Human papillomavirus (HPV) infection can lead to significant disease in males, including anogenital warts, intraepithelial neoplasias, and several types of oral and anogenital cancers. The quadrivalent HPV (type 6/11/16/18) L1 virus-like particle (VLP) vaccine (qHPV vaccine; Gardasil) has recently been demonstrated to prevent persistent infection and associated disease related to vaccine HPV types in males. We report the overall immunogenicity results from a trial of the quadrivalent HPV vaccine in males. Overall, 3,463 heterosexual men and 602 men who had sex with men were enrolled into a randomized, placebo-controlled, double-blind safety, immunogenicity, and efficacy study. Serum samples were collected prior to vaccination at day 1 and at months 7, 24, and 36 postvaccination. Immunogenicity was evaluated with a multiplex, competitive Lumiox immunoassay. Almost all subjects (97.4 to 99.2%) seroconverted for vaccine HPV types by month 7. At month 36, 88.9%, 94.0%, 97.9%, and 57.0% of subjects were still seropositive for HPV-6, -11, -16, and -18, respectively. For all vaccine HPV types, black subjects had significantly higher antibody titers at month 7 than did both Caucasian and Asian subjects. An anamnestic antibody response was seen in men seropositive before vaccination. The vaccine was highly immunogenic in males 16 to 23 years of age; responses were comparable to those observed in women. Furthermore, the immune responses were consistent with the established efficacy of the vaccine in the prevention of incident and persistent HPV infection, anogenital warts, and anal intraepithelial neoplasia.
The estimated GMTs and associated CIs are calculated using an analysis of variance model with a term for vaccination group. Seroconversion percent is calculated as 100 × (n/\( m \)). The seroconversion CIs are computed based on exact methods. \( n \), number of subjects contributing to the analyses; \( m \), number of subjects with the indicated response.

### TABLE 1 Summary of anti-HPV geometric mean titers and seroconversion percentage over time

| Response   | Study time | \( n \)   | GMT (mMU/ml)          | 95% CI      | \( m \) | Seroconversion (%) | 95% CI |
|------------|------------|----------|-----------------------|-------------|-------|--------------------|-------|
| Anti-HPV-6 | Day 1      | 1,092    | \(<7\)                | \(<7, <7\)  | 0     | 0.0                | 0.0, 0.3 |
|            | Mo 7       | 1,092    | 144.6                | 422.6, 474.1 | 1,080 | 98.9              | 98.1, 99.4 |
|            | Mo 24      | 941      | 79.8                 | 75.8, 84.1  | 855   | 90.9              | 88.8, 92.6 |
|            | Mo 36      | 847      | 71.5                 | 67.5, 75.8  | 753   | 88.9              | 86.6, 90.9 |
| Anti-HPV-11| Day 1      | 1,092    | \(<8\)               | \(<8, <8\)  | 0     | 0.0                | 0.0, 0.3 |
|            | Mo 7       | 1,092    | 624.0                | 594.1, 655.4 | 1,083 | 99.2              | 98.4, 99.6 |
|            | Mo 24      | 941      | 94.6                 | 90.0, 99.5  | 900   | 95.6              | 94.1, 96.9 |
|            | Mo 36      | 847      | 82.6                 | 78.3, 87.1  | 796   | 94.0              | 92.2, 95.5 |
| Anti-HPV-16| Day 1      | 1,135    | \(<11\)              | \(<11, <11\) | 0     | 0.0                | 0.0, 0.3 |
|            | Mo 7       | 1,135    | 2,403.4              | 2,272.2, 2,544.0 | 1,121 | 98.8              | 97.9, 99.3 |
|            | Mo 24      | 979      | 342.7                | 324.7, 361.7 | 970   | 99.1              | 98.3, 99.6 |
|            | Mo 36      | 877      | 293.3                | 276.5, 311.2 | 859   | 97.9              | 96.8, 98.8 |
| Anti-HPV-18| Day 1      | 1,174    | \(<10\)              | \(<10, <10\) | 0     | 0.0                | 0.0, 0.3 |
|            | Mo 7       | 1,174    | 402.3                | 380.2, 425.7 | 1,143 | 97.4              | 96.3, 98.2 |
|            | Mo 24      | 1,011    | 38.4                 | 36.0, 41.0  | 630   | 62.3              | 59.2, 65.3 |
|            | Mo 36      | 905      | 33.1                 | 30.9, 35.4  | 516   | 57.0              | 53.7, 60.3 |

a The estimated GMTs and associated CIs are calculated using an analysis of variance model with a term for vaccination group. Seroconversion percent is calculated as 100 × (\( n \)/\( m \)). The seroconversion CIs are computed based on exact methods. \( n \), number of subjects contributing to the analyses; \( m \), number of subjects with the indicated response.

The primary immunogenicity analyses were conducted in a population of individuals who were seronegative and PCR negative for the relevant HPV type(s) at day 1, remained HPV PCR negative for the relevant HPV type(s) through 1 month post-dose 3 (month 7), received all 3 vaccinations within prespecified day ranges, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine. Importantly, subjects who were seropositive and/or PCR positive for a vaccine HPV type through month 7 could still be analyzed for the vaccine HPV type for which they were seronegative and PCR negative through month 7 (excluding HPV-6/11 seropositivity due to antibody cross-reactivity), assuming that all other population criteria were met. Additional analyses were conducted on all randomized participants to evaluate immune responses to vaccine comparing those who entered the study as HPV seronegative/DNA negative with those who entered the study as HPV seronegative/DNA negative for each respective HPV type.

The institutional review board at each participating center approved the protocol, and informed consent was obtained from all subjects. Studies were conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations protecting the rights and welfare of human subjects participating in biomedical research.

**Vaccine and randomization.** The quadrivalent HPV (types 6/11/16/18) L1 virus-like particle (VLP) vaccine (qHPV [Gardasil/Silgard; Merck & Co., Inc.]) with amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant and a visually indistinguishable AAHS-containing placebo have been described previously (14). Subjects were randomized 1:1 to receive qHPV vaccine or placebo at day 1, month 2 (+3 weeks), and month 6 (+4 weeks). Vaccine or placebo was administered as an 0.5-ml injection in the deltoid muscle.

A computer-generated allocation schedule was produced by the sponsor. Following informed consent and determination that all entry criteria were met, eligible subjects were randomized to a vaccination group. All investigators and site personnel, subjects, monitors, and laboratory personnel remained blinded to treatment allocation throughout the study. Staff of the sponsor were blinded from the study onset through the database lock for this analysis.

**Study measurements.** Immunogenicity evaluations focused on an assessment of immunogenicity at the completion of the vaccination regimen (4 weeks post-dose 3) and on characterizing the persistence of vaccine-induced anti-HPV-6,-11,-16, and -18 responses. Serum samples were collected prior to vaccination at day 1 and at months 7, 24, and 36. Immunogenicity was evaluated, including a description of peak and persistent anti-HPV-6,-11,-16, and -18 responses. The response of the immune system to the vaccine was measured with a multiplex, competitive Luminex immunoassay (anti-HPV-6, -11, -16, and -18 clIA; developed by Merck Research Laboratories, West Point, PA, using technology from the Luminex Corporation, Austin, TX) (9). Briefly, this assay can simultaneously quantitate neutralizing antibodies to human papillomavirus types 6, 11, 16, and 18 in 50 μl of serum. The HPV-Luminex competitive immunoassay measures titers of polyclonal antibodies in serum capable of displacing phycoerythrin-labeled detection monoclonal antibodies binding to conformationally sensitive, neutralizing epitopes on the respective virus-like particles. Dilution-corrected serostatus cutoffs were 20 milli-Merck units (mMU)/ml for HPV-6, 16 mMU/ml for HPV-11, 20 mMU/ml for HPV-16, and 24 mMU/ml for HPV-18 (epitopes H6.M48, K11.B2, H16.V5, and H18.J4 for HPV types 6, 11, 16, and 18, respectively).

**RESULTS**

Almost all subjects (>97.4%) seroconverted for vaccine HPV types by month 7, with anti-HPV-6/11/16/18 geometric mean titers (GMTs) reaching peak values 1 month after dose 3 (month 7) (Table 1). After month 7, a gradual decline in HPV-6/11/16/18 GMTs was observed. By month 7, a gradual decline in HPV-6/11/16/18 GMT was seen. However, by month 36, 88.9%, 94.0%, 97.9%, and 57.0% of subjects remained seropositive for HPV-6, -11, -16, and -18, respectively.

Vaccine immunogenicity at month 7 stratified by baseline subject characteristics can be seen in Table 2. For all vaccine HPV types, black subjects had significantly higher GMTs at month 7 than did both Caucasian and Asian subjects. HPV-18 GMTs for black subjects were also significantly higher than those of Hispanic American subjects. Only HPV-18 GMTs were significantly different between younger (age 15 to 20 years) and older (age 21 to 27 years) subjects, with the GMTs of younger subjects being higher (473.5 mMU/ml [95% confidence interval (CI), 427.5 to 524.6] versus 339.1 mMU/ml [95% CI, 304.7 to 377.3], respectively).
### Table 2: Vaccine Immunogenicity at Month 7 Stratified by Baseline Subject Characteristics

| Race       | HPV-6 GMT (mMU/ml) 95% CI | HPV-11 GMT (mMU/ml) 95% CI | HPV-16 GMT (mMU/ml) 95% CI | HPV-18 GMT (mMU/ml) 95% CI |
|------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Caucasian  |                           |                           |                           |                           |
|            | 378.0 (331.7, 430.8)      | 595.0 (537.1, 659.0)      | 1,902.3 (1,675.8, 2,159.5)|                           |
| Black      |                           |                           |                           |                           |
|            | 407.1 (340.4, 486.8)      | 607.3 (540.5, 677.0)      |                           |                           |
| Other      |                           |                           |                           |                           |
|            | 528.1 (462.7, 602.7)      | 646.3 (583.9, 715.4)      |                           |                           |
| Age (yr)   |                           |                           |                           |                           |
| 15–20      | 484.1 (435.9, 537.6)      | 669.1 (615.5, 727.5)      |                           |                           |
|            |                           |                           |                           |                           |
| 21–27      | 410.8 (370.7, 455.3)      | 578.0 (531.7, 628.4)      |                           |                           |
|            |                           |                           |                           |                           |
| Region     |                           |                           |                           |                           |
| Africa     | 623.1 (492.6, 788.2)      |                           |                           |                           |
| Asia-Pacific|                           |                           |                           |                           |
|            |                           |                           |                           |                           |
| North America|                           |                           |                           |                           |
| Europe     | 477.8                     |                           |                           |                           |
| Latin America|                           |                           |                           |                           |
| Europe     | 365.9 (304.7, 440.2)      |                           |                           |                           |
| Circumcision status |               |                           |                           |                           |
| Circumcised | 421.3 (366.2, 484.6)      |                           |                           |                           |
| Not circumcised | 460.7 (422.8, 502.1)    |                           |                           |                           |
| Tobacco use status |               |                           |                           |                           |
| Current    | 443.7 (394.9, 498.6)      |                           |                           |                           |
| Ex-user    | 363.7 (257.3, 475.4)      |                           |                           |                           |
| Non-user   | 462.0 (418.0, 510.7)      |                           |                           |                           |
| No. of sexual partners |             |                           |                           |                           |
| 0          | 1.8 (0.1, 11.8)           |                           |                           |                           |
| 1          | 521.3 (443.9, 612.3)      |                           |                           |                           |
| 5 or more  | 404.0 (343.2, 475.7)      |                           |                           |                           |
| Presence of sexually transmitted disease |     |                           |                           |                           |
| Chlamydia  | 215.5 (83.8, 554.2)       |                           |                           |                           |
| Gonorrhea  | 192.0                    |                           |                           |                           |

*a The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at day 1 and PCR negative at day 1 through month 7 for the relevant HPV type(s), and had a month 7 serum sample collected within an acceptable day range.

n, number of subjects contributing to the analysis; NA, not available.
Tobacco use and lifetime number of sexual partners were not associated with month 7 GMT for vaccine HPV types. Overall, males from Africa had the highest month 7 GMT for vaccine HPV types, and males from the Asia-Pacific region had the lowest. GMTs at day 1, month 7, and month 24 stratified by HPV type and region can be seen in Fig. 1. The GMTs among men residing in Africa remained higher than those of men residing in other world regions at 24 months as well.

As seen in Fig. 2, subjects who were seropositive for a vaccine HPV type at baseline had a greater antibody response to that HPV type after vaccination than did men who were seronegative for that HPV type, indicating an anamnestic response. This trend is less evident for males who were seropositive for HPV-16 at baseline; however, low numbers of subjects in this category limit this analysis.

In general, HM subjects had higher GMT levels than did MSM for all vaccine HPV types at their peak (month 7) and at the end of the study (month 36) (Table 3). The differences observed are statistically significant for all of these time points except the HPV-11 and HPV-18 month 36 GMTs. Though not statistically significant, a higher proportion of HM subjects seroconverted for vaccine HPV types than did MSM subjects (Table 4).

**DISCUSSION**

We have demonstrated that the qHPV vaccine was highly immunogenic for all vaccine types in HM (aged 16 to 23 years) and MSM (aged 16 to 26 years). Almost all subjects seroconverted for vaccine HPV types by month 7. Some interesting differences in immune responses were noted. For example, HM subjects had higher GMT levels for all vaccine HPV types at their peak than did MSM. Likewise, black subjects had significantly higher GMTs at month 7 than did both Caucasian and Asian subjects. Consistent with this observation, seroconversion for vaccine HPV types was higher for men residing in Africa than for those in Asia. There was also a
suggestion of an age-dependent response, with the vaccine being more immunogenic in younger men than in older men. Given that high efficacy for all 4 vaccine HPV types was demonstrated across a wide range of antibody levels, the results suggest that any demonstrated differences in immune responses are not relevant to protective efficacy. Overall, the vaccine was highly immunogenic in all groups; titers achieved after vaccination were substantially higher than those seen during natural HPV infection.

In general, the GMTs to vaccine types were lower in men than were those seen in earlier studies of women. The GMTs to vaccine HPV types in males at month 7 were 448 mMU/ml for HPV-6, 624 mMU/ml for HPV-11, 2,404 mMU/ml for HPV-16, and 402 mMU/ml for HPV-18. In comparison, month 7 GMTs in females 16 to 23 years of age for HPV-6, -11, -16, and -18 were 549 mMU/ml, 635 mMU/ml, 3,870 mMU/ml, and 741 mMU/ml, respectively (8). It is not possible to make direct statistical comparisons across the populations as the trials were different from each other with respect to countries included, populations enrolled, number of sexual partners, and other factors.

Of note, other potential factors that might have affected immune responses to the vaccine such as tobacco use and lifetime number of sexual partners did not adversely influence month 7 mean GMTs for vaccine HPV types. As observed previously (8), subjects seropositive for a vaccine HPV type at baseline had a greater antibody response to that HPV type after vaccination, indicating an anamnestic response. Considering that the vaccine was shown to offer an excellent level of protection in this trial, there is no evidence that these differences in antibody levels are clinically relevant.

Our data show that immune responses to the qHPV vaccine are broadly comparable in men and women (3, 4). Furthermore, the observed responses were substantially higher than those seen during natural HPV infection and consistent with the established efficacy of the vaccine in the prevention of in-
cident and persistent HPV infection, anogenital warts, and anal intraepithelial neoplasia.

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TABLE 3 Summary of anti-HPV geometric mean titers over time among HM and MSM subjects

| Response | Study time | Vaccinated HM (N = 1,726) | Vaccinated MSM (N = 299) |
|----------|------------|----------------------------|--------------------------|
|          |            | n  | GMT (mMU/ml)  | 95% CI       | n  | GMT (mMU/ml)  | 95% CI       |
| Anti-HPV-6 | Day 1      | 978 | <7           | <7, <7       | 114 | <7           | <7, <7       |
|           | Mo 7       | 978 | 473.9        | 446.8, 502.7 | 114 | 274.3        | 222.5, 338.3 |
|           | Mo 24      | 851 | 81.6         | 77.4, 86.1   | 90  | 64.6         | 53.7, 77.8   |
|           | Mo 36      | 792 | 73.4         | 69.2, 77.8   | 55  | 49.2         | 37.3, 64.8   |
| Anti-HPV-11 | Day 1     | 978 | <8           | <8, <8       | 114 | <8           | <8, <8       |
|            | Mo 7       | 978 | 651.5        | 620.7, 683.7 | 114 | 431.3        | 348.2, 534.2 |
|            | Mo 24      | 851 | 94.9         | 90.1, 100.0  | 90  | 91.6         | 76.7, 109.4  |
|            | Mo 36      | 792 | 83.8         | 79.4, 88.5   | 55  | 66.2         | 51.8, 84.6   |
| Anti-HPV-16 | Day 1     | 999 | <11          | <11, <11     | 136 | <11          | <11, <11     |
|            | Mo 7       | 999 | 2,622.1      | 2,484.9, 2,766.9 | 136 | 1,271.6      | 996.0, 1,623.4 |
|            | Mo 24      | 869 | 355.7        | 335.8, 376.7 | 110 | 255.5        | 219.5, 297.4 |
|            | Mo 36      | 811 | 309.3        | 291.5, 328.1 | 66  | 153.0        | 116.1, 201.5 |
| Anti-HPV-18 | Day 1     | 1,032 | <10        | <10, <10     | 142 | <10          | <10, <10     |
|            | Mo 7       | 1,032 | 439.3     | 415.7, 464.3 | 142 | 212.1        | 170.0, 264.6 |
|            | Mo 24      | 897 | 39.4         | 36.8, 42.2   | 114 | 31.4         | 25.9, 38.0   |
|            | Mo 36      | 836 | 33.9         | 31.6, 36.4   | 69  | 24.7         | 19.0, 32.1   |

*The estimated GMTs and associated CIs are calculated using an analysis of variance model with a term for vaccination group. N, number of subjects randomized to the respective vaccination group who received at least 1 injection; n, number of subjects contributing to the analysis.
TABLE 4 Summary of anti-HPV seroconversion over time among HM and MSM subjects*

| cLIA (mMU/ml) | Study time | Vaccinated HM (N = 1,726) | Vaccinated MSM (N = 299) |
|---------------|------------|---------------------------|--------------------------|
|               | n | Seroconversion (%) | 95% CI | n | Seroconversion (%) | 95% CI |
| **HPV-6 (≥20)** |   |                       |         |   |                       |         |
| Day 1         | 978 | 0.0 | 0.0, 0.4  | 114 | 0.0 | 0.0, 3.2 |
| Mo 7          | 978 | 99.2 | 98.4, 99.6 | 114 | 96.5 | 91.3, 99.0 |
| Mo 24         | 851 | 91.3 | 89.2, 93.1 | 90 | 86.7 | 77.9, 92.9 |
| Mo 36         | 792 | 89.5 | 87.2, 91.6 | 55 | 80.0 | 67.0, 89.6 |
| **HPV-11 (≥16)** |   |                       |         |   |                       |         |
| Day 1         | 978 | 0.0 | 0.0, 0.4  | 114 | 0.0 | 0.0, 3.2 |
| Mo 7          | 978 | 99.4 | 98.7, 98.4 | 114 | 97.4 | 92.5, 99.5 |
| Mo 24         | 851 | 95.5 | 93.9, 96.8 | 90 | 96.7 | 90.6, 99.3 |
| Mo 36         | 792 | 94.3 | 92.5, 95.8 | 55 | 89.1 | 77.8, 95.9 |
| **HPV-16 (≥20)** |   |                       |         |   |                       |         |
| Day 1         | 999 | 0.0 | 0.0, 0.4  | 136 | 0.0 | 0.0, 2.7 |
| Mo 7          | 999 | 99.4 | 98.7, 99.8 | 136 | 94.1 | 88.7, 97.4 |
| Mo 24         | 869 | 99.2 | 98.3, 99.7 | 110 | 98.2 | 93.6, 99.8 |
| Mo 36         | 811 | 98.3 | 97.1, 99.1 | 66 | 93.9 | 85.2, 98.3 |
| **HPV-18 (≥24)** |   |                       |         |   |                       |         |
| Day 1         | 1,032 | 0.0 | 0.0, 0.4 | 142 | 0.0 | 0.0, 2.6 |
| Mo 7          | 1,032 | 98.4 | 97.5, 99.1 | 142 | 89.4 | 83.2, 94.0 |
| Mo 24         | 897  | 62.9 | 59.6, 66.0 | 114 | 57.9 | 48.3, 67.1 |
| Mo 6          | 836  | 57.3 | 53.9, 60.7 | 69  | 53.6 | 41.2, 65.7 |

*Abbreviations: N, number of subjects randomized to the respective vaccination group who received at least 1 injection; n, number of subjects contributing to the analysis.

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