**Supplementary Table 1.** Study design and comparison of protocols 013, 015 and 019.(1, 2, 7)

|  |  |  |  |
| --- | --- | --- | --- |
| Design feature | Protocol 013 | Protocol 015 | Protocol 019 |
| General |  |  |  |
| Number randomized to placebo arm | 2732 | 6080 | 1908 |
| Study dates | 2001–2007 | 2002–2007 | 2004–2009 |
| Study design | International, multicenter, double-blind, prospective parallel trial |
| Study vaccine and regimen | Quadrivalent vaccine or placebo; 0, 2, 6 months |
| Visit schedule | Months 0, 3, 7, 12, 18, 24, 30, 36, and 48 | Months 0, 7, 12, 24, 36, and 48 | Months 0, 7, 12, 18, 24, 30, 36, and 48 |
| Inclusion/exclusion criteria |  |  |  |
| Age, years | 16–23 | 15–26 | 24–45 |
| Lifetime no. of male sex partners | 0–4 | 0–4\* | ≥1† |
| Previous abnormal Pap test result or HPV disease | Not allowed‡ | Not allowed‡ | No prior hysterectomy. No cervical biopsy within past 5 years‡ |
| Cervical cancer screening |  |  |  |
| Pap test screening interval | Every 6 months | Every 12 months | Every 6 months |
| Screening triage strategy | Mandatory |
| Pap test referral threshold | ASCUS or HPV positive on HC2 |
| Colposcopy, biopsy, and LEEP |  |
| Requirement for biopsy | All abnormal areas |
| Pathology interpretation (end points) | Blinded pathology panel |
| HPV causality assessment | PCR assay on paraffin-embedded specimens |
| LEEP tissue analyzed | Entire LEEP specimen |

\*Protocol 015 recruited women who, at enrollment (day 1), reported having had 0-4 sex partners during their lifetime, with the exception of Finland (that enrolled 872 women in the vaccine group and 873 women in the placebo group), which had no such restriction.

†Virgins were excluded from the study, with the exception of those women who were seeking contraception at the time of enrollment or who had recently obtained contraception.

‡In Protocols 013 and 015, women were not eligible to participate if they had a history of genital warts or abnormal results on cervical cytologic testing. In Protocol 019 women were not eligible to participate if they had a history of genital warts or if they had undergone hysterectomy. Women with any previous cervical surgical procedure and those having undergone a cervical biopsy within the past 5 years were also excluded in Protocol 019. In each study, there was no exclusion on the basis of current/ongoing infection or disease (i.e., subjects who had an abnormal Pap test result at day 1 were enrolled); subjects with visible genital warts were not enrolled.

**Supplementary Table 2.** Selected Characteristics at Baseline by Histologic Diagnosis\*.

|  | Women aged 15 to 26 (Protocols 013 and 015) |  | Women aged 24 to 45 (Protocol 019) |
| --- | --- | --- | --- |
| Baseline Characteristic | NormalN = 7,294n (%) | CIN1N = 676n (%) | CIN2N = 226n (%) | CIN3n = 284n (%) | AISN = 16n (%) |  | NormalN = 1,739n (%) | CIN1N = 102n (%) | CIN2N = 21n (%) | CIN3N = 29n (%) | AISN = 4n (%) |
| Age by 5 year categories - years  |
| 16-20  | 3,904 (54) | 420 (62) | 146 (65) | 169 (60) | 9 (56) |  | NA | NA | NA | NA | NA |
| 21-24  | 3,366 (46) | 255 (38) | 79 (35) | 115 (40) | 7 (44) |  | NA | NA | NA | NA | NA |
| 24-29  | NA | NA | NA | NA | NA |  | 477 (27) | 49 (48) | 10 (48) | 6 (21) | 0 (0) |
| 30-34  | NA | NA | NA | NA | NA |  | 381 (2) | 15 (15) | 4 (19) | 8 (28) | 1 (25) |
| 35-39  | NA | NA | NA | NA | NA |  | 417 (24) | 24 (24) | 3 (14) | 10 (34) | 1 (25) |
| 40-45  | NA | NA | NA | NA | NA |  | 464 (27) | 14 (14) | 4 (19) | 5 (17) | 2 (50) |
| Region |
| North America  | 1,052 (14) | 100 (15) | 37 (16) | 25 (9) | 0 (0) |  | 260 (15)  | 10 (10)  | 2 (10)  | 0 (0)  | 0 (0)  |
| Europe | 3,780 (52) | 279 (41) | 104 (46) | 176 (62) | 11 (69) |  | 214 (12)  | 11 (11)  | 1 (5)  | 6 (21)  | 1 (25)  |
| Latin America  | 2,159 (30) | 274 (41) | 72 (32) | 74 (26) | 5 (31) |  | 716 (41)  | 58 (57)  | 14 (67)  | 9 (31)  | 2 (50)  |
| Asia/Pacific  | 303 (4) | 23 (3) | 13 (5) | 9 (3) | 0 (0) |  | 549 (32)  | 23 (23)  | 4 (19)  | 14 (48)  | 1 (25)  |
| Smoking Status  |
| Current  |  1,856 (25)  | 237 (35)  |  79 (35)  |  103 (36)  |  7 (44)  |  |  298 (17)  |  19 (19)  |  5 (24)  |  298 (17)  |  1 (25)  |
| Former  |  591 (8)  |  46 (7)  |  20 (9)  |  18 (6)  |  0 (0)  |  |  139 (8)  |  5 (5)  |  1 (5)  |  139 (8)  |  0 (0)  |
| Never  | 4,846 (66)  | 393 (58)  |  127 (56)  |  163 (57)  |  9 (56)  |  |  1,302 (75)  |  78 (76)  |  15 (71)  | 1,302 (75)  |  3 (75)  |
| Age at first intercourse, years |
| ≤17  | 4,531 (67)  | 475 (72)  |  162 (75)  |  207 (75)  | 14 (88)  |  |  686 (40)  |  42 (41)  |  10 (48)  |  12 (41)  |  1 (25)  |
| 18-19  |  1,730 (25)  | 140 (21)  |  46 (21)  |  61 (22)  |  2 (13)  |  |  441 (25)  |  24 (24)  |  3 (14)  |  10 (34)  |  2 (50)  |
| 20-22  |  509 (7)  |  42 (6)  |  9 (4)  |  9 (3)  |  0 (0)  |  |  329 (19)  |  21 (21)  |  6 (29)  |  4 (14)  |  0 (0)  |
| ≥23  |  23 (0.3)  |  1 (0.1)  |  0 (0)  |  0 (0)  |  0 (0)  |  |  280 (16)  |  15 (15)  |  2 (10)  |  3 (10)  |  1 (25)  |
| Lifetime # sex partners |
| 1  |  2,486 (37)  | 180 (27)  |  46 (21)  |  59 (21)  |  0 (0)  |  |  703 (40)  |  31 (31)  |  6 (29)  |  9 (31)  |  2 (50)  |
| ≥ 2 | 4308 (63) | 478 (73) | 171 (79) | 218 (79) | 16 (100) |  | 1033 (60) | 70 (69) | 15 (71) | 20 (69) | 2 (50) |
| 2-3  |  3,107 (46)  | 339 (52)  |  104 (48)  |  140 (51)  |  7 (44)  |  |  519 (30)  |  39 (39)  |  8 (38)  |  15 (52)  |  1 (25)  |
| ≥4  |  1,201 (18)  | 139 (21)  |  67 (31)  |  78 (28)  |  9 (56)  |  |  514 (30)  |  31 (31)  |  7 (33)  |  5 (17)  |  1 (25)  |
| # New sex partners in last 6 months |
| 0  | 4,848 (71)  | 414 (63)  |  125 (58)  |  178 (64)  |  7 (44)  |  |  1,588 (92)  |  86 (84)  |  16 (76)  |  27 (93)  |  4 (100)  |
| ≥ 1 | 1947 (29) | 244 (37) | 92 (42) | 99 (36) | 9 (56) |  | 146 (8) | 16 (16) | 5 (24) | 2 (7) | 0 (0) |
| 1  |  1,672 (25)  | 193 (29)  |  74 (34)  |  77 (28)  |  7 (44)  |  |  129 (7)  |  13 (13)  |  4 (19)  |  2 (7)  |  0 (0)  |
| 2-3  |  256 (4)  |  47 (7)  |  16 (7)  |  20 (7)  |  2 (13)  |  |  16 (1)  |  3 (3)  |  1 (5)  |  0 (0)  |  0 (0)  |
| ≥4  |  19 (0.3)  |  4 (1)  |  2 (0.1)  |  2 (1)  |  0 (0)  |  |  1 (0.06)  |  0 (0)  |  0 (0)  |  0 (0)  |  0 (0)  |
| Chlamydia/gonorrhea positive† |
| No  |  1,275 (94)  | 106 (90)  |  27 (93)  |  37 (97)  |  2 (67)  |  |  1,662 (97)  |  96 (94)  |  19 (90)  |  28 (97)  |  4 (100)  |
| Yes  |  84 (6)  |  12 (10)  |  2 (7)  |  1 (3)  |  1 (33)  |  |  57 (3)  |  6 (6)  |  2 (10)  |  1 (3)  |  0 (0)  |
| Pap results |
| Negative  | 6,476 (92) | 491 (75) | 142 (64) | 184 (66) | 10 (63) |  | 1,629 (96) | 66 (65) | 16 (76) | 12 (41) | 2 (50) |
| ASC-US  | 294 (4) | 48 (7) | 23 (10) | 27 (10) | 3 (19) |  | 42 (2) | 9 (9) | 3 (14) | 2 (7) | 0 (0) |
| LSIL  | 279 (4) | 106 (16) | 44 (20) | 42 (15) | 2 (13) |  | 28 (2) | 26 (25) | 1 (5) | 4 (14) | 0 (0) |
| ASC-H or HSIL  | 19 (0.3) | 12 (2) | 12 (5) | 23 (8) | 1 (6) |  | 3 (0.2) | 1 (1) | 1 (5) | 10 (34) | 2 (50) |
| AGC  | 2 (0.03) | 0 (0) | 0 (0) | 1 (0.4) | 0 (0) |  | 1 (0.06) | 0 (0) | 0 (0) | 1 (3) | 0 (0) |
| Baseline HPV Anogenital Infection‡ |
| 6/11  | 263 (4) | 51 (8) | 18 (8) | 28 (10) | 1 (6) |  | 31 (2) | 8 (8) | 0 (0) | 0 (0) | 0 (0) |
| 16/18  | 672 (9) | 121 (18) | 60 (27) | 112 (39) | 6 (38) |  | 72 (4) | 15 (15) | 2 (10) | 15 (52) | 2 (50) |
| 6/11/16/18  | 863 (12) | 156 (23) | 69 (31) | 125 (44) | 6 (38) |  | 97 (6) | 21 (21) | 2 (10) | 15 (52) | 2 (50) |
| 16/18/31/33/45/52/58  | 1,333 (18) | 247 (37) | 108 (48) | 172 (61) | 8 (50) |  | 197 (11) | 38 (37) | 8 (38) | 25 (86) | 2 (50) |
| 6/11/16/18/31/33/45/52/58  | 1,465 (20) | 263 (39) | 113 (50) | 178 (63) | 8 (50) |  | 214 (12) | 44 (43) | 8 (38) | 25 (86) | 2 (50) |
| 31/33/45/52/58 no 6/11/16/18  | 602 (8) | 107 (16) | 44 (19) | 53 (19) | 2 (13) |  | 117 (7) | 23 (23) | 6 (29) | 10 (34) | 0 (0) |

\*For CIN1, CIN2 and CIN3, the highest grade lesion for each women was used to assess the impact of baseline characteristics.

†Non-mandatory test at day 1 and performed at the discretion of the investigator

‡Categories are not mutually exclusive.