Figure 1. Trial profile: design and subject allocation

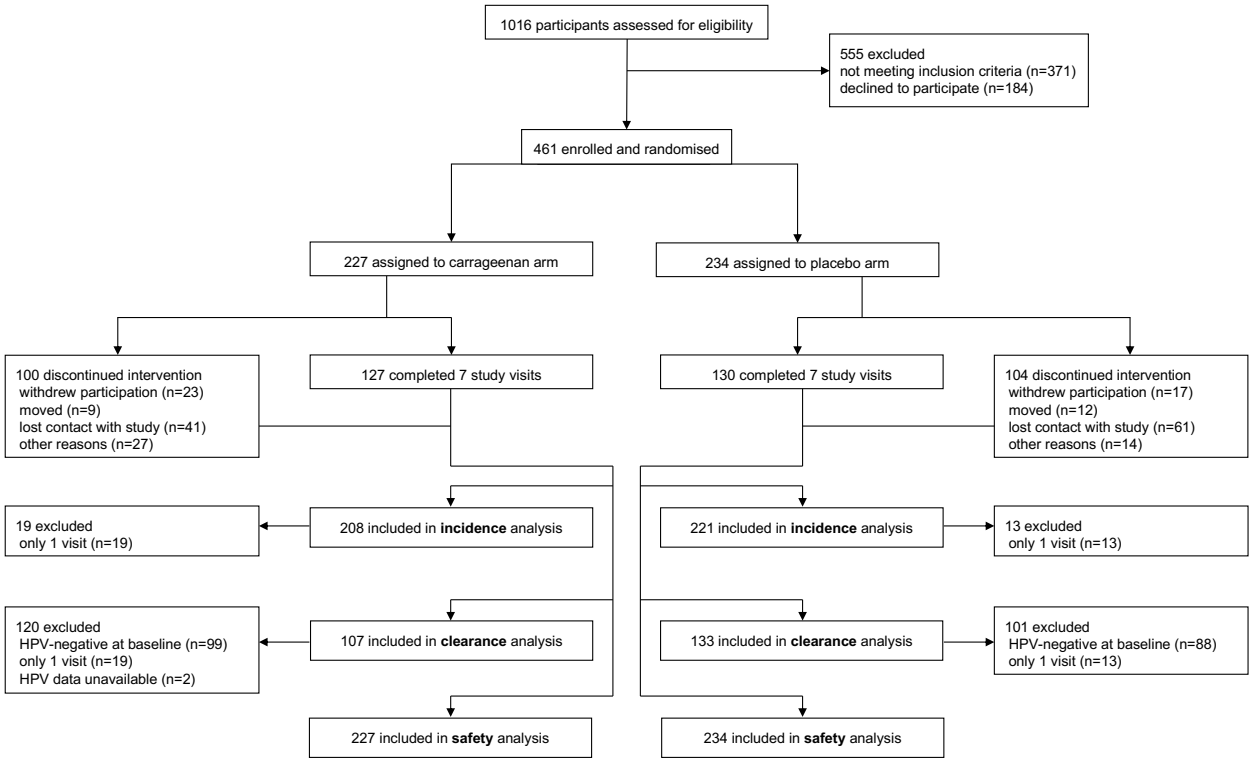

Figure 1 legend

The CONSORT flow diagram displays the total number of participants assessed for eligibility who were subsequently enrolled and randomised into either the carrageenan or placebo arm. Reasons for exclusion and discontinuing the intervention are provided. A total of 429 participants were included in the incidence analyses, 240 in the clearance analyses, and 461 in the safety analysis.

Table 1. Baseline characteristics of participants, by study arm

	Carrageenan (n=227)	Placebo (n=234)
Age – years		
Mean (SD)	25·5 (7·4)	23·4 (5·4)
Median (IQR)	23·0 (7.4)	21·9 (5.3)
Range	18·3-68·5	18·1-44·2
Ethnicity, n (%)		
French Canadian	53 (23·4)	47 (20·1)
English Canadian	62 (27·3)	68 (29·1)
Black Canadian	14 (6·2)	15 (6·4)
Latin American	22 (9·7)	22 (9·4)
South Asian	9 (4.0)	7 (3·0)
East Asian	16 (7·1)	24 (10·3)
Other or not reported	51 (22·5)	51 (21·8)
Marital status, n (%)		
Single	145 (63·9)	160 (68·4)
Living with a partner or married	22 (9·7)	23 (9·8)
Divorced, separated, or widowed	60 (26·4)	51 (21·8)
Smoking status, n (%)[a]		
Never	157 (69·2)	147 (62·8)
Former	50 (22·0)	59 (25·2)
Current	19 (8·4)	27 (11·5)
Age at first intercourse, years		
Mean (SD)	17·5 (3·0)	16·9 (2·2)
Median (IQR)	17 (3)	17 (2)
Range	13-28	12-23
Not reported, n	5	5
Lifetime sex partners – quantiles, n (%)		
<5	61 (26·9)	60 (25·6)
5-7	43 (18·9)	35 (15·0)
8-11	37 (16·3)	47 (20·1)
12-20	47 (20·7)	50 (21·4)
≥ 21	39 (17·2)	42 (18·0)
No. of sex partners in the past month, n (%)[b]		
0	42 (18·5)	36 (15·5)
1	144 (63·4)	144 (61·8)
≥ 2	41 (18·1)	53 (22·8)
Anal intercourse in the past month, n (%)[c]		
Yes	25 (11·0)	26 (11·2)
No	202 (89·0)	206 (88·8)
HPV DNA status, n (%)		

Any HPV[d]	115 (50·7)	141 (60·3)
Negative	109 (48·0)	93 (39·7)
Missing PCR results[e]	3 (1·32)	0 (0)
Subgenus 1[f]	38 (17·0)	55 (23·5)
Subgenus 2[g]	96 (42·9)	114 (48·7)
Subgenus 3[h]	60 (26·8)	76 (32·5)
HPV vaccination status, n (%)		
Yes	97 (42·7)	120 (51·3)
No	130 (57·3)	114 (48·7)
Validated HPV vaccination status[i], n (%)		
Yes	47 (20.7)	61 (26.1)
No	64 (28.2)	63 (26.9)
Missing	116 (51.1)	110 (47.0)

Race categories with fewer than 5 participants in each group were collapsed to respect participants anonymity.
[a,b,c] Data were not reported by 2, 1, and 2 participants, respectively.
[d] Participant tested positive for at least 1 of 36 HPV types.
[e] Missing results correspond to invalid or mishandled samples.
[f] Subgenus 1 group includes HPVs 6, 11, 40, 42, 44, and 54.
[g] Subgenus 2 group includes HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, and 82.
[h] Subgenus 3 group includes HPVs 61, 62, 71, 72, 81, 83, 84, and 89.
[i] Details of the validation of participants' vaccination status can be found in Supplmentary section 2 (Figure 2 and Tables 2A-2C).
SD: standard deviation, IQR: interquartile range, PCR: polymerase chain reaction, HPV: human papillomavirus, DNA: deoxyribonucleic acid.

Table 2. Incidence of any HPV infection and grouped infections at the participant- and HPV-level, by study arm

Analysis level	HPV infection grouping	Carrageenan				Placebo				Effect estimate
		N incident/ N at risk (%)	Actuarial mean[a] (95% CI)	Arithmetic mean[a] (95% CI)	Median[a] (95% CI)	N Incident/ N at risk (%)	Actuarial mean[a] (95% CI)	Arithmetic mean[a] (95% CI)	Median[a] (95% CI)	Hazard ratio (95% CI)
Participant	Any HPV	108/208 (51·9)	12·6[b] (10·6-14·7)	4·8 (3·8-5·7)	11·3 (6·2-14·3)	147/221 (66·5)	8·7[b] (7·1-10·3)	3·5 (2·8-4·2)	3·7 (3·0-6·0)	0·63 (0·49-0·81)
	Subgenus 1[c]	33/208 (15·9)	24·8[b] (22·9-26·7)	6·6 (4·8-8·3)	NR	56/221 (25·3)	22·7[b] (20·5-24·8)	5·3 (4·0-6·6)	NR (17·8-)[d]	0·58 (0·38-0·89)
	Subgenus 2[e]	84/208 (40·4)	16·1[b] (13·8-18·4)	5·0 (3·8-6·1)	14·9 (12·6-)[d]	124/221 (56·1)	11·1 (9·3-12·9)	4·4 (3·6-5·3)	8·6 (6.0-12.0)	0·61 (0·46-0·81)
	Subgenus 3[f]	55/208 (26·4)	20·7[b] (18·3-23·1)	5·7 (4·2-7·3)	23·7 (20·1-)[d]	79/221 (35·8)	19·2[b] (16·8-21·6)	5·5 (4·4-6·5)	22·4 (13·6-)[d]	0·70 (0·50-0·99)
HPV	Any HPV[g]	278/7,217 (3·9)	29·1[b] (28·9-29.3)	6·7 (6·0-7·3)	NR	438/7,586 (5·8)	29·7[b] (29·4-29·9)	6·4 (5·9-6·9)	NR	0·65 (0·50-0·83)

[a] Time in months. The actuarial mean accounts for censoring, whereas the arithmetic mean excludes participants who did not acquire a new HPV type.
[b] Mean was underestimated since the largest observed analysis time was censored.
[c] Subgenus 1 includes HPVs 6, 11, 40, 42, 44, and 54.
[d] Upper confidence limit was undetermined since the survival function did not fall below 0·5.
[e] Subgenus 2 includes HPVs 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, and 82.
[f] Subgenus 3 includes HPVs 61, 62, 71, 72, 81, 83, 84, and 89.
[g] Proportional hazards Cox regression models account for all incident HPV infections acquired over follow-up. Participants were considered at risk for any HPV type absent at baseline. Each participant could contribute up to 36 observations, each corresponding to an HPV type. The unit of analysis was each individual HPV type.
CI: confidence interval, HPV: human papillomavirus, NR: not reached, N: number

Table 3. Clearance, according to outcome and definition, of any HPV infection at the participant- and HPV-level, by study arm

Analysis level	Outcome	Clearance definition[a]	Carrageenan				Placebo				Effect estimate
			N cleared/ N at risk (%)	Actuarial mean[b] (95% CI)	Arithmetic mean[b] (95% CI)	Median[b] (95% CI)	N cleared/ N at risk (%)	Actuarial mean[b] (95% CI)	Arithmetic mean[b] (95% CI)	Median[b] (95% CI)	Hazard ratio (95% CI)
Participant	Time to clearance of all HPV types[c]	Liberal	62/107 (57·9)	10·0 (8·4-11·6)	5·4 (4·8-5·9)	9·3 (6·4-11·0)	66/133 (49·6)	13·0 (10·9-15·0)	5·8 (5·2-6·4)	11·1 (9·5-13·4)	1·41 (0·99-2·00)
		Conservative	34/107 (31·8)	14·8[d] (13·0-16·6)	5·7 (5·0-6·5)	16·0 (10·5-NR)	39/133 (29·3)	19·3 (16·8-21·7)	6·2 (5·4-7·0)	28·9 (13·6-NR)	1·16 (0·73-1·84)
	Time to first cleared HPV infection[e]	Liberal	85/107 (79·4)	4·7[d] (3·6-5·8)	5·0 (4·6-5·5)	3·0 (1·2-4·1)	105/133 (79·0)	4·8 (3·9-5·7)	5·4 (4·9-5·8)	3·2 (1·6-4·0)	1·03 (0·77-1·38)
		Conservative	67/107 (62·6)	6·8[d] (5·4-8·1)	5·4 (4·9-6·0)	6·0 (4·1-6·5)	81/133 (60·9)	7·6[d] (6·1-9·2)	5·7 (5·2-6·2)	5·8 (3·2-6·9)	1·04 (0·75-1·44)
HPV	Time to clearance of an individual HPV type[f]	Liberal	181/271 (66·8)	0.24 (0.2-0.3)	5.0 (4.2-5.7)	0.20 (0.1-0.2)	243/370 (65·7)	0.29 (0.26-0.32)	5.9 (5.3-6.5)	0.23 (0.21-0.25)	1·17 (0·90-1·51)
		Conservative	122/271 (45·0)	0.38[d] (0.3-0.4)	5.1 (4.4-5.9)	0.31 (0.3-0.4)	169/370 (45·7)	0.45 (0.40-0.50)	5.6 (4.8-6.3)	0.34 (0.27-0.38)	1·10 (0·84-1·43)

[a] Liberal clearance was defined as having a single HPV-negative visit following ≥ 1 HPV-positive visit(s). Conservative clearance was defined as having ≥ 2 consecutive HPV-negative visits following ≥ 1 HPV-positive visit(s).
[b] Time in months. The actuarial mean accounts for censoring, whereas the arithmetic mean excludes participants who did not acquire a new HPV type.
[c] Time to clearance of all baseline HPV infections (i.e., clearance was considered to have occurred once all baseline HPV infections cleared).
[d] Mean was underestimated since the largest observed analysis time was censored.
[e] Time to clearance of the first baseline HPV infection (i.e., clearance was considered to have occurred once the first of any baseline HPV infections cleared).
[f] Proportional hazards Cox regression models account for all baseline HPV types that cleared over follow-up. Participants were considered at risk for clearing any HPV type present at baseline. Each participant could contribute up to 36 observations, each corresponding to an HPV type. The unit of analysis was each individual HPV type.
CI: confidence interval, HPV: human papillomavirus, NR: not reached, N: number.

Table 4. Adverse events [n (%)] reported through different sources, overall and by study arm

	Overall (n=461)	Carrageenan (n=227)	Placebo (n=234)	+ (more AE in CG arm)
Any adverse event reported, overall[a]	**172 (37·3)**	**79 (34·8)**	**93 (39·7)**	
1. Daily calendar[b]	**76 (17·6)**	**37 (17·8)**	**39 (17·3)**	
Unusually heavy or painful period	9 (2·1)	1 (0·5)	8 (3·6)	
Vaginal bleeding in between menstrual periods	14 (3·2)	6 (2·9)	8 (3·6)	
Pain during vaginal sex[c]	19 (4·8)	13 (6·9)	6 (2·9)	+
Unusual vaginal discharge	15 (3·5)	11 (5·3)	4 (1·8)	+
Itching, burning, or pain in the genital area	42 (9·7)	23 (11·1)	19 (8·4)	+
Genital sore/ulcer	5 (1·2)	2 (1·0)	3 (1·3)	
Needing to urinate more often than usual	10 (2·3)	3 (1·4)	7 (3·1)	
Pain while urinating	9 (2·1)	6 (2·9)	3 (1·3)	+
Blood in urine	4 (0·9)	3 (1·4)	1 (0·4)	+
Lower abdominal pain	8 (1·9)	5 (2·4)	3 (1·3)	+
Lower back pain not caused by physical exertion	2 (0·5)	0 (0)	2 (0·9)	
Other[d]	42 (9·7)	21 (10·1)	21 (9·3)	+
2.1 Follow-up survey[e]	**55 (13·0)**	**24 (11·7)**	**31 (14·2)**	
Gel use caused discomfort/adverse reactions to participant	49 (11·6)	22 (10·7)	27 (12·4)	
Gel use caused discomfort/adverse reactions to partner	10 (2·4)	5 (2·4)	5 (2·3)	+
2.2 Follow-up survey, conditions[f]	**91 (21·3)**	**43 (20·7)**	**48 (21·8)**	
Vaginal yeast infection	70 (16·5)	35 (17·0)	35 (16·0)	+
Trichomonas vaginal infection	6 (1·4)	3 (1·5)	3 (1·4)	+
Venereal warts, condyloma, or HPV	10 (2·3)	5 (2·4)	5 (2·3)	+
Chlamydia	12 (2·8)	6 (2·9)	6 (2·7)	+
Genital herpes	8 (1·9)	3 (1·4)	5 (2·3)	
Syphilis	4 (0·9)	2 (1·0)	2 (0·9)	+
Gonorrhea	4 (0·9)	2 (1·0)	2 (0·9)	+
Ulcers or genital sores	5 (1·2)	2 (1·0)	3 (1·4)	
Human immunodeficiency virus	4 (0·9)	2 (1·0)	2 (0·9)	+
Hepatitis B	4 (0·9)	2 (1·0)	2 (0·9)	+
Bacterial vaginosis	24 (5·6)	11 (5·3)	13 (5·9)	
3. Adverse event module (nurse report)[g]	**75 (16·3)**	**38 (16·7)**	**37 (15·8)**	+
Unusually heavy or painful period	6 (1·3)	1 (0·4)	5 (2·1)	
Vaginal bleeding in between menstrual periods	13 (2·8)	5 (2·2)	8 (3·4)	
Pain during vaginal sex	18 (3·9)	12 (5·3)	6 (2·6)	+
Unusual vaginal discharge	14 (3·0)	10 (4·4)	4 (1·7)	+
Itching, burning, or pain in the genital area	43 (9·3)	24 (10·6)	19 (8·1)	+
Genital sore/ulcer	5 (1·1)	2 (0·9)	3 (1·3)	
Needing to urinate more often than usual	8 (1·7)	3 (1·3)	5 (2·1)	
Pain while urinating	9 (2·0)	6 (2·6)	3 (1·3)	+
Blood in urine	4 (0·9)	3 (1·3)	1 (0·4)	+
Lower abdominal pain	6 (1·3)	4 (1·8)	2 (0·9)	+
Lower back pain not caused by physical exertion	2 (0·4)	0 (0)	2 (0·9)	
Other[d]	25 (5·4)	11 (4·9)	14 (6·0)	
4. Adverse event follow-up[g]	**20 (4·3)**	**9 (4·0)**	**11 (4·7)**	

The percentage of adverse events was calculated as the number of participants affected by an AE divided by the number of participants who ever responded to the question. The protocol did not specify conditions would be included as AE.

[a] 15 participants in the carrageenan and 5 participants in the placebo arm never provided any information about adverse events. These participants only had 1 visit. However, these 20 participants were included in the calculation of any adverse reported overall, as for two sources (Adverse event module [nurse report] and (Adverse event follow-up), due to the nature of reporting, we used an inferred denominator that included all participants randomized.

[b] 28 participants were not included: 19 participants in the carrageenan arm and 9 participants in the placebo group never filled out the calendar.

[c] 63 participants were not included: 19 participants in the carrageenan and 16 participants in the placebo arm did not report intercourse, and 19 participants in the carrageenan arm and 9 participants in the placebo group never filled out the calendar.

[d] Other AEs reported included burning, irritation, urinary tract infection, spotting, and yeast infection among others.

[e] 37 participants were not included: 32 participants did not have a follow-up visit (19 in the carrageenan and 13 in the placebo group) and 5 participants (2 in the carrageenan arm and 3 in the placebo arm) did not respond to these questions in the follow-up survey.

[f] 33 participants were not included overall: 32 participants did not have a follow-up visit (19 in the carrageenan and 13 in the placebo group) and 1 participant (1 in the placebo group) did not respond to any of these questions in the follow-up survey.

[g] Due to the nature of reporting we used an inferred denominator, which included all participants randomized.

N: number of participants affected, +: a greater proportion of adverse events were reported in the carrageenan arm relative to the placebo arm, AE: adverse event, HPV: human papillomavirus.