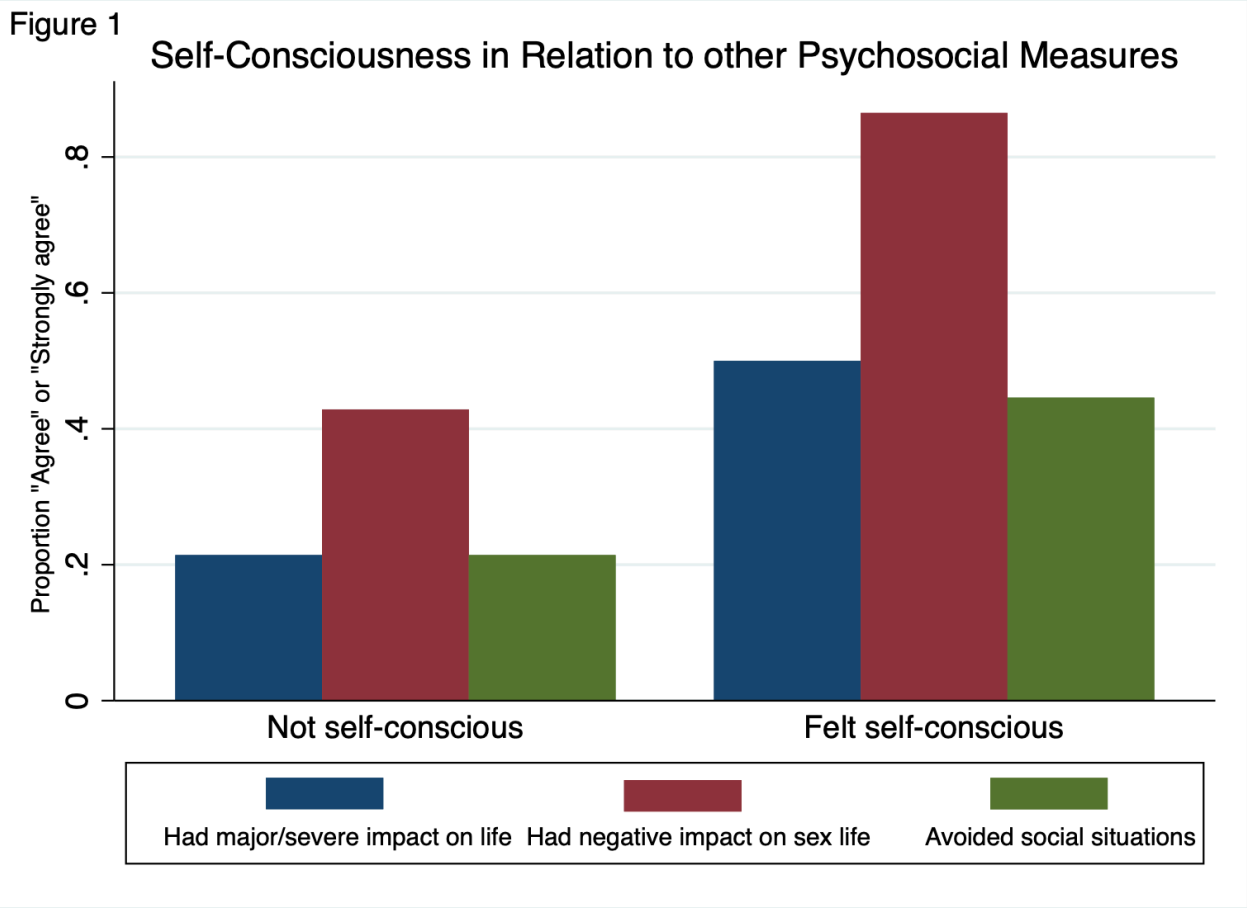
Prompt:	n (%)	n(%)	n(%)	n(%)	
	Total	1-2 BV Episodes	3-4 BV Episodes	5+ BV Episodes	p-value
	74(100.0)	20(100%)	22 (100.0)	32 (100.0)	
"Overall, what impact has BV had on your life? (socially, emotionally, physically, sexually)"					0.001*
No impact	4 (5.4)	3 (15.0)	1 (4.5)	0 (0.0)	
Minor impact	11 (14.9)	7 (35.0)	3 (13.6)	1 (3.1)	
Moderate impact	24 (32.4)	4 (20.0)	8 (36.4)	12 (37.5)	
Major impact	23 (31.1)	4 (20.0)	10 (45.5)	9 (28.1)	

	Severe impact	12 (16.2)	2 (10.0)	0 (0.0)	10 (31.2)	
"BV has a negative impact on my sex life"						0.001*
	Strongly disagree	3 (4.1)	0 (0.0)	1 (4.6)	2 (6.3)	
	Disagree	2 (2.7)	1 (5.0)	1 (4.6)	0 (0.0)	
	Neutral	9 (12.2)	8 (40.0)	0 (0.0)	1 (3.1)	
	Agree	29 (39.2)	7 (35.0)	12 (54.6)	10 (31.3)	
	Strongly agree	31 (41.9)	4 (20.0)	8 (36.4)	19 (59.4)	
"BV makes me feel self-conscious or embarrassed"						0.011*
	Strongly disagree	1 (1.4)	0 (0.0)	1 (4.6)	0 (0.0)	
	Disagree	3 (4.1)	3 (15.0)	0 (0.0)	0 (0.0)	
	Neutral	9 (12.2)	4 (20.0)	2 (9.1)	3 (9.38)	
	Agree	22 (29.7)	9 (45.0)	6 (27.3)	7 (21.9)	
	Strongly agree	39 (52.7)	4 (20.0)	13 (59.1)	22 (68.8)	
"When I have BV I avoid social situations or activities"						0.277
	Never	22 (29.7)	10 (50.0)	5 (22.7)	7 (21.9)	
	Rarely	19 (25.7)	3 (15.0)	7 (31.8)	9 (28.1)	
	Sometimes	18 (24.3)	3 (15.0)	8 (36.4)	7 (21.9)	
	Often	12 (16.2)	3 (15.0)	2 (9.1)	7 (21.9)	
	Always	3 (4.1)	1 (5.0)	0 (0.0)	2 (6.3)	

Self-consciousness was assessed by the prompt “BV makes me feel self-conscious or worried” and five options ranging from “Strongly disagree” to “Strongly agree” (Appendix 3, question 6). Self-consciousness also appeared to be a major factor in determining if a participant felt that BV had a negative impact on their sex life, and this categorization was statistically significant. While only 42.9% of those who did not feel self-conscious felt that BV had a negative impact on their sex life, 86.5% of those who did feel self-conscious felt that BV had a negative impact on their sex life and this difference was statistically significant (Figure 1). Similarly, those who did not feel self-conscious were significantly less likely to “agree” or “strongly agree” that BV had a major or severe impact (21.4% vs. 50.0%). The group that felt self-conscious did show an increase in the proportion of participants who at least sometimes avoid social situations (21.4% vs. 44.6%), but this

increase was not statistically significant (Figure 1).

Figure 1



3.4 Satisfaction with Previous Treatment

The third item on the Baseline Acceptability Questionnaire examined participants satisfaction with previous treatments for BV they had received. A significant portion remained neutral on this item, especially among those who had experienced five or more lifetime BV episodes (Table 4). Respondents who did not remain neutral were split fairly evenly above and below the "neutral" response. In total, 31.9% agreed or strongly agreed that the treatments they had previously used were effective, and 29.2% disagreed or strongly disagreed that the treatments they had previously used were effective. This question did not show a relationship with number of BV episodes via chi-squared analysis;

no significant difference was apparent when results were stratified into three BV groups (Table 3) or into two groups (1-2 episodes vs. 3 or more episodes).

Table 4. Effectiveness of Previous Treatment

"I believe that the treatments I have previously used are effective in treating BV."

	1-2 BV Episodes	3-4 BV Episodes	5 or more BV Episodes	Total	p-value
Strongly Agree	3 (16.7)	1 (4.6)	4 (12.5)	8 (11.1)	0.248
Agree	2 (11.1)	7 (31.8)	6 (18.75)	15 (20.8)	
Neutral	6 (33.3)	8 (36.4)	14 (43.8)	28 (38.9)	
Disagree	7(38.9)	6 (27.3)	5 (15.6)	18 (25.0)	
Strongly disagree	0 (0.0)	0 (0.0)	3 (4.2)	3 (4.2)	
Total	18 (100.0)	22 (100.0)	32 (100.0)	72 (100.0)	

3.4.1 Previous Treatments Used For BV

Most (80.7%) participants had treated previous episodes of BV with antibiotics. 31.8% of participants reported using an over-the-counter probiotic to treat BV in the past, and this percentage was highest among participants who had experienced five or more episodes of BV (46.9%), and lowest among participants who had only experienced one or two episodes of BV (19.1%). Similarly, 21.6% of participants reported using a home remedy to treat BV, and the usage of home therapies was highest among participants who had experienced five or more episodes of BV (31.3%) and lowest among participants who had only experienced one or two episodes of BV (9.5%).

3.4.2 Alternative Treatments

It is important to note that participants used a wide range of treatments beyond standard antibiotics prescribed by a clinician. The item on the Baseline Acceptability Questionnaire assessing previous treatments allowed for hand-written responses specifying what treatments participants had used to treat BV in the past.

The most common alternative therapies mentioned were boric acid (eight mentions), apple cider vinegar (seven mentions), and hydrogen peroxide (three mentions). Two participants each mentioned using monostat vaginal cream (a medication to treat vaginal yeast infections).

Vaginal yogurt douches and herbal suppositories to treat BV, diet alterations or vaginal administrations of tea tree oil, coconut oil, iodine, garlic, and fluconazole (an antifungal agent) were each mentioned once.

3.5 Experience with Symptoms

Using a set of visual analog scales (VAS), participants' experiences with common BV symptoms were assessed. Zero was labeled "not at all bothersome" while ten was labeled with "extremely bothersome." Participants who had experienced three or more lifetime BV episodes of BV, found "increased vaginal discharge" and "vaginal odor" significantly more bothersome than participants who had experienced only one or two lifetime episodes of BV (Table 5). Both groups rated "pain with urination" as the least bothersome symptom listed. At least a third of the respondents in each group, in fact, assigned a zero to the "pain with urination" visual analog scale. In contrast, no respondents who had experienced three or more episodes of BV labeled "vaginal odor" with a zero and the group on average labeled it as the most bothersome symptom. Sixteen participants marked the "other symptom" VAS option with a score of five or above and hand-wrote in symptoms including two mentions each of pain during sex, pain in lower abdomen, and abnormal discharge, and one mention each of fatigue, urge to urinate, numbness, and inflammation.

Table 5. BV Symptoms (visual analog scale, 0-10)			
Prompt: "I have found the following symptoms of BV:"			
	Mean (std) 1-2 BV Episodes	Mean (std) 3+ BV Episodes	p-value
Increased vaginal discharge	6.07 (2.97)	7.62(1.88)	0.0090*
Vaginal odor	5.92 (2.99)	8.50 (2.43)	0.0003*
Vaginal irritations and itching	6.77 (2.89)	6.36 (3.26)	0.6259
Pain with urination	3.32 (2.62)	3.08 (2.46)	0.7836

3.6 Product Expectations

Participants were highly interested in using a "non-antibiotic, clinically proven lactobacillus product," and the level of interest was not related to the number of BV episodes a participant had experienced. 56.2% of participants reported that they were "certain, almost certain" that they would use such a product if it became available for treatment, and another 31.5% reported there was a "very probable" chance they would use such a product.

Expectations for a "non-antibiotic, clinically proven lactobacillus product" were analyzed using eight VAS items on potential positive characteristics and six VAS items on potential negative characteristics. Each scale ranged from zero to ten, labeled "not at all important" and "extremely important" respectively for the positive characteristics and "not at bothersome and "extremely bothersome" for the negative characteristics. None of the Items were significantly different between participants who had experienced one or two episodes and participants who had experienced three or more episodes (Table 6).

Table 6. Product Expectations (visual analog scale, 0-10)

Question: "I would find the following characteristics important about such a product:"

	Mean (std) 1-2 BV Episodes	Mean (std) 3+ BV Episodes	p-value
Effective to treat BV	9.68 (0.65)	9.62 (1.03)	0.779
Comfortable	7.51 (2.80)	8.51(1.99)	0.093
Easy to use	7.89 (2.10)	8.25 (2.06)	0.500
Improved vaginal health	8.63 (2.66)	9.00 (2.59)	0.590
Availability without prescription	7.61 (2.37)	7.55 (2.76)	0.9372
All-natural ingredients of the product	6.245 (3.58)	7.43 (2.61)	0.122
Partner's approval of the product	4.75 (3.95)	3.68 (3.78)	0.285

Question: "I would find the following characteristics bothersome about such a product:"

	1-2 BV Episodes	3+ BV Episodes	p-value
High frequency or strict timing of using the product	5.66 (3.30)	6.24 (2.52)	0.431
Vaginal dryness	6.97 (2.45)	7.27 (2.40)	0.633
Vaginal discomfort	8.05 (2.15)	7.95 (2.11)	0.861
"Messiness" or leakage/discharge of the product	5.87 (3.13)	6.22 (3.24)	0.682
Partner's disapproval of using the product	4.14 (3.36)	3.10 (3.39)	0.244

3.6.1 Potential Positive Characteristics

Among both groups, it was most important to participants that the product be “effective to treat BV” (77.8% of participants marked a ten labeled with “extremely important”) and least important to participants to have their “partner’s approval of the product,” though this characteristic did have the largest standard deviation of all the positive characteristics and 21.4% of participants did in fact mark “partner’s approval” with a ten. In the open ended response, three participants wrote that affordability was important to them, two wrote that it was important to them that the product be painless to use, two mentioned overall health improvement (“I don't want it to make something else in the body sick”), one

mentioned discreetness of use, and one mentioned speed of being able to obtain the product.

3.6.2 Potential Negative Characteristics

Among both groups, participants reported that they would be most bothered by "vaginal discomfort" (50% of participants rated eight or above) from the product and least bothered by a "partner's disapproval of using the product" (50% of the participants rated 3 or lower), though, similar to the positive framing of partner support, this characteristic had the largest standard deviation of all the negative characteristics. Participants were somewhat less concerned with "high frequency or strict timing of using the product" and "'messiness' or leakage/discharge of the product," just under half of the sample reported that they were neutral or lower (closer to "not at all bothersome") for both measures.

In the open-ended response, one participant each mentioned that expensiveness, lack of privacy, long-term usage, and uncomfortable discharge caused by the product would be bothersome.

3.6.3 Partner Support

People who reported being single rated "partner's disapproval of the product" as significantly more bothersome (one-sided p-value < 0.05) than people who were not single, and this pattern was consistent with the positive characteristics items, where participants who were single rated "partner's approval of the product" as more important that those who were not single, though the difference there was not statistically significant (one-sided p-value $= 0.0828$). Rating of partner support did not appear to be related to race.

4. Discussion

In this analysis of prior experiences with BV and product expectations, we found that participants screened for a *lactobacillus* probiotic intervention are reporting that BV is having a significant impact emotionally, physically, and sexually, and this impact increases as the number of lifetime BV episodes increases. Among participants who had experienced three or more lifetime episodes of BV, over half report that BV has had a major or severe impact on their life and just under half report that they at least sometimes avoid social situations when they have BV. Participants who had experienced at least three episodes of BV reported being most bothered by the vaginal odor associated with BV, followed up by the increased vaginal discharge. This finding is consistent with literature reporting that women feel embarrassed and worried that intimate partners or coworkers could detect the odor, perhaps explaining why participants found odor to be the most bothersome symptom. Our data also showed that feeling self-conscious was a major factor in the impact participants felt that BV was having on their lives. While only 42.9% of those who did *not* feel self-conscious felt that BV had a negative impact on their sex life, 86.5% of those who *did* feel self-conscious felt that BV had a negative impact on their sex life.

Surprisingly, there was not a clear pattern between the number of BV episodes a participant had experienced and their satisfaction with previous treatment. Even among participants who had experienced five or more episodes of BV, only 19.8% disagreed or strongly disagreed that the treatments they had previously used were effective in treating BV. Based on this result, it is possible that the structure of the question biased responses or that participants do believe that antibiotics are sufficiently clearing the infection at hand.

Not surprisingly, given that 72% of our sample had experienced three or more episodes of BV, there was overwhelming interest in a proven *lactobacillus* product to treat BV. Over 87.7% of the sample said that there was a very probable or certain chance they would use a *lactobacillus* product if it became available. Though this high interest in a probiotic treatment is consistent with the literature, it is crucial to remember, however, that this sample is highly self-selecting in that most participants came to the study with the knowledge that they were being screened to participate in a probiotic intervention.

When participants' expectations for a potential *lactobacillus* product were examined, it was most important to participants that the product be effective to treat BV and improve their vaginal health. Participants reported that it would be most bothersome if the product caused vaginal discomfort and that they would be relatively less bothered by high frequency or strict timing of using the product and messiness or leakage/discharge of the product. In terms of both positive and negative characteristics, participants showed little concern for partner's approval or disapproval of using the product. This result, however, may not be generalizable to other populations given that the social and cultural norms in the San Francisco Bay Area can be quite different than other locations, even within the United States.

This study has several limitations, most notably that lifetime BV episodes were self-reported and there may have been a significant portion of participants who were experiencing urogenital infections other than BV, especially among those who self-reported one or two BV episodes. In addition, we cannot draw conclusions about acceptability among these participants who did not use the product. Thus, we look forward to comparing

these results with enrolled participants who had laboratory confirmed BV and used the study product.

Though the generalizability of these results is limited, these results emphasize that recurrent BV is indeed a major burden on the lives of people who suffer from it and show a clear need for more progress towards therapies that decrease recurrence of BV and address the symptoms that people with BV find most bothersome. In addition, these results highlight the factors that will impact real-world efficacy and marketability. It is important that we continue to examine the social and cultural norms that shape people's experiences with BV and could impact the success of potential probiotic intervention.

Supplemental Figures

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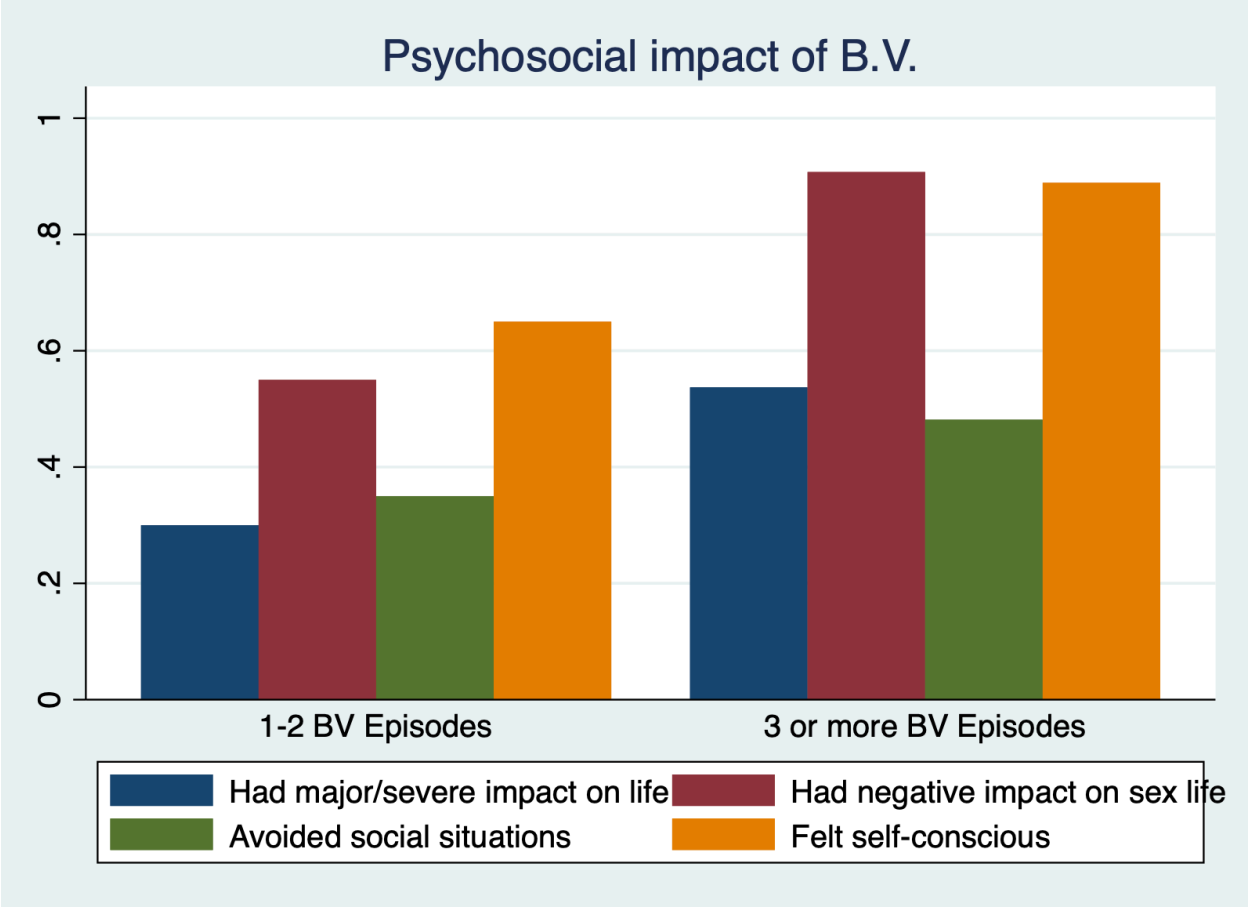
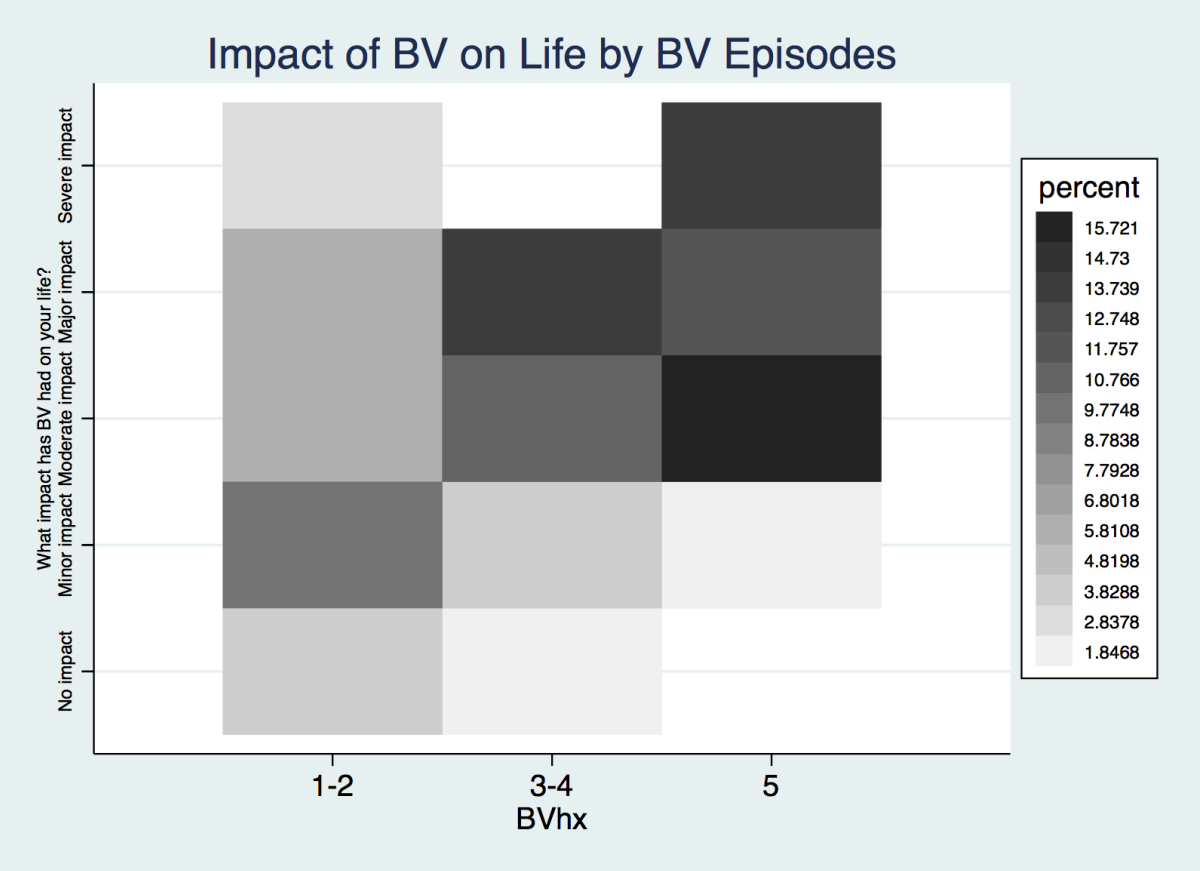
1. Psychosocial Impact of BV by number of lifetime episodes

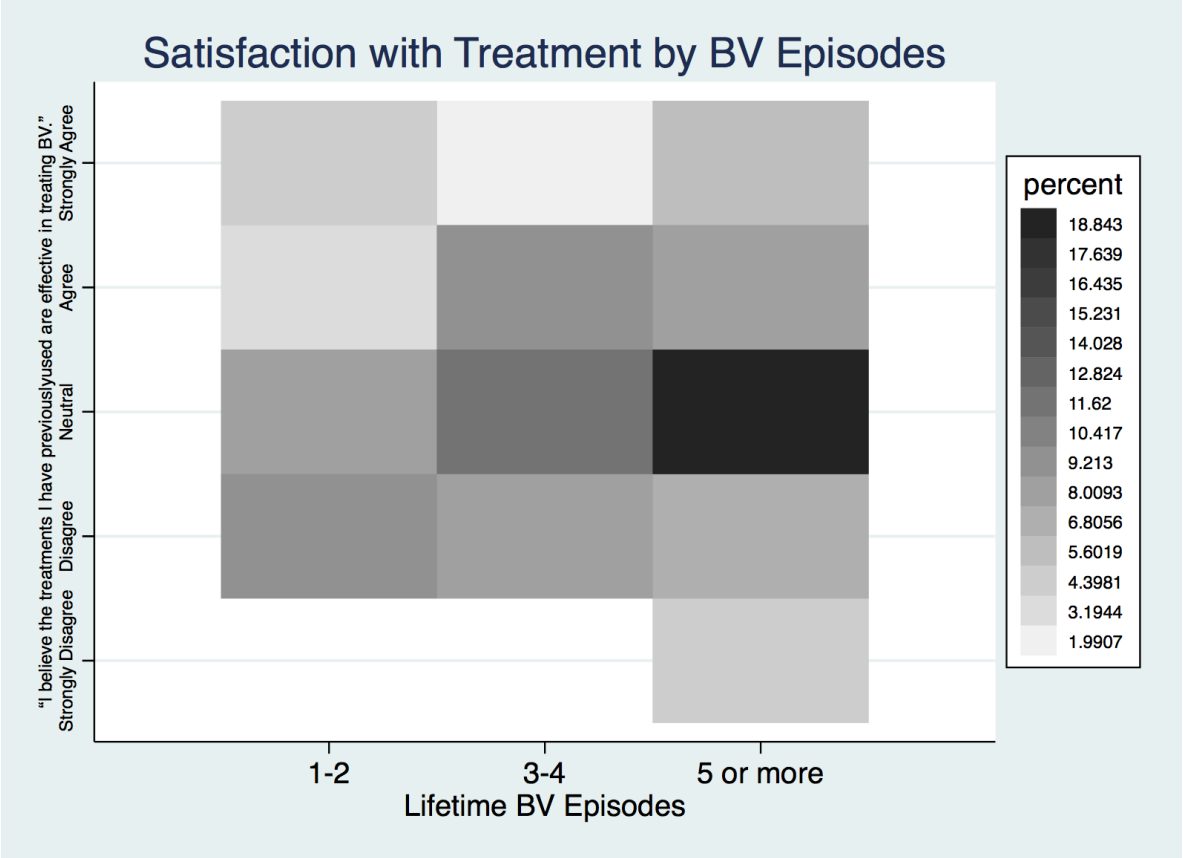
Note: I did not think this figure was useful in the paper because it felt redundant given the more detailed information in Table 3, but I found it useful for my own visualization and when presenting. Perhaps it would be useful in the future if grouped by question instead of BV episodes and marked with which were statistically significant increases (all but "avoided social situations").



2. Visualizing categorical variables

Note: For the following two figures, I found these heat maps (made using STATA "heatplot" function") to be the most useful way to visualize the data (and the surprising lack of pattern in participants' satisfaction with previous treatment). Since both variables are categorical, scatter plots or linear regression are not appropriate and I struggled with how to represent the positive trend in reported impact on life by number of BV episodes beyond tables with chi-squared testing. Again, I did not think these figures added enough for inclusion in the final paper, but could be useful in the future with some cleaning.




Satisfaction with Treatment by BV Episodes
"I believe the treatments I have previouslyused are effective in treating BV."
Strongly Disagree
Disagree
Neutral
Agree
Strongly Agree
1-2
3-4
5 or more
Lifetime BV Episodes
percent
18.843
17.639
16.435
15.231
14.028
12.824
11.62
10.417
9.213
8.0093
6.8056
5.6019
4.3981
3.1944
1.9907

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Appendix 1

DMID 14-0029 Data Collection Form

Eligibility Checklist (ENR)
Screening Visit
Segment: Screening

Subject: ___ ___ ___ ___ ___ ___ ___ ___

Screening date: ___ ___/ ___ ___ ___/ ___ ___ ___ ___ (dd/MMM/yyyy)

Inclusion Criteria

All answers must be YES or N/A for the subject to be eligible

The Not assessed *option is only for those subjects who* ***fail to meet eligibility criteria****, to document which criteria were not assessed (i.e., evaluation discontinued once volunteer was identified as ineligible).*

1.	Capable of reading and writing English and voluntarily provide written informed consent to participate in the study and comply with all study procedures	☐ No	☐ Yes	☐ Not assessed
2.	Untreated BV (asymptomatic or symptomatic) as diagnosed during the screening visit defined by ≥ 3 Amsel criteria Note: Amsel criteria include the following: • Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls • Vaginal ph > 4.5 • Positive whiff-amine test, defined as the presence of a fishy odor when a drop of 10% potassium hydroxide (KOH) is added to a sample of vaginal discharge • Presence of clue cells (>20% on microscopy)	☐ No	☐ Yes	☐ Not assessed
3.	Otherwise healthy pre-menopausal women 18-45 years of age on the day of screening	☐ No	☐ Yes	☐ Not assessed
4.	Regular predictable menstrual cycles or amenorrheic for at least 3 months due to use of a long-acting progestin or continuous use of oral contraceptives	☐ No	☐ Yes	☐ Not assessed
5.	Willing to be asked questions about personal medical health and sexual history	☐ No	☐ Yes	☐ Not assessed
6.	Willing to apply study agent vaginally and comply with study examinations	☐ No	☐ Yes	☐ Not assessed
7.	Agree to abstain from sexual intercourse during the first 5 consecutive days of study product administration, 12 hours prior to study visits and for 12 hours after the study product application	☐ No	☐ Yes	☐ Not assessed
8.	Agree to abstain from the use of any other intravaginal product throughout the trial period from the time of screening through Visit 7 (Week 24, Day 168) Note: Intravaginal products include contraceptive creams such as Gynol II, gels, foams, sponges, lubricants not approved by the study investigators, and douches. Limit use of tampons during menstruation to unscented products.	☐ No	☐ Yes	☐ Not assessed
9.	Must be of non-childbearing potential or if of childbearing potential, must agree to use a reliable method of birth control for the duration of the study Note: Reliable methods of birth control include tubal ligation, male partner with a vasectomy, a steroidal contraceptive (oral, patch, injectable or implantable), IUD, condoms or abstinence.	☐ No	☐ Yes	☐ Not assessed

DMID 14-0029 Data Collection Form

Eligibility Checklist (ENR)
Screening Visit
Segment: Screening

Subject: ___ ___ ___ ___ ___ ___ ___ ___

Exclusion Criteria

All answers must be No or Not applicable for the subject to be eligible.
The Not assessed *option is only for those subjects who* ***fail to meet eligibility criteria****, to document which criteria were not assessed (i.e., evaluation discontinued once volunteer was identified as ineligible).*

1.	Urogenital infection at screening Note: Urogenital infection includes urinary tract infection, *Trichomonas (T.) vaginalis, Neisseria (N.) gonorrhoeae, Chlamydia (C.) trachomatis, Treponema (T.) pallidum,* or vulvo-vaginal candidiasis.	☐ No	☐ Yes	☐ Not assessed
2.	Diagnosis of two or more outbreaks of *N. gonorrhoeae, C. trachomatis, T. pallidum, T. vaginalis,* or herpes simplex virus (herpes genitalis) within 6 months prior to screening	☐ No	☐ Yes	☐ Not assessed
3.	Positive for syphilis or HIV at screening	☐ No	☐ Yes	☐ Not assessed
4.	Current pregnancy or within 2 months of last pregnancy and/or currently breastfeeding	☐ No	☐ Yes	☐ Not assessed
5.	Vaginal or systemic antibiotic or antifungal therapy (other than MetroGel given as part of study procedures) within 21 days of screening or within 30 days of enrollment	☐ No	☐ Yes	☐ Not assessed
6.	Use of disulfiram within past 2 weeks or other contraindication to use of MetroGel.	☐ No	☐ Yes	☐ Not assessed
7.	Any condition requiring regular periodic use of systemic antibiotics during participation in the trial	☐ No	☐ Yes	☐ Not assessed
8.	Active genital herpes lesion (if not resolved by enrollment)	☐ No	☐ Yes	☐ Not assessed
9.	Investigational drug use other than LACTIN-V within 30 days or 10 half-lives of the drug, whichever is longer, of enrollment visit	☐ No	☐ Yes	☐ Not assessed
10.	Other planned participation in an investigational drug study while participating in this study	☐ No	☐ Yes	☐ Not assessed
11.	Menopause defined as more than 12 consecutive months of amenorrhea without another known cause including pregnancy	☐ No	☐ Yes	☐ Not assessed
12.	IUD insertion or removal, pelvic surgery, cervical cryotherapy or cervical laser treatment within the last 2 months prior to screening	☐ No	☐ Yes	☐ Not assessed
13.	Use of vaginal ring (e.g., NuvaRing) within 3 days of screening or during the course of the study	☐ No	☐ Yes	☐ Not assessed
14.	Use of new long-acting hormonal treatments. Participant may be enrolled if stable (>3 months) on existing therapy as determined by the principal investigator	☐ No	☐ Yes	☐ Not assessed
15.	Known allergy to any component of LACTIN-V/placebo or MetroGel nitroimidazole derivatives, or latex (condoms)	☐ No	☐ Yes	☐ Not assessed
16.	Any social, medical, or psychiatric condition, including history of drug or alcohol abuse that in the opinion of the investigator would make it unlikely for the participant to comply with the study	☐ No	☐ Yes	☐ Not assessed

Appendix 2

Amsel Criteria

Three of the four Amsel criteria must be met to be eligible at enrollment.

Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls?	☐ Absent	☐ Present	☐ Not assessed
Vaginal pH: (>4.5)	___.___ (x.x)		☐ Not assessed
Amine (“whiff”) test on KOH wet mount:	☐ Negative	☐ Positive	☐ Not assessed
Percentage of clue cells on wet mount: (>20%)	___ ___ (xx %)		☐ Not assessed

Appendix 3

DMID 14-0029 Data Collection Form

Acceptability Questionnaire (AQN) – Screening

Visit Number: 00 Subject: ___ ___ ___ ___ ___ ___ ___ ___

Please answer all the following questions to the best of your ability and memory. Please be sure to read all of the questions and answer choices carefully to reflect your true answer.

Some questions are answered using a Visual Analog Scale from 0-10. Please mark an "X" on a spot along the line that best reflects your answer.

Example:

0 X 5 10
Very uncomfortable Neutral Very comfortable

Visit date: ___ ___/ ___ ___/ ___ ___ ___ ___ (mm/dd/yyyy)

Acceptability Questionnaire	
1. How many episodes of Bacterial Vaginosis (BV) have you experienced in your life?	☐ None *(skip to Question 9)* ☐ 1-2 ☐ 3-4 ☐ 5 or more ☐ Unknown
2. If you have had BV in the past, what have you used for treatment?	☐ Nothing *(skip to Question 4)* ☐ Antibiotics ☐ Probiotics ☐ Home remedies, specify: _____ ☐ Other, specify: _____ ☐ Unknown
3. If you ever had BV and treated it, how would you reply to the following statement: "I believe the treatments I have previously used are effective in treating BV."	☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree
4. Overall, what impact has BV had on your life? (socially, emotionally, physically, sexually)	☐ No impact ☐ Minor impact ☐ Moderate impact ☐ Major impact ☐ Severe impact

Acceptability Questionnaire (AQN) – Screening

Visit Number: 00 Subject: ___ ___ ___ ___ ___ ___ ___ ___

Acceptability Questionnaire	
5. BV has a negative impact on my sex life.	☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree
6. BV makes me feel self-conscious or embarrassed.	☐ Strongly agree ☐ Agree ☐ Neutral ☐ Disagree ☐ Strongly disagree
7. When I have BV I avoid social situations or activities	☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
8. I found the following symptoms of BV:	On a scale of 0 to 10, with 0 being “not at all bothersome” to 10 being “extremely bothersome”, please mark an “X” on a spot along the line that best reflects your answer.
Increased vaginal discharge	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
Vaginal odor	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
Vaginal irritation and itching	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
Pain with urination	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
Other, specify: _____ _____	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome

Acceptability Questionnaire (AQN) – Screening

Visit Number: 00 Subject: ___ ___ ___ ___ ___ ___ ___ ___

Acceptability Questionnaire	
9. If a non-antibiotic, clinically proven lactobacillus product were available for the treatment and prevention of BV, what are the chances that you would use it?	☐ Certain, almost certain ☐ Very probable ☐ Good possibility ☐ Slight possibility ☐ No chance; almost no chance
10. I would find the following characteristics important about such a product:	On a scale of 0 to 10, with 0 being "not at all important" to 10 being "extremely important", please mark an "X" on a spot along the line that best reflects your answer.
Effective to treat BV	_____ 0 5 10 Not at all Neutral Extremely important
Comfortable	_____ 0 5 10 Not at all Neutral Extremely important
Easy to use	_____ 0 5 10 Not at all Neutral Extremely important
Improved vaginal health	_____ 0 5 10 Not at all Neutral Extremely important
Availability without prescription	_____ 0 5 10 Not at all Neutral Extremely important
All-natural ingredients of the product	_____ 0 5 10 Not at all Neutral Extremely important
Partner's approval of the product	_____ 0 5 10 Not at all Neutral Extremely important
Other, specify: _____ _____	_____ 0 5 10 Not at all Neutral Extremely important

Acceptability Questionnaire (AQN) – Screening

Visit Number: 00 Subject: ___ ___ ___ ___ ___ ___ ___ ___

Acceptability Questionnaire	
11. I would find the following characteristics bothersome about such a product:	On a scale of 0 to 10, with 0 being "not at all bothersome" to 10 being "extremely bothersome", please mark an "X" on a spot along the line that best reflects your answer.
High Frequency or strict timing of using the product	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
Vaginal dryness	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
Vaginal discomfort	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
"Messiness" or leakage/discharge of the product	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
Partner's disapproval of using the product	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome
Other, specify: _____ _____	_____ 0 5 10 Not at all bothersome Neutral Extremely bothersome