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Safety Testing of Ovaprene: an Investigational Non-Hormonal Monthly Vaginal Contraceptive

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ABSTRACT

Objective: Evaluate safety of Ovaprene, an investigational non-hormonal vaginal contraceptive designed for monthly use.

Study design: Open-label, multicenter study enrolling heterosexually-active women with previous permanent contraception who underwent assessments during five menstrual cycles: baseline postcoital test cycle, diaphragm postcoital test cycle, Ovaprene safety cycle, and two Ovaprene postcoital test cycles. Safety outcomes included treatment emergent adverse events (TEAEs), systemic laboratory findings, pelvic examinations, colposcopies, Nugent scores, determination of community state types of vaginal microbiota, and anti-*Escherichia coli* activity and inflammatory markers in cervicovaginal fluids.

Results: We enrolled 38 participants. Of these, 33 used Ovaprene and completed 77 Ovaprene cycles. The most common product-related urogenital TEAEs were bacterial vaginosis (BV) and vaginal odor. The frequency of transitioning from *Lactobacillus*-dominated community state type to community state type IV (not *Lactobacillus*-dominated) was similar before Ovaprene use and afterwards. Mean Nugent scores were <4 at each visit without a discernable upward trend. Inflammatory markers showed wide variation but no upward trend, and *E. coli* inhibitory activity of cervical secretions did not change. We found no *Staphylococcus aureus*, the causative agent in Toxic Shock Syndrome, on used Ovaprenes or in vaginal samples. No clinically important changes in systemic laboratory findings, pelvic examinations, or colposcopies occurred during Ovaprene use.

Conclusion: Ovaprene use did not result in cervicovaginal irritation or adverse effects on resident vaginal microbiota, and did not impact transitions from a *Lactobacillus*-dominated community state type to community state type IV.

Implications: The finding that use of Ovaprene, an investigational monthly user-controlled nonhormonal vaginal contraceptive, does not appear to result in adverse changes in vaginal health during short term use supports further evaluation of the contraceptive potential of the device.

1 INTRODUCTION

Ovaprene (Poly-Med Inc, Anderson, SC), an investigational monthly non-hormonal vaginal contraceptive, consists of a 55 mm silicone ring with a central permeable barrier (Figure 1). The barrier's pore size inhibits sperm movement while allowing fluid passage. Ferrous gluconate released from the ring causes oxidative damage to the sperm tail's lipid bilayer, causing spermiostasis [1]. Ascorbic acid is released to maintain ferrous gluconate in its ferrous state. Ovaprene is inserted at the end of one menstrual period and left until the beginning of the next, requiring no action at intercourse. It requires no clinician fitting and a new product is used each month.

Ovaprene has been evaluated in two postcoital test studies. The first, published by others in 2009, enrolled 20 sexually active women who used Ovaprene for one cycle [2]. No changes in vaginal mucosa or semi-quantitative cultures were seen, and wet mount examinations were normal. Subjects reported no pain, bleeding, or discharge.

We recently conducted a second postcoital test study, with a more complete evaluation of safety, *i.e.,* pelvic examinations, colposcopy, vaginal microbiota, and innate immunity, over multiple cycles of use. This paper reports effects on vaginal health and other safety outcomes.

2 METHODS

2.1 DESIGN

We conducted a multi-center, open-label study with the primary objective of assessing Ovaprene's ability to prevent sperm from penetrating midcycle cervical mucus, described elsewhere [3]. Here we describe the secondary objective of safety and its endpoints: 1) treatment-emergent adverse events (TEAEs) among female

participants; 2) urogenital, product-related, and serious TEAEs among female and male participants; 3) changes in complete blood count (CBC), serum chemistries, serum ferritin, pelvic examinations, colposcopy findings, Nugent scores, vaginal microbiota community state types, anti-*E. coli* activity and concentrations of immune proteins in cervicovaginal fluid collected from the vagina; and 4) presence of *Staphylococcus aureus* on used Ovaprenes.

We initiated the study at six sites: Eastern Virginia Medical School, Norfolk, VA; Oregon Health and Science University, Portland, OR; University of Pennsylvania, Philadelphia, PA; Clinical Research Prime, Idaho Falls, ID; University of California Davis, Sacramento, CA; and Segal Institute for Clinical Research Inc., Miami, FL. We consented and screened but did not enroll at the last two sites. The study followed the Helsinki Declaration of 1975, revised in 2013. It was approved by a central Institutional Review Board (Advarra, Columbia, MD) before screening began.

2.2 ELIGIBILITY CRITERIA

We recruited healthy, heterosexually-active women aged 18-50 not at risk for pregnancy due to previous permanent contraception and their male partners [3]. Key inclusion criteria included having regular menstrual cycles of 24-35 days, and being able to insert, position, and remove both devices. Key exclusion criteria included having a positive test for *Trichomonas vaginalis, Neisseria gonorrhea, Chlamydia trachomatis*, or HIV, or a Nugent score $\geq$ 7 at screening, inability to achieve adequate cervical mucus in two attempts at the baseline cycle, and inadequate sperm in endocervical aspirate during baseline testing without any device, despite adequate mucus and presence of sperm in the vaginal pool.

2.3 STUDY VISITS

Informed consent occurred at the beginning of a screening visit, where we began assessing eligibility. Eligible female participants completed 21 visits during five menstrual cycles (Table 1): one baseline postcoital test cycle with one act of unprotected intercourse at ovulation; one postcoital test cycle using the Caya diaphragm (HPSRx Enterprises, Inc., Salem, VA) with 3% nonxynol-9 (Gynol II™ Vaginal Contraceptive Gel, Revive Personal Products Company, Madison, NJ); one "safety cycle" without intercourse during which safety, ferrous gluconate release, acceptability, and fit/placement of Ovaprene were assessed; and two postcoital test cycles using Ovaprene. Enrollment occurred at the fourth visit (the third visit in the baseline postcoital test cycle, or BP3 –Table 1) after all screening criteria, including a satisfactory baseline postcoital test cycle, had been met.

2.4 STUDY DIARY, CAPTURE OF ADVERSE EVENTS

We instructed participants about a web-based electronic diary (Trials.ai, San Diego, CA) through which they were prompted daily to report menses, intercourse, use of intravaginal products, whether they or their partner felt unwell or had used any medications, and any device issues. We assessed adverse events (AEs) at each visit, including nature, dates of onset and resolution, severity, seriousness, and relatedness to Ovaprene. We coded AEs using MedDRA 21.0.

2.5 SYSTEMIC LABORATORY EXAMINATIONS

To evaluate whether ferrous gluconate could result in adverse effects through systemic uptake, we measured serum ferritin, CBCs, and serum chemistries at screening and first and last visits in the safety cycle (n=3 assessments per participant).

2.6 PELVIC EXAMINATIONS, COLPOSCOPY

During each visit, we performed vaginal/cervical (pelvic) examinations (n=21 assessments per participant). At the screening visit, and at the first and fifth (final) visits of the three Ovaprene cycles (n=7 assessments per participant), we also recorded the presence of any lesions visible with and without magnification, using colposcopy developed by the World Health Organization for evaluating new vaginal products [4].

2.7 BV DIAGNOSIS, VAGINAL MICROBIOTA

2.7.1 Nugent scoring, use of Amsel's criteria

We performed Nugent scoring using established protocols at screening (to determine eligibility), every visit in the safety cycle, and the first and fifth (final) visit in both Ovaprene postcoital test cycles (n=10 assessments per participant). The Nugent score is the gold standard for diagnosing bacterial vaginosis (BV) in research settings [5]. Investigators evaluated vaginal smears for Gram-positive rods (lactobacilli), and the Gram-negative and Gram-variable rods and curved Gram-negative rods associated with BV. Values of 0–3 were considered negative, 4–6 indeterminate, and 7-10 diagnostic for BV [6]. Participants with Nugent scores $\geq$7 with or without symptoms at screening were treated for BV per standard of care; Nugent scores of <7 were needed for entry into the baseline cycle.

After screening, however, BV diagnosis and treatment were not based on Nugent scores, but on Amsel's criteria (discharge, abnormal pH, presence of clue cells, and positive "whiff" test) [6], assessed only if participants reported symptoms (*i.e.*, discharge, odor, or irritation). Subjects were discontinued for symptomatic BV based on Amsel's criteria. Nugent scores obtained after screening became available and were also assessed after the study was completed.

2.7.2 **Vaginal microbiota**

We assessed composition and structure of the vaginal microbiota by amplification and sequencing of the V3-V4 regions of the 16S rRNA gene using previously validated and published laboratory and analytical procedures [7,8]. Taxonomy was assigned to each amplicon sequence variant generated by *dada2* using SpeciateIT (version 1.0), a rapid per sequence classifier [9,10]. Read counts for amplicon sequence variants assigned to the same taxonomy were summed for each sample and relative abundance of each taxa calculated. Bacterial taxa were filtered prior to analysis if observed in fewer than three samples or if present at a frequency of ≤ 10^{-4} frequency study-wide. A final taxonomic table was generated and used for community state type assignments using VALENCIA [11]. A total of five broad community state types were identified. Four community state types (I, II, III, and V) are dominated by *Lactobacillus* species, namely *L. crispatus, L. gasseri, L. iners* and *L. jensenii*, respectively. Community state type IV is comprised of a wide array of strict and facultative anaerobic bacterial species, including *Gardnerella vaginalis, Atopobium vaginae* and *Megasphera* species. In community state type IV, the loss of acid-producing *Lactobacillus (L. crispatus, L. gasseri, L. iners,* and *L. jensenii)* and the overgrowth of anaerobes resemble the vaginal microbiota associated with BV [12]. Community state types I, II, III, and V were grouped together and presented as "Lb," indicating *Lactobacillus* spp. dominance.

Microbiota were assessed at all visits in baseline and safety cycles, and the first and fifth (final) visit in both Ovaprene postcoital test cycles (n=12 assessments per participant). Changes in vaginal community state type were compared as follows: BP1 (first visit, baseline cycle) vs. OS1 (first visit, safety cycle, before first insertion of Ovaprene); OS1 vs. OS5 (last visit, safety cycle); and OP1 vs. OP5 (first and last

visits, Ovaprene postcoital test cycles). Differences between community state types of vaginal samples and swabs of Ovaprene at the same visit were also evaluated.

2.7.3 Testing for *Staphylococcus aureus*

We assessed the presence of *S. aureus*, the causative agent of Toxic Shock Syndrome, in the vaginal samples, and also on used Ovaprenes using the ThermoFisher assay Ba04646259.s1 that targets *S. aureus* Ribonuclease P RNA gene. Results became available after study completion and did not influence diagnosis or treatment during the study.

2.8 CERVICOVAGINAL FLUID ANTI-E. COLI ACTIVITY, SOLUBLE MARKERS OF INFLAMMATION, SLPI

Safety was also assessed by quantifying changes in cervicovaginal fluid inflammatory cytokines (Interleukin [IL]-1ß and IL-8) and secretory leukocyte peptidase inhibitor (SLPI), an enzyme that protects epithelial tissues from serine proteases. Changes in the *ex vivo* anti-*E. coli* activity of cervicovaginal fluid, *i.e.*, its ability to inhibit *E. coli* growth, was an additional safety endpoint. Anti-*E coli* activity reflects the cumulative action of inflammatory and antimicrobial proteins such as defensins and SLPI, which are secreted by genital epithelium and immune cells, combined with activity of lactic acid, antimicrobials, and surface proteins secreted by lactobacilli [13,14], and is considered a biomarker of female mucosal defenses [15]. A loss of anti-*E. coli* activity has been observed 2-14 hours after intercourse [9]. Inflammatory markers and anti-*E. coli* activity were assessed twice in the baseline cycle, at all five visits in the safety cycle, and at the first, third, and fifth (final) visits in both Ovaprene postcoital test cycles (n=13 assessments per participant).

2.9 STATISTICAL ANALYSIS

Statistical analysis was done using SAS Version 9.4. Summary tables and data listings were created for all TEAEs, including frequency of events, and frequency and percentage of participants, by system organ class and preferred term, and by severity and relatedness to Ovaprene. However, the primary evaluation of safety was the subpopulation of TEAEs that were urogenital, product-related, and/or serious. There were no planned statistical significance tests for this objective. For other safety endpoints, baseline and post-baseline time points were qualitatively compared. No statistical significance tests between Ovaprene and the diaphragm were planned or performed. We based our sample size of 25 on feasibility and experience with prior phase I studies, not statistical considerations.

3 RESULTS

Results of the primary objective are reported elsewhere [3]. Briefly, the definition of a successful postcoital test was met in all 49 Ovaprene postcoital test cycles.

3.1 ENROLLMENT, SUBJECT DISPOSITION, DEMOGRAPHICS

We screened 135 participants and enrolled 38 (Figure 2). The first was consented on 23 May 2018 and the last contact was 15 November 2019. Most screen fails occurred due to failure to achieve midcycle cervical mucus and/or an adequate number of progressively motile sperm after intercourse in the baseline cycle.

Thirty-three participants used Ovaprene for at least part of a cycle and 23 completed the study. Participants completed 77 Ovaprene cycles: 28 safety cycles, 25 Ovaprene postcoital test Cycles A, and 24 Ovaprene postcoital test Cycles B. (One participant completed Cycle B but did not complete Cycle A.) The most

common reasons for discontinuation were a non-severe TEAE of BV or withdrawing consent (four participants each).

Demographics are shown in Table 2.

3.2 TREATMENT-EMERGENT ADVERSE EVENTS

Most participants (29/33, 87.9%) reported at least one TEAE (Table 3). Approximately half (17/33, 51.5%) experienced mild TEAEs and approximately one quarter (9/33, 27.3%) experienced TEAEs unrelated to Ovaprene. All but one TEAE were mild or moderate, with approximately half (41/79, 51.9%) unrelated to Ovaprene (Table 4). There were no serious AEs.

There were 42 urogenital TEAEs involving 21/33 (63.6%) female participants and one male partner (Appendix 1, Supplementary Material). About three-quarters (31/42, 73.8%) were mild and the rest moderate. About three-quarters (33/42, 78.6%) were at least possibly product-related.

The two most common product-related urogenital TEAEs were BV (see Section 3.5) and vaginal odor: nine TEAEs of BV among eight participants, and nine participants with 11 TEAEs of vaginal odor, all but one product-related. TEAEs of “odor” were recorded only when a simultaneous TEAE of BV or other condition was not recorded.

3.3 SYSTEMIC LABORATORY EXAMINATIONS

There were no clinically significant systemic laboratory findings. There was a clinically insignificant increase in mean ferritin from 33.3 ng/mL at OS1 to 41.6 ng/mL at OS5. No participant’s ferritin level went from a normal level to a high one.

3.4 PELVIC EXAMINATIONS, COLPOSCOPY

There were five participants with a total of six pelvic examination findings: three findings of vaginal discharge associated with yeast infection or BV, which was treated, one finding of cervical petechiae, and one finding of vaginal ~~or~~ and cervical erythema. The latter was felt to be related to the device. All six findings resolved by the next visit.

Colposcopy was done at 200 study visits, with 23 colposcopy findings seen in 12 participants. Ten product-related findings were found in six participants (Appendix 2, Supplementary Material); all resolved except for ecchymosis present at OP5B not requiring follow-up.

3.5 NUGENT SCORES, BV, MICROBIOTA

3.5.1 Nugent scores

Mean Nugent scores were <4 at each visit, and mean changes between visits and baseline were <1.3. All nine cases of BV were determined in retrospect to be associated with a Nugent score of 7 or above with three exceptions (Appendix 3, Supplementary Material), but there was no apparent upward trend in Nugent scores during Ovaprene use (Appendix 4, Supplementary Material).

3.5.2 Bacterial vaginosis

As stated in Section 3.2, there were nine TEAEs of BV among eight participants. Figure 3 shows cases of BV by participant number, visit, and prior history of BV. Narratives of BV cases are in Appendix 3, Supplementary Material. Subjects 14 and 24 were asymptomatic and Subject 24 probably did not have BV.

3.5.2.1 Effect of prior history of BV and BV diagnosed at the screening visit

Of the 33 participants who completed OS1 (first visit, safety cycle, at which Ovaprene was inserted for the first time), 10 had a history of BV prior to screening (one additional subject, Subject 11, was uncertain). Of these, two (20%, Subjects 14 and 19) developed BV during participation. Of the remaining 23 participants without prior BV history, about a quarter (6/23 or 26.1%; includes asymptomatic Subject 24) developed BV. Thus, a history of BV prior to screening did not appear to be associated with BV development.

Of the 33 participants who completed the OS1 visit, six were treated for BV during screening, prior to BP1. (Subjects 8 and 19 also had a history of BV prior to screening.) Of these six, three (50%) developed BV after OS1. Of the 27 participants not treated for BV at screening, only five (18.5%) developed BV. This suggests that having recently undergone BV treatment, i.e., at screening, may be associated with BV recurrence.

3.5.3 Vaginal microbiota

Figure 3 shows community state types of all 33 participants during baseline and Ovaprene cycles.

3.5.3.1 Microbiota prior to Ovaprene use

Prior to first Ovaprene use (baseline cycle or at OS1 prior to product insertion), community state type IV was common; 13 of 33 participants (39%) had at least one community state type IV (Figure 3). Vaginal microbiota frequently transitioned from one community state type to another. Prior to Ovaprene insertion (BP1 through OS1), 20/28 (71%) of participants who had a *Lactobacillus*-dominated community state type (Lb community state type) at BP1 maintained it, but 6/28 (21%)

transitioned from Lb community state type to community state type IV (Appendix 5, Supplementary Material).

3.5.3.2 Microbiota after beginning Ovaprene use

After beginning Ovaprene use, less than 21% transitioned from Lb community state type to community state type IV: during the safety cycle, 3/22 (14%) transitioned from Lb community state type to community state type IV, (Appendix 6, Supplementary Material); during the first Ovaprene postcoital test cycle, 3/19 (16%) transitioned from Lb community state type to community state type IV (Appendix 7, Supplementary Material); and during the second Ovaprene postcoital test cycle, 1/14 (7%) transitioned from Lb community state type to community state type IV (Appendix 8, Supplementary Material).

3.5.3.3 Association of BV with community state type IV

As expected, BV was associated with community state type IV. Among the nine BV cases, six were associated with a community state type IV at the visit when BV was diagnosed or the previous visit (exceptions are noted in Appendix 3, Supplementary Material).

Thirteen participants had a community state type IV during either the baseline cycle or OS1, before beginning Ovaprene use, and of these, five (38.5%) developed BV. Of the remaining 20 participants without a community state type IV before Ovaprene use, only three (Subjects 24, 28, and 14, 15.0%) developed BV.

All six of the participants treated for BV at screening achieved a *Lactobacillus*-dominated community state type at BP1. However, four were unable to maintain it preceding Ovaprene use, developing a community state type IV on or before OS1. All three of the participants who developed BV during the study after being treated

at screening were in this group. Thus, as expected, having community state type IV appeared to be a risk factor for BV in this study.

3.5.3.4 Association of odor with community state type IV

All 11 TEAEs of vaginal odor were associated with community state type IV, *i.e.*, the TEAE began during or after a visit when community state type IV was found, or the community state type that followed TEAE onset was community state type IV, indicating that odor was more likely associated with community state type than Ovaprene.

3.5.4 Testing for Staphylococcus aureus

We did not identify *S. aureus* on used Ovaprenes or vaginal samples. Microbiota on used Ovaprenes was very similar to that in the vagina.

3.6 CERVICOVAGINAL FLUID ANTI-*E. COLI* ACTIVITY, SOLUBLE MARKERS OF INFLAMMATION, SLPI

There was wide variation in anti-*e. coli* results (Appendix 9, Supplementary Material), but also a suggestion of a decrease after intercourse in baseline and Ovaprene cycles, consistent with the effect of intercourse [9]. It does not appear that Ovaprene use was associated with clinically significant loss of anti-*E. coli* activity.

IL-1β and IL-8 demonstrated high variability, but median cytokine values did not change post Ovaprene insertion (Appendices 10 and 11, Supplementary Material). Similarly, there was little change in SLPI during the safety cycle (Appendix 12, Supplementary Material).

4 DISCUSSION

Ovaprene use over three consecutive cycles resulted in no important safety signals. Taken together, the 77 cycles of Ovaprene use observed in this study would equate to over four years and five months of exposure in one participant. The two most common urogenital TEAEs were BV and vaginal odor. A limitation of this study was the absence of a control group not using Ovaprene. Thus, it is not possible to estimate with certainty the effect of Ovaprene on BV risk. According to the Centers for Disease Control and Prevention (CDC), “The prevalence [of BV] in the United States is estimated to be 21.2 million (29.2%) among women ages 14–49, based on a nationally representative sample of women who participated in NHANES 2001–2004” [16]. Recurrence is common: approximately 80% have a recurrence 3 months after effective treatment [17].

Eight of 33 participants in this study were diagnosed with BV, giving an incidence of 24.2%, similar to the national prevalence of 29%. A history of BV prior to screening did not appear associated with BV during the study, although having BV treatment at screening seemed to be associated with recurrence. As expected, community state type IV appeared to be a risk factor, but Ovaprene did not encourage development of community state type IV. There was no apparent upward trend in Nugent scores. Thus, it does not appear that Ovaprene predisposes users to BV, whether they experienced prior BV or, more importantly, not.

Odor affects acceptability and may indicate infection. All TEAEs of vaginal odor were associated with community state type IV, but TEAEs were recorded as “odor” only when a simultaneous TEAE of BV or other condition was not recorded. This, and the evidence that Ovaprene does not encourage transitioning to community state type

IV, makes odor more likely associated with community state type IV state than with Ovaprene.

Safety was supported by the lack of clinically important changes in laboratory findings, pelvic examinations, and colposcopies. Inflammatory markers showed wide variation but no apparent upward trend, and antibacterial activity showed no apparent trend toward loss of inhibition, suggesting preservation of vaginal innate immunity. *S. aureus* was not found on used Ovaprenes or vaginal samples, suggesting the risk of Toxic Shock Syndrome is low.

This study demonstrated that short-term use of Ovaprene was not associated with cervicovaginal irritation or adverse effects on vaginal microbiota. Safety will be further monitored in an upcoming pivotal study, in which participants will use Ovaprene for 13 consecutive cycles.

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5 TABLES

Table 1. Study Visits and Timing of Safety Endpoints in a 2019 United States multicenter study evaluating safety of Ovaprene, an investigational vaginal contraceptive[1]

		Baseline cycle			Ovaprene safety cycle					First Ovaprene postcoital test cycle					Second Ovaprene postcoital test cycle				
Visit →	Screening	BP1	BP2	BP3	OS1*	OS2	OS3	OS4	OS5	OP1*	OP2	OP3	OP4	OP5	OP1*	OP2	OP3	OP4	OP5
Collect adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC, chemistry, serum ferritin	X				X				X										
Pelvic examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Colposcopy	X				X				X	X				X	X				X
Nugent Score	X				X	X	X	X	X	X				X	X				X
Microbiota, vagina		X	X	X	X	X	X	X	X	X				X	X				X
Microbiota, used Ovaprenes									X					X					X
Anti-*e. coli* activity, soluble markers		X	X		X	X	X	X	X	X		X		X	X		X		X

[1] Participants were seen in a total of 21 visits, including a cycle in which the Caya diaphragm was used, not shown above

* Ovaprene was inserted at this visit, AFTER vaginal samples were collected
CBC = complete blood counts
BP = Baseline Postcoital test cycle. Enrollment took place at BP3.
OS = Ovaprene Safety cycle
OP = Ovaprene Postcoital test cycle

Table 2. Baseline demographics of participants enrolled in a 2019 United States multicenter study evaluating safety of Ovaprene, an investigational vaginal contraceptive

Parameter		All Enrolled Participants (N = 38)
Age Category, n (%)		
	18 - 35	23 (61)
	365 - 49	15 (40)
Ethnicity		
	Hispanic or Latino	3 (8)
	Not Hispanic or Latino	34 (90)
	Not Reported	1 (3)
Race†, n (%)		
	American Indian or Alaska Native	0
	Asian	2 (5)
	Black or African American	6 (16)
	Native Hawaiian or Other Pacific Islander	0
	White	30 (79)
	Other‡ or does not identify with any	2 (5)
Body Mass Index Category, n (%)		
	Underweight (<18.5)	0
	Normal (18.5-24.9)	13 (34)
	Overweight (25.0-29.9)	8 (21)
	Obese (≥30.0)	17 (44)

*SD = standard deviation

†Race was a “Check All that Apply” question, *i.e.*, a participant could check multiple races.

‡“Other” was a prespecified formal category in the database.

Table 3. Number and Percent of Participants with Treatment-Emergent Adverse Events among participants enrolled in ~~in~~ a 2019 United States multicenter study evaluating safety of Ovaprene, an investigational vaginal contraceptive

	Completed Safety Cycle (N = 33) n (%)
Number (%) of Participants with at Least One TEAE	29 (88)
Severity*	
Mild	17 (51)
Moderate	11 (33)
Severe	1 (3)
Potentially Life-Threatening	0
Product-relatedness†	
Unrelated	9 (27)
Possibly	13 (39)
Probably	6 (18)
Definitely	1 (3)
Urogenital TEAEs	
(Female) Participants	21 (64)‡
Male Partners	1 (3)

* Participants reporting more than one TEAE are only counted once in the greatest severity they ever had.

† Participants reporting more than one TEAE are only counted once in the strongest relatedness category they ever had.

‡One f~~F~~emale participant ~~25 a~~and her male partner both had urogenital TEAEs. There were 20 other female participants with urogenital TEAEs.

Table 4. Number of Treatment-Emergent Adverse Events by Severity and Relatedness to Ovaprene among participants enrolled in a 2019 United States multicenter study evaluating safety of Ovaprene, an investigational vaginal contraceptive

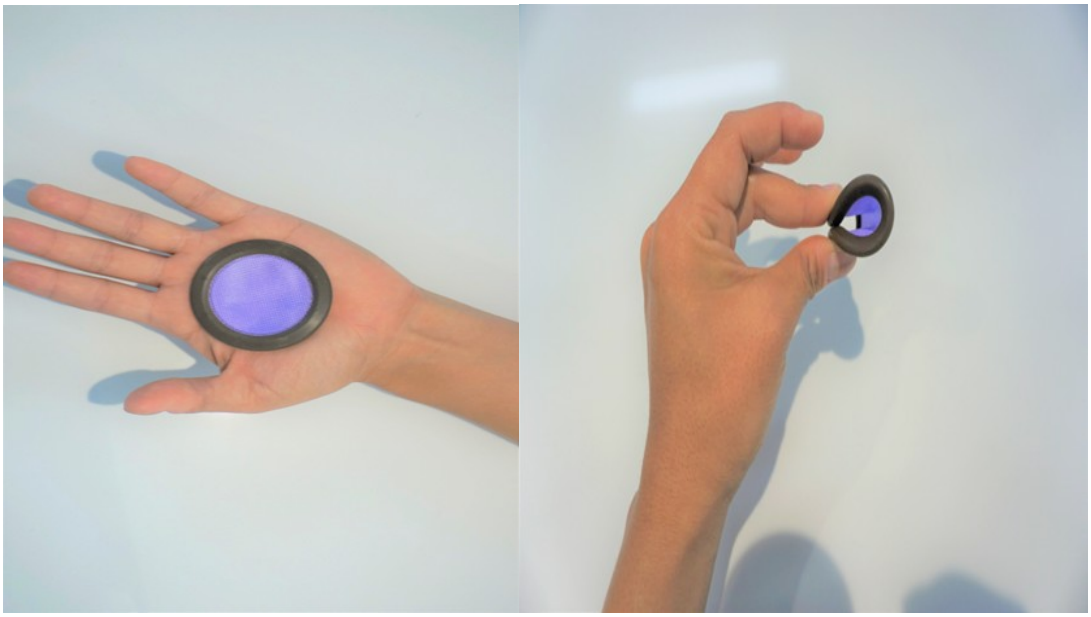
	Severity				
Relatedness	**Mild**	**Moderate**	**Severe**	**Potentially life-threatening**	**Total n (%)**
Unrelated	32	8	1*	0	41 (51.9)
Possibly	21	9	0	0	30 (38.0)
Probably	5	2	0	0	7 (8.9)
Definitely	1†	0	0	0	1 (1.3)
Total Events	59 (74.7)	19 (24.0)	1 (1.3)	0	79 (100.0)

* Severe abdominal pain unrelated to product

† Dyspareunia lasting less than one day

6 FIGURES

Figure 1. Ovaprene, an investigational vaginal contraceptive evaluated for safety in a 2019 United States multicenter study



Ovaprene consists of a silicone ring which releases the spermiostatic agent ferrous gluconate, and a central permeable barrier which inhibits movement of sperm while allowing passage of fluids. Ovaprene is inserted at the end of one menstrual period and left in place until the beginning of the next.

Figure 2. Participant Disposition Flow Diagram in a 2019 United States multicenter study evaluating safety of Ovaprene, an investigational vaginal contraceptive

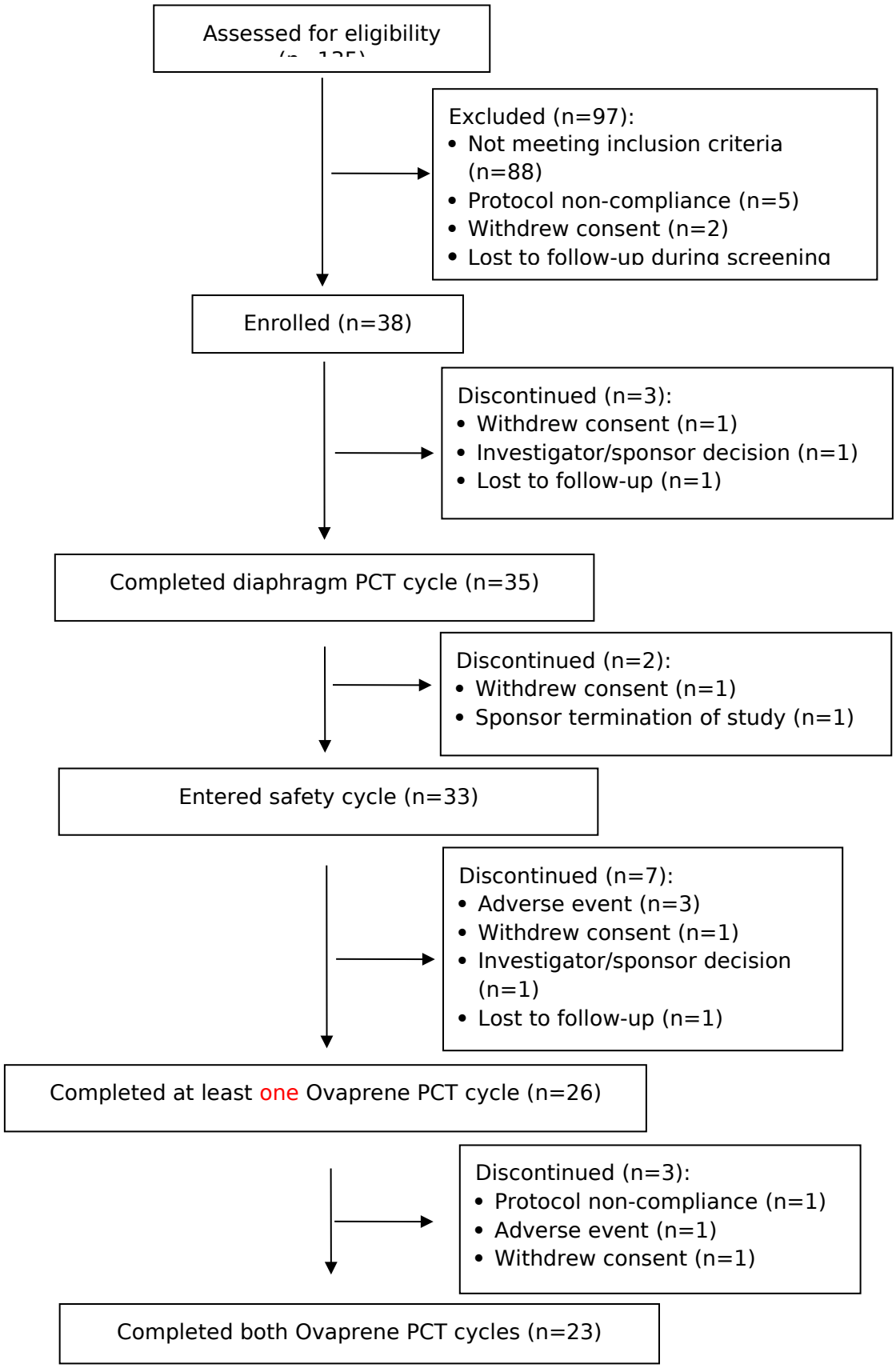
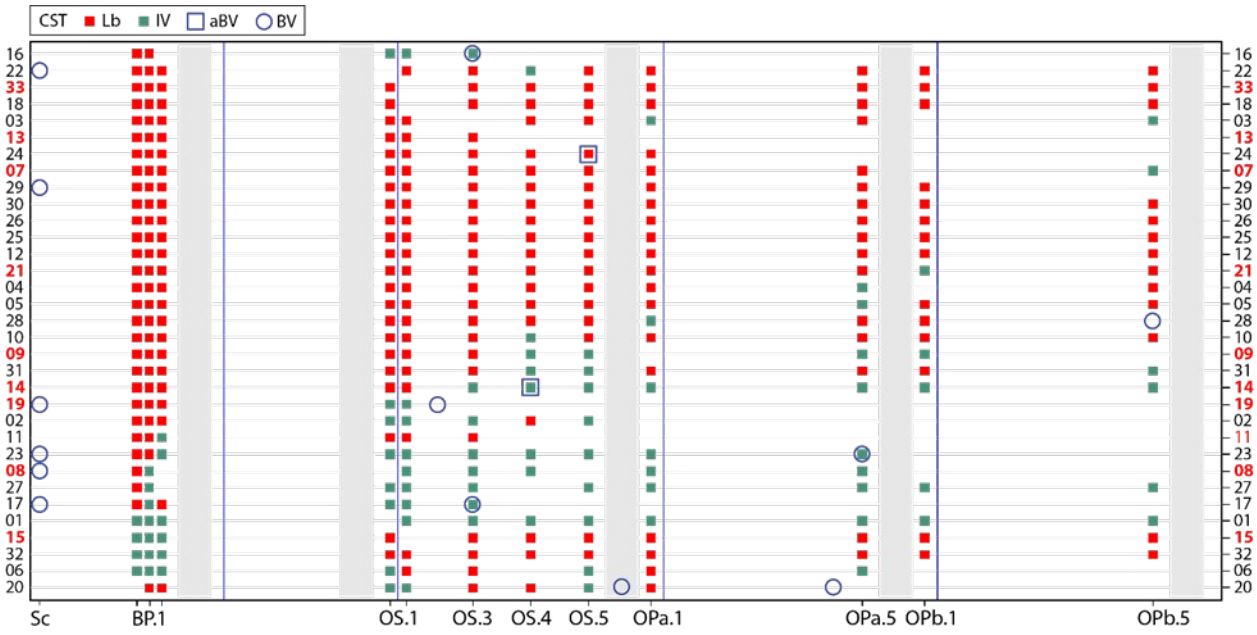


Figure 3: Two categories of community state type profiles (Lb community state type, community state type IV) among participants enrolled in a 2019 United States multicenter study evaluating safety of Ovaprene, an investigational vaginal contraceptive.



Participants are ordered by community state type at baseline, from first timepoint to third time point.

Participants numbers in bold red indicate those with a history of BV. Participant 11 was uncertain of her history.

Vertical gray bars indicate menses.

Vertical blue lines indicate device insertion events.

CST – Community State Type

Lb- Lactobacillus dominant

IV – type IV

aBV = asymptomatic BV

BV – bacterial vaginosis

Sc – Screening visit

BP.1 – Baseline Postcoital test cycle: first, second, and third visits

OS.1 – Safety cycle, first visit. NOTE: OS.2 (safety cycle, second visit) is not labeled separately, but is the column to the right of the blue line following OS.1.

OS.3 – Safety cycle, third visit

OS.4 – Safety cycle, fourth visit

OS.5 – Safety cycle, fifth visit

OPa.1 – First Ovaprene Postcoital test cycle, first visit

OPa.5 – First Ovaprene Postcoital test cycle, fifth visit

OPb.1 – Second Ovaprene Postcoital test cycle, first visit

OPa.5 – Second Ovaprene Postcoital test cycle, fifth visit