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Expanded safety and acceptability of the candidate vaginal microbicide Carraguard® in South Africa

The Carraguard Phase II South Africa Study Team

Abstract

Background—Carraguard's safety and acceptability was assessed among women in Gugulethu and Ga-Rankuwa, South Africa.

Study Design—A randomized, placebo-controlled, triple-blind trial was conducted in HIV-negative, non-pregnant women who inserted Carraguard or placebo at least 3 times/week, including before vaginal sex for 6-12 months. Monthly visits included pelvic exam, STI testing/treatment, and HIV counseling/testing. Acceptability was assessed quarterly.

Results—Of 400 women (205 Carraguard; 195 placebo) enrolled; 328 (77%) completed at least 6 months. Genital epithelial disruption was similar between the Carraguard (13.6 per 100 woman-years) and placebo (21.3 per 100 WY) groups (RR 0.64; 95% CI 0.37, 1.10); there were no significant differences in rates of HIV/STI, though the study was not powered to determine effectiveness. Only 2% of adverse events were judged possibly related to (either) gel. Over 94% of women reported liking the gel very much at least once.

Conclusions—Carraguard was not associated with more vaginal, cervical or external genital irritation than placebo, and was acceptable when used approximately 3.5 times per week, including during sex.

Keywords

HIV prevention; microbicide; Carraguard; safety; acceptability; South Africa

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1. Introduction

The greatest burden of the HIV pandemic is in sub-Saharan Africa, where 61% of those infected are women and girls [1]. Women are more likely to be infected than men for biological, sociocultural and economic reasons [2], and the vast majority of new infections are acquired through heterosexual intercourse [1]. Women have a particularly crucial need for HIV prevention methods that are within their personal control, because gender dynamics may limit their ability to negotiate consistent condom use with their sexual partners.

The candidate microbicide, Carraguard® (PC-515), was developed by the Population Council as a non-contraceptive, vaginal gel for the prevention of HIV and other sexually transmitted infections (STIs). The main ingredient in Carraguard is a mixture of lambda- and kappa-carrageenan (PDR98-15, FMC, Philadelphia, PA), derived from seaweed. In vitro and in vivo evidence from laboratory studies suggests that carrageenans may inhibit herpes simplex virus type-2 (HSV-2) and HIV infection, and are safe for vaginal use [3-6]. Results from two Phase I clinical studies of similar carrageenan formulations showed that none of the women experienced any significant irritation [7,8].

In this paper, we report the results of a Phase II expanded safety and acceptability study of Carraguard that was conducted at two sites in South Africa. Based on results from this study and from a similar Phase II trial conducted in Thailand [9], Carraguard was tested in a large-scale efficacy trial that did not show it to be effective for HIV prevention [10]. However, Carraguard continues to be developed as a microbicide in combination with other compounds [11]. In addition, researchers have called for data from early testing to be published to help identify ways to improve the selection and testing of novel compounds in the future [12].

2. Methods

We conducted a randomized, placebo-controlled, triple-blind trial in South Africa, implemented at the University of Cape Town (UCT) and the Medical University of Southern Africa (Medunsa, now part of the University of Limpopo). The primary aims of this study were to assess Carraguard gel's safety when applied vaginally at least three times per week for six to 12 months, and its acceptability, particularly in communities where dry sex was believed to be common. A secondary aim was to gather preliminary data on whether women using Carraguard had lower rates of HIV seroconversion, Chlamydia trachomatis, Neisseria gonorrhea, Trichomonas vaginalis, and *Treponema pallidum* when compared to women using the placebo; however, the study was not powered to determine effectiveness of the study gel in preventing HIV or other STIs. The study was designed based on recommendations of the International Working Group on Microbicides (IWGM) [13,14] and from a symposium on practical and ethical challenges in microbicide clinical trials [15].

Eligible participants were HIV-negative women 18 years or older, who were in good health based on medical history, physical examination and laboratory screening tests. Participants were recruited from peri-urban family planning and general health clinics in Gugulethu (outside Cape Town) and Ga-Rankuwa (near Pretoria) and had to be willing and able to comply with the study protocol and give informed consent.

Women were excluded if they were pregnant or wanted to become pregnant at the time of study participation; had had a delivery, abortion or genital surgery within six weeks of screening; had a recent history of non-menstrual vaginal bleeding with intercourse; had a clinically detectable genital abnormality; had clinical signs of a reproductive tract infection (defined as the presence of a genital ulcer visible to the naked eye; an abnormal vaginal discharge or purulent cervicitis; or untreated positive STI test result); had an abnormal Pap smear; had a history of sensitivity/allergy to latex; were participating in a trial of another vaginal product;

or reported injection of recreational drugs. Women could be enrolled after treatment of curable STI and could be screened up to three times.

Participants were randomly assigned in a 1:1 ratio to either Carraguard or placebo (methylcellulose) gel. Methylcellulose was selected as the placebo based on its safety profile, its lack of microbicidal effects in an HSV-2 mouse system, and because it neither kills nor immobilizes sperm [4,6,16-19]. Both Carraguard and placebo gels were manufactured by Clean Chemical Sweden (CCS, Borlange, Sweden) and packaged in boxes of 12 single-use Microlax®-type applicators (TecTubes Sweden AB, Astorp, Sweden), each filled with 7 mL to dispense approximately 4 mL of gel.

The randomization scheme, which utilized six different color groups (three for Carraguard and three for placebo), was created using the pseudo-random number generator of the statistical software package SPSS (Version 7.0, Chicago, IL). Colored stickers with identification numbers were placed in sequentially numbered, opaque envelopes at the Population Council in New York. At enrollment, each woman was assigned to the next sequential identification number and was given a supply of the same colored box of applicators at each visit. Site and Population Council staff members were blinded throughout the trial, and data analysis was conducted by independent statisticians on blinded data.

Participants were instructed to insert a minimum of one applicator of gel vaginally at least three times per week for six to 12 months, with or without vaginal intercourse. Women were also instructed to insert the gel 1 h or less before each act of vaginal intercourse, with no maximum limit, and to use a male condom together with gel during every act. Women were encouraged to use contraception, and to use gel during menses, particularly if they had vaginal intercourse during that time. Products to dry, clean or tighten the vagina were permitted and use of such products recorded at each visit.

Study participants returned to the clinic two weeks and one month after enrollment, and monthly thereafter. At each visit, epithelial safety was assessed by clinician naked-eye visual examination of the vagina, cervix and external genitalia for epithelial disruption (ulcer, fissure, or abrasion), edema (swelling), erythema, or petechial hemorrhage during a pelvic examination. At monthly visits, vaginal and cervical specimens were also collected to diagnose bacterial vaginosis (BV; Nugent score interpretation of Gram stain [20]) and candidiasis (Gram stain), *T. vaginalis* (Modified Diamond's medium culture system, Microbiology Laboratory, Ga-Rankuwa Hospital, South Africa), *C. trachomatis* and *N. gonorrhoeae* (Gen-Probe Pace 2, San Diego, CA, USA and Amplicor PCR, Roche Molecular System Inc., Branchburg, NJ, USA). Participants also gave monthly urine samples for pregnancy testing. At 3-month intervals, blood was collected to test for *T. pallidum* (Immuntrep-RPR, Omega Diagnostics Ltd., Casebridge Court, Scotland, UK) and HIV (Abbott AxSYM Elisa HIV 1/2,0, Abbott, Wiesbaden, Germany with Abbott Murex Elisa HIV 1/2,0, Murex Biotech Ltd, Dartford, UK as confirmation; or Capillus Latex Agglutination test, Trinity Biotech, Bray Co. Wicklow, Ireland with Abbott (as above) or Vironostica HIV Uniform II, BioMerieux supplied by Omnimed (Pty) Ltd, Randburg, South Africa as confirmation).

Adherence was assessed through women's self-reports of gel and condom use and sexual activity, and a count of used and unused applicators returned at each study visit. Gel acceptability was evaluated through face-to-face interviews at selected visits.

The study protocol was reviewed and approved by the Population Council Institutional Review Board, the Research Ethics and Publications Committee at Medunsa, the Research Ethics Committee at the University of Cape Town, the Ethics Committee of the Medical Research Council in Durban, South Africa, the Protection of Human Subjects Committee of Family Health International, and the South African Medicines Control Council. In addition, the

protocol was reviewed by members of the IWGM, staff at the Office for Human Research Protection at the United States National Institutes of Health, and several women's health advocates.

2.1. Sample size

This study required 150 woman-years of observation: 75 woman-years of exposure to Carraguard and 75 woman-years of exposure to placebo, an amount of exposure considered meaningful and adequate for an expanded safety trial of a candidate microbicide. A sample size of 300 women, randomized to Carraguard or placebo in a 1:1 ratio, and followed for an average of 6 months, was selected to reach the target exposure goal. However, after the trial began, the sample size was increased to 400 women due to concerns about retention rates. Although power for a formal hypothesis test was not pre-specified, the follow-up achieved provided approximately 90% power to detect a doubling of the risk of genital epithelial disruption in the Carraguard arm compared to the assumed rate in the placebo arm, with a two-sided 0.05 level test.

2.2. Statistical methods

We measured safety by comparing the proportion of women in each study arm with genital findings with epithelial disruption on the vagina, cervix or external genitalia, calculating crude incidence rates of these findings with 95% confidence intervals using Poisson assumptions [21]. The frequency, percentage and incidence of epithelial disruption were tabulated by treatment group, location (vagina, cervix or external genitalia) and study interval. Our primary outcome was the time-to-first occurrence of genital epithelial disruption. The intent-to-treat population (all women enrolled and randomized) was used for all analyses of safety outcomes. However, primary time-to-event safety analyses excluded data collected after any interruption of product use that lasted more than 14 days or for women who were missing for more than 60 days, since failure to do so could bias estimates of treatment effects towards the null. The primary analyses were censored at one year, corresponding to the planned follow-up time for each participant. We also compared the percentage of women in each group who were diagnosed with BV and candida, and compared the percentage of women who experienced adverse events (AEs) by body system, as well as incidence of AEs between the two groups.

We measured acceptability using both open-ended and closed-ended questions about overall product acceptability, the applicator, volume of gel, effects on sexual activity, partner opinions, and use during menses. We tabulated simple frequencies and compared study arms.

Preliminary effectiveness data were analyzed by looking at time-to-first incident STI (HIV infection, chlamydia infection, gonorrhea, syphilis and trichomoniasis), using survival analysis methods (e.g., Kaplan-Meier estimates of cumulative probabilities and crude incidence density estimates).

Data were captured on carbonless case report forms and entered into an SPSS (Version 7.0, Chicago, IL) database in the Population Council's Johannesburg office. Analyses were conducted using SAS (version 9.1, SAS Institute, Cary, NC). AEs were coded by an obstetrician/gynecologist at the Population Council who was not part of the study team using a modified version of the World Health Organization's Adverse Reaction Terminology (WHO-ART) dictionary [22].

3. Results

Between October 1999 and January 2002, we enrolled and followed 400 women (200 per site) who contributed a total of 378.5 woman-years of exposure to the study gels (192.5 woman-

years Carraguard, 186.0 woman-years placebo). As shown in Fig. 1, we screened a total of 900 women, resulting in an enrollment rate of 44%. Of the 400 women enrolled (n=205 Carraguard, n=195 placebo), 77% completed at least six months (77.6% Carraguard, 76.4% placebo); 18.5% withdrew prior to completing six months in the study, (19% Carraguard, 18% placebo); and 4.5% were lost to follow-up (7 women Carraguard, 11 women placebo). Four participants (two per group) withdrew early because of self-reported AEs, all of which were rated by study clinicians as mild or moderate and classified as “probably not related” to study gel use. The major reasons for early withdrawal were moving out of the study area (16.2%), schedule conflict (13.5%), partner disapproval (12.2%), and wanting to or becoming pregnant (5.4%), with no differences between the two groups.

Baseline characteristics were evenly balanced between the two groups (Table 1). Study participants at both sites were young (approximately 70% of women were under 30), almost 90% had completed some secondary school, and more than 80% were unemployed. More than 80% of women were using contraception, mainly injectable methods. However, fewer participants in Ga-Rankuwa than in Gugulethu reported having a steady partner (8.5% and 19%, respectively) and almost three times as many women in Ga-Rankuwa (32%) than Gugulethu (11.5%) reported inserting any vaginal products (data not shown).

3.1. Adherence

Based on a count of the used applicators returned at each study visit, women used a mean of 3.5 and 3.8 applicators per week in the Carraguard and placebo groups, respectively. Minimum adherence, defined as having used at least nine applicators per month (three per week, taking into consideration that many women might not use the gel during menses even though they were instructed to do so) ranged from 84.5% to 96.6% of women at any follow-up visit, with no differences between the two groups (data not shown). Used applicators were also weighed to determine the volume of study gel dispensed at each application; women in both groups squeezed out a mean of 4.8 mL of gel from each applicator.

A total of 197 participants (49.3%) reported at least one gel interruption during the study (105 Carraguard, 92 placebo) and 87 women interrupted gel use permanently (45 Carraguard, 42 placebo), though they were encouraged to remain in the study. The main reason for gel interruptions was missing study visits by more than the ± 14 -day visit window (86 Carraguard, 81 placebo). The mean duration of temporary interruptions was 73.6 days (66.5 days Carraguard, 82.6 days placebo), with no significant differences between groups in mean duration ($p=0.19$).

Participants reported an average of four vaginal sex acts per month with similar reports of gel and condom use in the two groups. Participants in both groups reported using gel in over 80% of sex acts, and using condoms together with the gel during approximately half of all sex acts (55.1% placebo, 51.3% Carraguard); women reported using condoms alone 9.3% and 9.9% of the time in the placebo and Carraguard groups, respectively (data not shown). Gel use during menses, primarily in the absence of intercourse, increased from approximately 27% of women at Month 1 to more than 50% of women at Month 12 (58.4% Carraguard, 52.3% placebo). Insertion of vaginal products other than the gel was reported by 16.3% and 13.5% of participants in the Carraguard and placebo groups, respectively.

3.2. Safety

The time to first epithelial disruption, our main safety measure, was not statistically different between the two groups. The incidence density of epithelial disruption was 13.6 events per 100 woman-years in the Carraguard group compared to 21.3 events per 100 woman-years in the placebo group (RR 0.64; 95% CI 0.37, 1.10). Table 2 indicates no difference between groups

in rates of epithelial disruption, genital lesions or genital itching, burning, or pain when incidence densities were evaluated.

Signs and symptoms at follow-up and closing were similar in both groups. Sixty-six participants (32.2%) in the Carraguard and 56 participants (28.7%) in the placebo group had a genital finding (with or without epithelial disruption) identified during study follow-up, with no significant difference between the two groups. Abnormal findings on the external genitalia were detected by a clinician in 19% of women in both groups; vaginal findings were detected in 6% and 4% of women in the Carraguard and placebo groups, respectively; cervical findings were detected in 14% and 12% of women in the Carraguard and placebo groups, respectively (Table 3). Findings indicative of pelvic inflammatory disease or other gynecological conditions were extremely rare in both groups.

Most women in both groups reported no vaginal, cervical, or external genital irritation. The majority of participants (87% Carraguard, 85% placebo) reported having a menstrual period during the study; of those, the majority reported no changes in bleeding (81% Carraguard, 73% placebo) or pain during menses (89% Carraguard, 92% placebo), and no intermenstrual bleeding (80% Carraguard, 79% placebo).

Rates of BV and candida were high throughout the trial; 58.5% and 64.6% of women ever tested positive for BV in the Carraguard and placebo groups, respectively, and 42.9% and 42.1% of women ever tested positive for candida in the Carraguard and placebo groups, respectively (data not shown).

There were no significant differences in numbers of AEs between the two groups (Table 4). More than half of the 2,463 AEs were reproductive disorders (882 Carraguard, 825 placebo) as women were asked detailed questions about genital symptoms and underwent a pelvic exam at each visit. Only 69 AEs (2%) were judged as related or possibly related to study gel use (34 Carraguard, 35 placebo), of which the majority were reproductive disorders (32 in each group); 54 were rated as mild, 10 as moderate (4 Carraguard, 6 placebo), and none as severe. Twenty-one serious AEs were reported (14 Carraguard, 7 placebo), only one of which was judged possibly related to study gel (a case of pelvic inflammatory disease, placebo group). Twenty participants in the Carraguard group (9.7%) and 17 participants in the placebo group (8.7%) became pregnant during the trial, with no differences between the groups in terms of pregnancy outcomes (data not shown).

3.3. Acceptability

Overall, women in both arms reported the gel and applicator were highly acceptable. Over 94% of women in both groups reported at least once during the study that they liked the gel very much and only one participant in each group ever reported strongly disliking the gel. More than 96% of women in both groups ever reported that the application of study gel was very easy, and no women ever reported that the study gel was very difficult to apply. About 97% of women in both groups ever rated the study gel applicator to be appealing. Most women reported at least once that the study gel was not messy (86.6% Carraguard, 88.4% placebo), though a majority also reported at least once that it was somewhat messy (53.7% Carraguard, 61.1% placebo); only 5.5% of women in the Carraguard group and 12.1% of women in the placebo group ever reported that the gel was very messy.

A substantial proportion of women in both groups (59.4% and 63.2% in the Carraguard and placebo groups, respectively) ever reported that using the gel made sex more pleasurable. Less than 5% of women in both groups ever reported that using the gel made sex somewhat or a lot less pleasurable.

Most women (97.3% Carraguard, 99.4% placebo) reported telling their partners that they were using the gel. While partners' reactions varied, the most frequent response (41.8% Carraguard, 45.5% placebo) was that the partner agreed and liked the idea. Less than 6% of women in each group reported having partners who resisted gel use. The majority of women in both groups (67.9% Carraguard, 65.3% placebo) felt that they would not be able to use the gel without their partners' knowledge. More than 98% of women in each group would recommend the gel to a friend.

3.4. Preliminary effectiveness

There was no significant difference between the placebo and Carraguard group in rates of HIV, chlamydia, or gonorrhea infection throughout study period, although the study was not powered to determine whether Carraguard could prevent STIs (Table 5). Sixteen women (8 per group) seroconverted during the trial (RR 0.96, 95% CI 0.32, 2.94).

4. Discussion

In this study, Carraguard use was not associated with vaginal, cervical, or external genital irritation when compared with a methylcellulose placebo. Signs and symptoms during follow-up were similar in both groups, as were rates of AEs, vaginal infections (BV and candida) and STIs. In addition, the time to first epithelial disruption, the main safety measure, was not statistically different between the two groups.

While nearly one-third (30.5%) of the participants ever had an abnormal genital finding, incidence of epithelial disruption was much less common. These results are consistent with findings from a study among healthy sexually-active women not using any vaginal product, in which 38.3% of the volunteers had changes in vaginal surface appearance [23], as well as results from two previous safety studies of Carraguard conducted in Thailand [9,24].

Rates of BV were higher in this trial than in the two Thai studies, probably due to the high background rate of BV in these communities [25,26]. However, prevalence was similar between the two groups, indicating that Carraguard does not disturb vaginal flora, an important finding given the potential increased HIV risk among women with BV and candida [27]. Based on the promising safety data from this study and the two Thai trials [9,23], a Phase III efficacy trial was implemented [10].

One specific aim of this study was to assess microbicide acceptability and use dynamics in communities where "dry sex" was thought to be common [28,29]. However, in this study, less than 20% of participants reported inserting any vaginal products, other than the study gel.

The vast majority of women rated the gels and applicator as acceptable, which was consistent with self-reports of gel use (with or without condom) during at least 80% of sex acts (once a week, on average, in this study). However, although emptied applicators were counted and tallied for each monthly visit, there is no way to determine whether applicators were inserted in conjunction with sex. In addition, data from two ancillary studies conducted by independent researchers among a subset of Phase II participants revealed that women had sometimes provided inaccurate information to the study staff regarding adherence and acceptability for fear of displeasing them or losing study benefits [30,31]. Therefore, women may have over-reported gel use during sex. One of the limitations of this study was that the same study staff members interviewed participants and counseled them on adherence due to budget constraints. Future studies should employ separate staff for interviewing and counseling in an effort to improve adherence and accuracy of reports, and better tools for assessing adherence, including biomarkers, if possible, should be developed.

In conclusion, Carraguard appears to be safe and acceptable for vaginal use at frequencies of approximately 3.5 times per week, with or without vaginal sexual intercourse (once a week on average in this study). Although recent data did not show Carraguard to be effective in preventing HIV transmission [10], Carraguard's safety and acceptability profile are important as Carraguard continues to be investigated for use with other compounds being developed for both HIV and STI indications.

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Fig. 1.
Participant flow diagram in a randomized, controlled trial of Carraguard in Gugulethu and Ga-Rankuwa, South Africa (1999-2002)

Table 1

Baseline characteristics of women participating in a randomized, controlled trial of Carraguard in Gugulethu and Ga-Rankuwa, South Africa, by treatment group; intent-to-treat population (1999-2002)

Characteristic at screening	Treatment group				Total	
	Carraguard (n=205)		Placebo (n=195)		N=400	
	n	(%)	n	(%)	n	(%)
Mean age, in years (range)	27.8 (18-55)		27.2 (18-55)		27.5 (18-55)	
Years education completed						
None	0	(0.0)	2	(1.0)	2	(0.5)
Primary (1-5)	19	(9.3)	13	(6.7)	32	(8.0)
Secondary (6-12)	180	(88.2)	175	(89.7)	355	(88.8)
College (13+)	5	(2.5)	5	(2.6)	10	(2.5)
Currently working	22	(10.7)	27	(13.8)	49	(12.3)
Current relationship						
No steady partner	30	(14.6)	25	(12.8)	55	(13.8)
Steady partner – not living with him	121	(59.0)	116	(59.5)	237	(59.3)
Steady partner – living with him	26	(12.7)	24	(12.3)	50	(12.5)
Married – not living with him	6	(2.9)	4	(2.1)	10	(2.5)
Married – living with him	22	(10.7)	26	(13.3)	48	(12.0)
Has other partners	19	(9.3)	11	(5.6)	30	(7.5)
Number of live births						
0	59	(28.8)	65	(33.3)	124	(31.0)
1	68	(33.2)	69	(35.4)	137	(34.3)
2	42	(20.5)	32	(16.4)	74	(18.5)
3	26	(12.7)	21	(10.8)	47	(11.8)
4 or more	10	(4.9)	8	(4.1)	18	(4.5)
Current contraceptive use*						
None	39	(19.0)	35	(17.9)	74	(18.5)
Injectables	106	(51.7)	109	(55.9)	215	(53.8)
Oral pills	31	(15.1)	31	(15.9)	62	(15.5)
Male condoms	10	(4.9)	6	(3.1)	16	(4.0)
Female sterilization	15	(7.3)	10	(5.1)	25	(6.3)

Characteristic at screening	Treatment group				Total	
	Carraguard (n=205)		Placebo (n=195)		N=400	
	n	(%)	n	(%)	n	(%)
Other [†]	5	(2.5)	5	(2.5)	10	(2.5)
Used any vaginal product in past year	45	(22.0)	42	(21.5)	87	(21.8)
Had vaginal sex in past year	192	(93.7)	184	(94.4)	376	(94.0)
One or more times a week	146	(71.2)	148	(75.9)	294	(73.5)
Had anal sex in past year	7	(3.4)	6	(3.1)	13	(3.25)
Had oral sex in past year	23	(11.2)	24	(12.3)	47	(11.8)
Condom use in past year for vaginal sex [‡]						
Always	26	(13.5)	29	(15.8)	55	(13.8)
Usually	7	(3.6)	6	(3.3)	13	(3.25)
Sometimes	62	(32.3)	48	(26.1)	110	(27.5)
Once in a while	10	(5.2)	11	(6.0)	21	(5.25)
Never	87	(45.3)	90	(48.9)	177	(44.3)

Source: Eligibility checklist and Screening questionnaire databases.

* The n's may not add up to the totals because the participants may answer more than one response.

[†] Includes implants, female condoms, male sterilization, IUD, withdrawal, periodic abstinence, spermicides, other.

[‡] The totals are the number reporting sex in the previous year.

Table 2

Summary of incidence density estimates of the occurrence of epithelial disruption, genital findings, and self-reported genital itching, burning, and pain throughout study period in a randomized, controlled trial of Carraguard in Gugulethu and Ga-Rankuwa, South Africa, by treatment group; modified intent-to-treat population* (1999-2002)

Carraguard						Placebo			p-value [§]
Incidence density estimates of ...	No. of women	Woman-years [†]	No. who had event	Event rate (per 100 woman-years)	95% confidence interval [‡]	No. of women	Woman-years [†]	No. who had event	
Clinician-observed genital findings with epithelial disruption [¶]	198	162.3	22	13.6	(8.93, 20.59)	188	145.4	31	21.3 (14.00, 30.32) 0.1012
Clinician-observed genital findings with or without epithelial disruption [¶]	198	135.3	66	48.8	(38.32, 62.09)	188	125.8	56	44.5 (34.26, 57.84) 0.6058
Self-reported genital itching, burning, or genital pain ^{**}	198	135.0	63	46.7	(36.46, 59.74)	188	130.9	51	39.0 (29.61, 51.27) 0.3512

* Excludes data collected after any interruption of product use that lasted more than 14 days or for women who were missing for more than 60 days.

[†] Due to rounding, the total number of person-years throughout the study period may not add up to the sum of person-years across study periods; data are censored at one year.

[‡] 95% confidence intervals computed under a Poisson assumption.

[§] P-values based on two-sided log-rank tests.

// Crude risk ratio is 0.64 (Carraguard vs. placebo) with an approximate 95% confidence interval of (0.37, 1.10).

¶ Crude risk ratio is 1.10 (Carraguard vs. placebo) with an approximate 95% confidence interval of (0.77, 1.56).

** Crude risk ratio is 1.20 (Carraguard vs. placebo) with an approximate 95% confidence interval of (0.83, 1.72).

Table 3

Summary of genitourinary signs and symptoms at follow-up and closing in a randomized, controlled trial of Carraguard in Gugulethu and Ga-Rankuwa, South Africa, by treatment group; modified intent-to-treat population* (1999-2002)

	Carraguard		Placebo	
	N	(%)	N	(%)
Clinician findings ever detected				
Mean vaginal pH (SD)*	4.8	(0.26)	4.8	(0.27)
Any abnormalities present:				
External genitalia	37	(18.7)	36	(19.1)
Vagina	11	(5.6)	7	(3.7)
On the cervix	28	(14.1)	22	(11.7)
Cervical contact bleeding	3	(1.6)	3	(1.6)
Pain on bimanual exam [†]				
None	186	(93.9)	178	(94.7)
Mild	7	(3.5)	4	(2.1)
Moderate	5	(2.5)	6	(3.2)
Severe	0	(0.0)	0	(0.0)
Cervical motion tenderness [†]				
None	192	(99.0)	183	(99.5)
Mild	2	(1.0)	1	(0.5)
Moderate	0	(0.0)	0	(0.0)
Severe	0	(0.0)	0	(0.0)
Adnexal masses	0	(0.0)	0	(0.0)
Any other abnormal signs	13	(6.6)	9	(4.8)
Participant symptoms ever reported				
Genital itching, burning, or pain	65	(32.8)	55	(29.3)
Abnormal vaginal dryness	7	(3.5)	6	(3.2)
Had vaginal sex during follow-up	192	(97.0)	176	(93.6)
Any pain during intercourse [†]				
None	181	(94.3)	157	(89.2)
Mild	4	(2.1)	10	(5.7)
Moderate	7	(3.6)	7	(4.0)
Severe	0	(0.0)	5	(2.8)
Urinate more often than usual	31	(15.7)	38	(20.2)
Painful urination [†]				
None	173	(87.4)	168	(89.4)
Mild	9	(4.5)	8	(4.3)
Moderate	15	(7.6)	12	(6.4)

	Carraguard		Placebo	
	N	(%)	N	(%)
Severe	6	(3.0)	3	(1.6)
Lower abdominal pain [†]				
None	165	(83.3)	145	(77.1)
Mild	21	(10.6)	29	(15.4)
Moderate	22	(11.1)	15	(8.0)
Severe	4	(2.0)	5	(2.7)
Ever had any genital sore [†]				
None	170	(85.9)	154	(82.4)
Internal	6	(3.0)	3	(1.6)
External	26	(13.1)	31	(16.5)
Ever had any other symptoms [†]				
None	172	(86.9)	161	(85.6)
Mild	11	(5.6)	15	(8.0)
Moderate	11	(5.6)	9	(4.8)
Severe	6	(3.0)	5	(2.7)

Source: Clinician follow-up database

* The mean reported here represents the mean of individual woman means.

[†] One woman may have more than one response during her follow-up. The n's may not add up to the totals.

Table 4

Summary of number of adverse events in a randomized, controlled trial of Carraguard in Gugulethu and Ga-Rankuwa, South Africa, by treatment group; intent-to-treat population (1999-2002)

System Organ Class*	Carraguard		Placebo		Total		p-value
	Related [†]	Not related [‡]	Related [†]	Not related [‡]	Related [†]	Not related [‡]	
Application site disorders	0	2	0	0	0	2	n/a
Body as a whole – general systems	0	36	0	67	0	103	n/a
Cardiovascular disorders	0	1	0	2	0	3	n/a
Gastrointestinal/liver/biliary disorders	1	77	0	84	1	161	0.4815
Menstrual disorders	1	81	0	70	1	151	1.000
Musculoskeletal system disorders	0	5	0	4	0	9	n/a
Nervous system and senses	0	43	0	41	0	84	n/a
Psychiatric disorders	0	1	0	2	0	3	n/a
Red/white cell/platelet/bleeding disorders	0	0	0	1	0	1	n/a
Reproductive disorders, female	32	882	32	825	64	1707	0.8004
Resistance mechanism disorders	0	4	0	2	0	6	n/a
Respiratory system disorders	0	45	0	39	0	84	n/a
Secondary terms – events	0	1	0	1	0	2	n/a
Skin and appendages disorders	0	12	1	18	1	30	1.000
Urinary system disorders	0	55	2	62	2	117	0.4986
Total	34	1245	35	1218	69	2463	0.9030

Source: Adverse event database.

* Coded per WHOART dictionary

[†] Possibly or probably related as judged by study clinician.

[‡] Unrelated or probably unrelated as judged by study clinician.