Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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We received approval from the institutional review boards of the four collaborating institutions prior to study initiation.

NIAID/DMID had no direct role in designing the study; collecting, handling, analyzing, or interpreting data; writing the manuscript; and the decision to publish this manuscript.

Methods

Participants met the following inclusion and exclusion criteria:

1. Capable of reading and writing in English and voluntarily provide written informed consent to participate in the study and comply with all study procedures.
2. Untreated BV (asymptomatic or symptomatic) as diagnosed during the screening visit defined by $\geq$3 Amsel criteria.
3. Untreated BV (asymptomatic or symptomatic) as confirmed in the laboratory using the Nugent scoring system (Nugent score ≥4)
4. Otherwise healthy pre-menopausal women 18–45 years of age on the day of screening.
5. 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.

6. Willing to be asked questions about personal medical health and sexual history.
7. Willing to apply study agent vaginally and comply with study examinations.
8. 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 each study product application.
9. 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.)
10. 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.

Participants meeting any of the following criteria at screening, or when assessed at the enrollment visit, were excluded from study enrollment.

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.)
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.
3. Positive for syphilis or HIV at screening.
4. Current pregnancy or within 2 months of last pregnancy and/or currently breastfeeding.
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.
6. Use of disulfiram within past 2 weeks or other contraindication to use of MetroGel.
7. Any condition requiring regular periodic use of systemic antibiotics during participation in the trial.
8. Active genital herpes lesion (if not resolved by enrollment).
9. Investigational drug use other than LACTIN-V within 30 days or 10 half-lives of the drug, whichever is longer, of enrollment visit.
10. Other planned participation in an investigational drug study while participating in this study.
11. Menopause defined as more than 12 consecutive months of amenorrhea without another known cause including pregnancy.
12. IUD insertion or removal, pelvic surgery, cervical cryotherapy or cervical laser treatment within the last 2 months prior to screening.
13. Use of vaginal ring (e.g., NuvaRing) within 3 days of screening or during the course of the study.
14. Failure to complete 5 days of MetroGel with the last dose taken no later than 48 hours prior to randomization.
15. Use of new long-acting hormonal treatments. Participant may be enrolled if stable (>3 months) on existing therapy as determined by the principal investigator.
16. Known allergy to any component of LACTIN-V/placebo or MetroGel or to nitroimidazole derivatives or latex (condoms).
17. 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. Treatments

Treatment Adherence: All participants received a total of 25 doses of study product. Adherence was assessed by participant's self-report and by staining of the returned applicators, organized in pre-labelled pouches provided for each week. Treatment adherence was part of the review of the blinded case review committee. Treatment adherence was defined as having taken at least four of five doses during week one and 75% of total doses required per protocol, which allowed skipping or delaying a dose during menstruation or BV retreatment during weeks 2-11.

Lactobacillus PCR protocol:

200μL of sample volume was extracted using EZ1 DNA Tissue kit (Qiagen) and eluted into 50μL volume. PCR reactions were setup in duplicate with 25μL QuantiTect SYBR Green RT-PCR Master Mix (Qiagen), 2.5μL forward primer (10μM), 2.5 μL reverse primer (10μM), 10μL extract and 10μL H_2O for a total volume of 50μL. Following initial denaturation at 95°C for 15 minutes, PCR cycling consisted of 40 cycles at 95°C for 30 seconds, 58°C for 60 seconds, and 72°C for 60 seconds. Gene targets for strain and species-specific PCR were selected using genes identified in *Lactobacillus crispatus* CTV-05 and *L. crispatus*-specific regions which were absent in other sequenced bacterial strains and with low numbers of homologs in vaginal metagenome datasets. Primer sequences consisted of forward and reverse primers targeting *L. crispatus* CTV-05 strain (LBKG_01471, GCTGTTGCAGCCAGACAGTT, TCTCTGGGACATCCATAAGTTG, 206bp), *L. crispatus* (LBKG_00854, AAAGTCCTGGTTTGATCTGCGT, CACTTCCTAGCCACTGTGTTGT, 101bp), *Lactobacillus* species (16S ribosomal DNA, AGAGTTTGATYMTGGCTCAG, CACCGCTACACATGGAG, 667bp) and total bacteria (16S ribosomal DNA, AGAGTTTGATCCTGGCTCAG, GCTGCCTCCCGTAGGAGT, 312bp). (1-5) Bacterial concentration was calculated from mean sample Ct values using a standard curve based on serial dilutions of CTV-05 strain of *L. crispatus*. Limits of detection determined for each target at the 95% detection threshold were 6.60 x 10^2 CFU/mL (CTV-05 strain), 9.53 x 10^2 CFU/mL (*L. crispatus*) and 1.01 x 10^2 CFU/mL (*Lactobacillus* species). Detection of *L. crispatus* CTV-05 by qPCR assay was defined as *L. crispat*us species and *L. crispatus* CTV-05 strain both above the lower limit of detection as defined above.

References:

1. Heilig HGHJ, Zoetendal EG, Vaughan EE, Marteau P, Akkermans ADL, de Vos WM. Molecular Diversity of Lactobacillus spp. and Other Lactic Acid Bacteria in the Human Intestine as Determined by Specific Amplification of 16S Ribosomal DNA. Appl Environ Microbiol 2002;68:114-123.
2. Kibe R, Sakamoto M, Yokota H, Ishikawa H, Aiba Y, Koga Y, Benno Y. Movement and Fixation of Intestinal Microbiota after Administration of Human Feces to Germfree Mice. Appl Environ Microbiol 2005;71:3171-3178.
3. Ling Z, Liu X, Chen X, Zhu H, Nelson KE, Xia Y, Li L, Xiang C. Diversity of Cervicovaginal Microbiota Associated with Female Lower Genital Tract Infections. Microb Ecol 2011;61:704-714.

Case Review Committee

Prior to unblinding, a case review committee was convened (Supplementary Appendix Methods). to review participants with any reported concomitant medications (e.g. antibiotics) or out of window visits, poor adherence to study product, and all reported protocol deviations, to

determine if any of the cases or events could potentially impact study product effectiveness or study analyses. Afterwards, the study biostatistician used the review to determine participant allocation to the modified intention-to-treat, complete case, and per-protocol analyses. All enrolled participants were included in the intention-to-treat analysis.

Statistical Methods: Definition of Analyses Cohorts

The modified-(m)ITT analyses excluded participants with baseline concomitant vaginal/cervical infections, who did not receive study product, or who did not return for at least one post-baseline visit. The complete case analyses further excluded participants who were not followed up until either the first BV diagnosis or the Week 12 visit. The per-protocol analyses further restricted the complete case analyses to exclude those who did not meet all enrollment eligibility criteria, were not compliant with the study product dosing regimen, or who used prohibited medications prior to either their first BV diagnosis or the Week 12 visit. Week 24 analyses were defined similarly. To be considered compliant with the dosing regimen, a participant must have used at least four of the first five daily doses and at least 75% of doses overall.

Supplementary Results Tables

Table S1: BV Recurrence by Week 12 by Analysis Population and Treatment Group

Study Arm	Proportion with BV	RR (95% CI)
Intention-to-Treat (LOCF)		
LACTIN-V (n=152)	46 (30%)	0.68 (0.48, 0.96)
Placebo (n=76)	34 (45%)	-
Modified-Intention-to-Treat (LOCF)		
LACTIN-V (n=140)	46 (33%)	0.65 (0.46, 0.90)
Placebo (n=67)	34 (51%)	-
Complete Case		
LACTIN-V (n=132)	46 (35%)	0.66 (0.47, 0.91)
Placebo (n=64)	34 (53%)	-
Per-Protocol (self-report)		
LACTIN-V (n=118)	36 (31%)	0.57 (0.40, 0.82)
Placebo (n=58)	31 (53%)	-
Per-Protocol (by applicator staining)		
LACTIN-V (n=112)	35 (31%)	0.60 (0.41, 0.88)
Placebo (n=54)	28 (52%)	

Table S2: BV Recurrence by Week 24 by Analysis Population and Treatment Group

Study Arm	Proportion with BV	RR (95% CI)
Intention-to-Treat (LOCF)		
LACTIN-V (n=140)	59 (39%)	0.72 (0.54, 0.96)
Placebo (n=67)	41 (54%)	-
Modified-Intention-to-Treat (LOCF)		
LACTIN-V (n=140)	59 (42%)	0.69 (0.52, 0.90)
Placebo (n=67)	41 (61%)	-
Complete Case		
LACTIN-V (n=132)	59 (48%)	0.73 (0.57, 0.94)
Placebo (n=64)	41 (66%)	-
Per-Protocol (self-report)		
LACTIN-V (n=118)	48 (45%)	0.71 (0.53, 0.95)
Placebo (n=58)	35 (64%)	-
Per-Protocol (by applicator staining)		
LACTIN-V (n=112)	45 (45%)	0.71 (0.52, 0.96)
Placebo (n=54)	32 (63%)	

Additional Detection of *L. crispatus* CTV-05 Results

Table S3: Detection of *Lactobacillus crispatus* CTV-05 among participants randomized to the LACTIN-V arm compared by product compliance, menses and condomless sex at 12-week and 24-week visits

Variable	Detection of *L. crispatus* CTV-05	RR (95% CI)
Product compliance at 12-weeks		
≥75% of doses (n=116)	91 (78%)	1.07 (0.78, 1.47)
<75% of doses (n=15)	11 (73%)	-
Product compliance at 24-weeks		
≥75% of doses (n=108)	52 (48%)	1.04 (0.56, 1.94)
<75% of doses (n=13)	6 (46%)	-
Effect of menses since last visit at 12-weeks		
History of menses (n=98)	74 (76%)	0.89 (0.74,1.07)
No history of menses (n=33)	28 (85%)	-
Effect of menses since last visit at 24-weeks		
History of menses (n=98)	45 (46%)	0.81 (0.53, 1.23)
No history of menses (n=23)	13 (57%)	-
History of condomless sex at 12-weeks		
Condomless sex (n = 49)	38 (78%)	0.99 (0.82, 1.20)
Abstinence or sex with condom (n = 82)	64 (78%)	
History of condomless sex at 24-weeks		
Condomless sex (n = 44)	19 (43%)	0.85 (0.57, 1.28)
Abstinence of sex with condom (n = 77)	39 (51%)	

Additional Safety Results (see Table S8 for additional details)
None of the participants with a severe grade 3 AE or the participant with a serious AE (multiple lower limb fractures after a hiking accident) were classified as related to study product.

In the LACTIN-V group three participants experienced a severe unrelated AE, one subject reported upper limb fracture, and two became pregnant and reported spontaneous abortions. Study treatment was withdrawn for the two participants who experienced spontaneous abortions.

One SAE was reported for a participant in the LACTIN-V arm, multiple lower limb fractures after a fall during a hike on Study Day 155, requiring prolonged hospitalization for surgical correction. The SAE was considered resolved after 7 days and not related to study treatment.

In the placebo group three subjects experienced severe unrelated AEs: one subject was diagnosed with type 2 diabetes mellitus, one subject underwent an ovarian cystectomy, and one subject was diagnosed with severe hypertension.

Additional Safety Tables

Table S4: Number and Percentage of Subjects Experiencing Solicited Local Events by Symptom, Maximum Severity, and Treatment Group - Safety Population

		LACTIN-V (N=141)			Placebo (N=66)		
Solicited Adverse Event	**Severity[a]**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Solicited Local Event[b]	None	17	12	7.4, 18.6	7	11	4.8, 20.1
	Mild	58	41	33.2, 49.6	23	35	23.9, 46.9
	Moderate	66	47	38.6, 55.4	36	55	42.3, 66.4
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Vaginal bleeding other than menstruation	None	103	73	65.0, 80.0	44	67	54.6, 77.7
	Mild	33	23	16.8, 31.1	19	29	18.5, 40.8
	Moderate	5	4	1.4, 7.9	3	5	1.3, 12.4
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Abnormal vaginal discharge	None	46	33	25.0, 40.7	20	30	20.1, 42.3
	Mild	59	42	33.8, 50.4	23	35	23.9, 46.9
	Moderate	36	26	18.6, 33.2	23	35	23.9, 46.9
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Abnormal vaginal odor	None	61	43	35.0, 51.8	32	48	36.2, 60.7
	Mild	50	35	27.9, 43.9	14	21	12.4, 32.4
	Moderate	30	21	15.0, 28.9	20	30	20.1, 42.3
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Genital itching	None	54	38	30.4, 46.8	32	48	36.2, 60.7
	Mild	42	30	22.5, 37.9	19	29	18.5, 40.8
	Moderate	45	32	24.6, 40.0	15	23	14.0, 34.6
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Genital burning	None	93	66	57.7, 73.6	47	71	59.2, 81.5
	Mild	26	18	12.5, 25.7	7	11	4.8, 20.1
	Moderate	22	16	10.3, 22.5	12	18	10.1, 29.3
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
External genital irritation	None	79	56	47.5, 64.3	46	70	57.7, 79.9
	Mild	34	24	17.5, 31.8	12	18	10.1, 29.3
	Moderate	28	20	13.9, 27.2	8	12	5.4, 22.3
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
External genital swelling	None	111	79	71.1, 85.0	56	85	74.5, 92.2
	Mild	15	11	6.1, 16.8	5	8	3.0, 16.2
	Moderate	15	11	6.1, 16.8	5	8	3.0, 16.2
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4

		LACTIN-V (N=141)			Placebo (N=66)		
Solicited Adverse Event	**Severity[a]**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Genital rash	None	120	85	78.2, 90.3	59	89	79.9, 95.2
	Mild	13	9	5.0, 15.0	4	6	2.1, 14.7
	Moderate	8	6	2.5, 10.7	3	5	1.3, 12.4
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4

Notes: Denominator for percentages is the number of subjects in the Safety Population (N) with solicited adverse event data available after the first dose of study product.

[a]Each subject's maximum severity is reported for each solicited adverse event across all doses.

[b]Subjects are classified by their worst severity across all AEs

95% CI=95% Blaker Confidence Interval.

Table S5: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom and Treatment Group - Safety Population

		LACTIN-V (N=141)			Placebo (N=66)		
Category	**Solicited Adverse Event**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Solicited Adverse Events	Any Solicited Adverse Event	130	92	86.7, 95.9	60	91	81.5, 96.0
Solicited Local Adverse Events	Any Local Adverse Event	124	88	81.4, 92.6	59	89	79.9, 95.2
	Vaginal bleeding	38	27	20.0, 35.0	22	33	22.3, 45.4
	Abnormal vaginal discharge	95	67	59.3, 75.0	46	70	57.7, 79.9
	Abnormal vaginal odor	80	57	48.2, 65.0	34	52	39.3, 63.8
	Genital itching	87	62	53.2, 69.6	34	52	39.3, 63.8
	Genital burning	48	34	26.4, 42.3	19	29	18.5, 40.8
	External genital irritation	62	44	35.7, 52.5	20	30	20.1, 42.3
	External genital swelling	30	21	15.0, 28.9	10	15	7.8, 25.5
	Genital rash	21	15	9.7, 21.8	7	11	4.8, 20.1
Solicited Systemic Adverse Events	Any Systemic Adverse Event	87	62	53.2, 69.6	38	58	45.4, 69.2
	Nausea	26	18	12.5, 25.7	8	12	5.4, 22.3
	Vomiting	15	11	6.1, 16.8	7	11	4.8, 20.1
	Abdominal pain/cramps	59	42	33.8, 50.4	27	41	29.3, 53.1
	Diarrhea	31	22	15.8, 29.7	12	18	10.1, 29.3
	Constipation	34	24	17.5, 31.8	6	9	4.0, 18.5
	Pain/burning with urination	29	21	14.3, 27.9	8	12	5.4, 22.3
	Frequent urination	36	26	18.6, 33.2	13	20	11.5, 30.8
	Blood in urine	6	4	1.9, 9.0	0	0	0.0, 5.4
	Headache	48	34	26.4, 42.3	16	24	14.7, 36.2

Table S6: Number and Percentage of Subjects Experiencing Solicited Systemic Events by Symptom, Maximum Severity, and Treatment Group - Safety Population

		LACTIN-V (N=141)			Placebo (N=66)		
Solicited Adverse Event	**Severity[a]**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Solicited Systemic Event	None	54	38	30.4, 46.8	28	42	30.8, 54.6
	Mild	41	29	21.8, 37.2	17	26	16.2, 37.7
	Moderate	46	33	25.0, 40.7	21	32	21.4, 43.9
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Nausea	None	115	82	74.3, 87.5	58	88	77.7, 94.6
	Mild	17	12	7.4, 18.6	5	8	3.0, 16.2
	Moderate	9	6	3.2, 11.5	3	5	1.3, 12.4
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Vomiting	None	126	89	83.2, 93.9	59	89	79.9, 95.2
	Mild	12	9	4.7, 14.3	4	6	2.1, 14.7
	Moderate	3	2	0.6, 6.1	3	5	1.3, 12.4
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Abdominal pain/cramps	None	82	58	49.6, 66.2	39	59	46.9, 70.7
	Mild	34	24	17.5, 31.8	13	20	11.5, 30.8
	Moderate	25	18	12.0, 25.0	14	21	12.4, 32.4
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Diarrhea	None	110	78	70.3, 84.2	54	82	70.7, 89.9
	Mild	18	13	7.9, 19.3	8	12	5.4, 22.3
	Moderate	13	9	5.0, 15.0	4	6	2.1, 14.7
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Constipation	None	107	76	68.2, 82.5	60	91	81.5, 96.0
	Mild	22	16	10.3, 22.5	4	6	2.1, 14.7
	Moderate	12	9	4.7, 14.3	2	3	0.5, 10.1
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Pain/burning with urination	None	112	79	72.1, 85.7	58	88	77.7, 94.6
	Mild	17	12	7.4, 18.6	3	5	1.3, 12.4
	Moderate	12	9	4.7, 14.3	5	8	3.0, 16.2
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Frequent urination	None	105	74	66.8, 81.4	53	80	69.2, 88.5
	Mild	24	17	11.5, 24.0	5	8	3.0, 16.2
	Moderate	12	9	4.7, 14.3	8	12	5.4, 22.3
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4

		LACTIN-V (N=141)			Placebo (N=66)		
Solicited Adverse Event	**Severity[a]**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Blood in urine	None	135	96	91.0, 98.1	66	100	94.6, 100.0
	Mild	4	3	1.0, 6.8	0	0	0.0, 5.4
	Moderate	2	1	0.3, 5.0	0	0	0.0, 5.4
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4
Headache	None	93	66	57.7, 73.6	50	76	63.8, 85.3
	Mild	24	17	11.5, 24.0	10	15	7.8, 25.5
	Moderate	24	17	11.5, 24.0	6	9	4.0, 18.5
	Severe	0	0	0.0, 2.5	0	0	0.0, 5.4

Notes: Denominator for percentages is the number of subjects in the Safety Population (N) with solicited adverse event data available after the first dose of study product.
[a]Each subject's maximum severity is reported for each solicited adverse event across all doses.
[b]Subjects are classified by their worst severity across all AEs
95% CI=95% Blaker Confidence Interval.

Table S7: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events with 95% Confidence Intervals by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

		LACTIN-V (N=151)				Placebo (N=76)			
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**95% CI**	**Freq**	**n**	**%**	**95% CI**	**Freq**
Any SOC	Any PT	63	42	34.0, 50.0	104	22	29	19.4, 40.0	31
Cardiac disorders	Any PT	2	1	0.2, 4.7	3	1	1	0.1, 6.8	1
	Tachycardia	2	1	0.2, 4.7	3	1	1	0.1, 6.8	1
Eye disorders	Any PT	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Eye inflammation	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
Gastrointestinal disorders	Any PT	3	2	0.5, 5.7	4	0	0	0.0, 4.7	0
	Dyspepsia	1	<1	0.0, 3.4	2	0	0	0.0, 4.7	0
	Food poisoning	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Toothache	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
General disorders and administration site conditions	Any PT	4	3	0.9, 6.4	4	3	4	1.1, 10.7	4
	Pyrexia	4	3	0.9, 6.4	4	3	4	1.1, 10.7	4
Infections and infestations	Any PT	35	23	16.9, 30.7	55	13	17	9.8, 27.4	16
	Bronchitis	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Chlamydial infection	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Cystitis	0	0	0.0, 2.4	0	1	1	0.1, 6.8	1
	Diarrhoea infectious	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Ear infection	1	<1	0.0, 3.4	1	1	1	0.1, 6.8	1
	Genital herpes	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Gonorrhoea	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Gynaecological chlamydia infection	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Influenza	0	0	0.0, 2.4	0	1	1	0.1, 6.8	1
Infections and infestations	Laryngitis	0	0	0.0, 2.4	0	1	1	0.1, 6.8	1
	Lymphangitis	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Pharyngitis	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Pharyngitis streptococcal	0	0	0.0, 2.4	0	1	1	0.1, 6.8	1
	Pneumonia	0	0	0.0, 2.4	0	1	1	0.1, 6.8	1
	Respiratory tract infection	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Sinusitis	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Staphylococcal infection	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Subcutaneous abscess	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Tinea infection	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Tooth infection	2	1	0.2, 4.7	2	0	0	0.0, 4.7	0

	Trichomoniasis	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Urinary tract infection	4	3	0.9, 6.4	5	2	3	0.5, 8.8	2
	Viral infection	2	1	0.2, 4.7	2	0	0	0.0, 4.7	0
	Vulvovaginal candidiasis	14	9	5.4, 15.0	16	3	4	1.1, 10.7	3
	Vulvovaginal mycotic infection	11	7	3.8, 12.4	15	5	7	2.6, 14.7	5
Injury, poisoning and procedural complications	Any PT	3	2	0.5, 5.7	4	1	1	0.1, 6.8	1
	Animal bite	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Fall	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Lower limb fracture	1	<1	0.0, 3.4	1	0	0	0.0, 4.7	0
	Upper limb fracture	1	<1	0.0, 3.4	1	1	1	0.1, 6.8	1

Table S8: Subjects Reporting Unsolicited Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

MedDRA System Organ Class	MedDRA Preferred Term	LACTIN-V (N=151)	Placebo (N=76)
Infections and infestations	Vulvovaginal candidiasis	14 (9.3%)	3 (3.9%)
	Vulvovaginal mycotic infection	11 (7.3%)	5 (6.6%)
Vascular disorders	Hypertension	11 (7.3%)	4 (5.2%)

Notes: Denominator for percentages is the number of subjects in the Safety Population

Table S9: Listing of Severe Adverse Events, Including Single Serious Adverse Event (SAE)

Adverse Event	Study Day	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: LACTIN-V, **Subject ID:** STI.00311, **AE Number:** 001									
Spontaneous abortion	87	Severe	Not Related	Other: Probable spontaneous abortion	Drug withdrawn	N	Recovered/Resolved	Pregnancy, puerperium and perinatal conditions	Abortion spontaneous
Comments: None									
Treatment Group: LACTIN-V, **Subject ID:** STI.00414, **AE Number:** 001									
Elbow fracture	87	Severe	Not Related	Other: Accidental injury	Dose not changed	N	Recovered/Resolved	Injury, poisoning and procedural complications	Upper limb fracture
Comments: None									
Treatment Group: LACTIN-V, **Subject ID:** STI.00671, **AE Number:** 001									
Spontaneous abortion	37	Severe	Not Related	Other: Spontaneous abortion/miscarriage (<20weeks)	Drug withdrawn	N	Recovered/Resolved	Pregnancy, puerperium and perinatal conditions	Abortion spontaneous
Comments: As per protocol appendix B. Grade 3 for first trimester bleeding: spontaneous abortion.									
Treatment Group: Placebo, **Subject ID:** STI.00586, **AE Number:** 001									
Ovarian cyst removal	107	Severe	Not Related	Other: Ovarian cyst	Dose not changed	N	Recovered/Resolved	Surgical and medical procedures	Ovarian cystectomy
Comments: None									
Treatment Group: Placebo, **Subject ID:** STI.00905, **AE Number:** 004									
Type II diabetes	159	Severe	Not Related	Other condition/illness: Type II diabetes	Not applicable	N	Recovering/Resolving	Metabolism and nutrition disorders	Type 2 diabetes mellitus
Comments: Diagnosed 1 June 2018 with diabetes and started oral metformin. Under the care of her primary and monitored weekly in clinic and daily at home. Stable on medication.									
Treatment Group: Placebo, **Subject ID:** STI.01089, **AE Number:** 002									
Hypertension	176	Severe	Not Related	Other condition/illness: Preexisting hypertension	Not applicable	N	Not Recovered/Not Resolved	Vascular disorders	Hypertension
Comments: Clinician considered the condition stable at participant's last visit. Clinician also directed participant to follow up with her primary care physician the following week.									

Adverse Event	Study Day the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: LACTIN-V, **Subject ID:** STI.01085, **AE Number:** 001										
Multiple lower limb fractures	155	Persistent or significant disability/incapacity; Requires or prolongs hospitalization	Severe	Not Related	Other condition/ illness: Trauma	Not applicable	N	Recovered/ Resolved	Injury, poisoning and procedural complications	Lower limb fracture
Comments: Serious adverse event (SAE)										