Three-Year Follow-up of 2-Dose Versus 3-Dose HPV Vaccine

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abstract

BACKGROUND AND OBJECTIVES: Human papillomavirus (HPV) antibody responses to the 9-valent human papillomavirus (9vHPV) vaccine among girls and boys (aged 9–14 years) receiving 2-dose regimens (months 0, 6 or 0, 12) were noninferior to a 3-dose regimen (months 0, 2, 6) in young women (aged 16–26 years) 4 weeks after last vaccination in an international, randomized, open-label trial (NCT01984697). We assessed response durability through month 36.

METHODS: Girls received 2 (months 0 and 6 [0, 6]: *n* = 301; months 0 and 12 [0, 12]: *n* = 151) or 3 doses (months 0,2, and 6 [0, 2, 6]: *n* = 301); boys received 2 doses ([0, 6]: *n* = 301; [0, 12]: *n* = 150); and young women received 3 doses ([0, 2, 6]: *n* = 314) of 9vHPV vaccine. Anti-HPV geometric mean titers (GMTs) were assessed by competitive Luminex immunoassay (cLIA) and immunoglobulin G-Luminex immunoassay (IgG-LIA) through month 36.

RESULTS: Anti-HPV GMTs were highest 1 month after the last 9vHPV vaccine regimen dose, decreased sharply during the subsequent 12 months, and then decreased more slowly. GMTs 2 to 2.5 years after the last regimen dose in girls and boys given 2 doses were generally similar to or greater than GMTs in young women given 3 doses. Across HPV types, most boys and girls who received 2 doses (cLIA: 81%–100%; IgG-LIA: 91%–100%) and young women who received 3 doses (cLIA: 78%–98%; IgG-LIA: 91%–100%) remained seropositive 2 to 2.5 years after the last regimen dose.

CONCLUSIONS: Antibody responses persisted through 2 to 2.5 years after the last dose of a 2-dose 9vHPV vaccine regimen in girls and boys. In girls and boys, antibody responses generated by 2 doses administered 6 to 12 months apart may be sufficient to induce high-level protective efficacy through at least 2 years after the second dose.

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WHAT'S KNOWN ON THIS SUBJECT: The 9-valent human papillomavirus vaccine is licensed as a 2-dose vaccine in many countries after demonstration of noninferiority of human papillomavirus antibody responses to 2 doses in girls and boys versus 3 doses in young women at 1 month after the last dose.

WHAT THIS STUDY ADDS: Human papillomavirus antibody responses persisted through 2 to 2.5 years after the last dose of 2-dose 9-valent human papillomavirus vaccine regimens in girls and boys, suggesting 2-dose regimens may be sufficient to induce high-level protective efficacy through at least 2 years after the second dose.

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The quadrivalent and bivalent human papillomavirus (HPV) vaccines (first licensed in 2006 and 2007, respectively[1]) were developed to protect against infection and disease caused by HPV types 16 and 18, which account for ~70% of cervical cancers.[2] The quadrivalent human papillomavirus (qHPV) vaccine also protects against HPV types 6 and 11, which cause ~90% of genital warts.[3] The 9-valent human papillomavirus (9vHPV) vaccine was developed to protect against the same 4 types as the qHPV vaccine (HPV types 6, 11, 16, and 18) and extend coverage to an additional 5 oncogenic HPV types (HPV types 31, 33, 45, 52, and 58), with the potential to prevent ~90% of cervical cancers; HPV-related vulvar, vaginal, and anal cancers; and genital warts, on the basis of epidemiological data.[3–7] On the basis of results of a pivotal efficacy trial of a 3-dose regimen in young women[8,9] and 2 noninferiority immunobridging trials from young women to girls and boys[10] and young men,[11] the 9vHPV vaccine was first licensed in 2014 and has received regulatory approval in >80 countries.

These 3 HPV vaccines were initially developed by using 3-dose schedules. In aiming to increase the public health impact of HPV vaccines, vaccine uptake is a critical issue. A step toward increasing uptake is to move from 3-dose HPV vaccine regimens to 2-dose regimens. Clinical efficacy cannot be assessed in young adolescents because of limited exposure to HPV. Therefore, efficacy is inferred on the basis of the demonstration of noninferior immunogenicity compared with an adult population in whom efficacy was demonstrated. A study of the qHPV vaccine revealed that antibody responses at 1 month after the last dose in girls 9 to 13 years of age who received 2 doses were noninferior to responses in women 16 to 26 years of age who received 3 doses.[12] Similar results were obtained in studies of the bivalent HPV vaccine.[13,14] For both vaccines, noninferiority was shown to persist through several years of follow-up.[15,16] In consideration of these results, the World Health Organization (WHO) is recommending a 2-dose schedule for routine HPV vaccination of individuals 9 to 14 years of age.[17] An immunogenicity assessment of 2- vs 3-dose regimens of 9vHPV vaccine, including the long-term comparative durability of antibody responses, is needed.

We have conducted a 3-year study of the 9vHPV vaccine (NCT01984697) to compare antibody responses in boys and girls 9 to 14 years of age who received 2 doses with those of young women 16 to 26 years of age who received 3 doses (ie, the population in whom efficacy was demonstrated[8,9]). Early analyses from this study revealed that 2 doses of 9vHPV vaccine elicited noninferior antibody responses in girls and boys, compared with 3 doses in young women at 1 month after the last dose, as previously reported.[18] On the basis of this result, the 9vHPV vaccine was licensed as a 2-dose vaccine in girls and boys aged 9 to 14 years in the European Union, the United States, Canada, Australia, and many other countries,[1,19] and, in 2016, the Advisory Committee on Immunization Practices (ACIP) recommended a 2-dose schedule for HPV vaccines in that population.[20] Herein, we report the final study analyses, including antibody persistence through 3 years postvaccination onset.

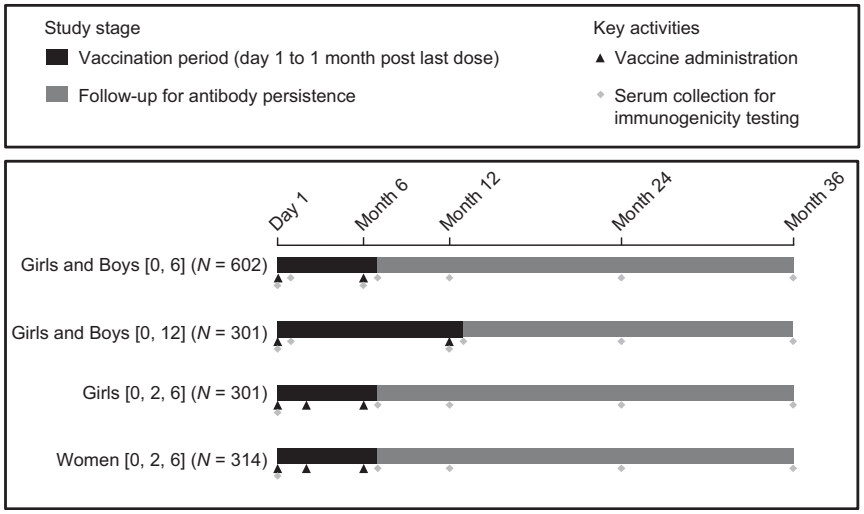

FIGURE 1

Study design. Girls and boys aged 9 to 14 years received 2 doses of the 9vHPV vaccine 6 months apart (girls [0, 6], boys [0, 6]) or 12 months apart (girls and boys [0, 12]). In addition, girls aged 9 to 14 years and young women aged 16 to 26 years received 3 doses of the 9vHPV vaccine at day 1, month 2, and month 6 (girls [0, 2, 6]; young women [0, 2, 6]). For the (0, 6) and (0, 2, 6) groups, serum was collected for immunogenicity testing at months 7, 12, 24, and 36 (1, 6, 18, and 30 months after the last dose, respectively). Additionally, for the girls and boys (0, 6) group, serum was collected at month 1 (subset of participants) and month 6 (before the second dose). For the (0, 12) group, serum was collected for immunogenicity testing at month 12 (before the second dose) as well as months 13, 24, and 36 (1, 12, and 24 months after the last dose, respectively).

METHODS

Study Design and Participants

Protocol V503-010 (NCT01984697) was an international, 3-year safety and immunogenicity study, in which we compared administration of 2-dose regimens of 9vHPV vaccine, separated by either 6 or 12 months, in girls and boys with administration of a 3-dose regimen in a control group of young women (Fig 1).

Participants were enrolled from 52 sites in 15 countries (Canada, Chile, Colombia, Czech Republic, Denmark, Israel, Malaysia, Norway, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, and the United States).

Participants were healthy girls and boys aged 9 to 14 years who were not sexually active before enrollment or young women aged 16 to 26 years with ≤4 lifetime sexual partners and no history of abnormal Papanicolaou test results or other cervical abnormalities, who agreed to use effective contraception through month 7.

The enrollment of girls and boys was stratified into 3 age strata (9–10, 11–12, and 13–14 years) of similar size.

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies; all participants (for minors, the parent or legal guardian and participant) provided written informed consent.

Vaccination

The vaccine was administered as 0.5 mL intramuscular injections at each vaccination visit as a 2-dose regimen administered at 0 and 6 months ([0, 6] regimen), as a 2-dose regimen administered at 0 and 12 months ([0, 12] regimen), or as a 3-dose regimen administered at 0, 2, and 6 months ([0, 2, 6] regimen). Girls were randomly assigned 2:1:2 within each age stratum to the (0, 6) or (0, 12) 2-dose regimen or the 3-dose regimen. Boys were randomly assigned 2:1 within each age stratum to the (0, 6) or (0, 12) 2-dose regimen. Young women were assigned to the 3-dose regimen. The last dose of the assigned regimen was the month 12 vaccination for the (0, 12) regimen and the month 6 vaccination for all other regimens (Fig 1). Participants who received a 2-dose regimen received an additional vaccine dose at month 36 for exploratory immunogenicity analyses (to be reported separately).

Follow-up

HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses were assessed in serum samples collected prevaccination through month 36 by using a competitive Luminex immunoassay (cLIA).[21] The original version of the cLIA was used through 2015 for the testing of all samples up to month 13. A new version of the cLIA was used starting in 2016 for the testing of all samples from month 24 onward. The newer version of the assay was bridged to the earlier version to ensure comparable antibody measurements between the 2 versions. Supportive analyses were conducted by using the immunoglobulin G-Luminex immunoassay (IgG-LIA).[22] The results of these assays are reported in milli-Merck units (mMU) per mL. Although the same designation is used for the unit of measurement in both assays, cLIA mMU per mL and IgG-LIA mMU per mL are different units of measurement and cannot be directly compared.

Serious adverse events (SAEs) regardless of causality were reportable from day 1 through 6 months after the last dose of the vaccination regimen, as previously described.[18] Deaths and SAEs judged by the investigator to be related to the 9vHPV vaccine were reported throughout the study.

Statistical Analysis

Immunogenicity was assessed in the per-protocol immunogenicity (PPI) population, consisting of participants who received all planned vaccinations within acceptable day ranges, provided serology samples within 21 to 49 days post last dose of the assigned regimen, were seronegative at day 1 for the HPV type being analyzed, and had no other protocol violations that could interfere with immunogenicity assessments. Safety was assessed in all participants who received at least 1 study vaccination and had follow-up data.

Geometric mean titers (GMTs) and associated 95% confidence intervals (CIs) were computed for all immunogenicity assessment time points between day 1 and month 36. GMTs at months 7, 12, 24, and 36 in girls and boys who received the (0, 6) regimen were compared with GMTs in girls and young women who received 3 doses. The summary measures used for the comparison were the point estimates and 95% CI estimates of the ratio of the GMTs. The month 24 and month 36 visits represent 1.5 and 2.5 years post last dose of both the (0, 6) and (0, 2, 6) dose regimens (Fig 1); therefore, immunogenicity results at months 24 and 36 can be directly compared for these dose regimens. However, the month 24 and 36 visits represent 1 and 2 years post last dose, respectively, of the (0, 12) regimen (Fig 1). Because of the different time intervals between the last dose and the month 24 and month 36 visits, the immunogenicity results at months 24 and 36 in the (0, 12) regimen cannot be directly compared with the corresponding results in the (0, 6) and (0, 2, 6) regimens.

RESULTS

Participants

The study was conducted between December 16, 2013, and July 24, 2017. Of 1518 enrolled participants (Fig 2), 159 discontinued the study, most commonly because of loss to follow-up or withdrawn consent. Participant baseline characteristics have been described previously.[18] Briefly, the mean age of the girls and boys 9 to 14 years of age was 11.5 years, and the mean age of the young women 16 to 26 years of age was 21 years. The study was diverse with respect to race and region of residence.

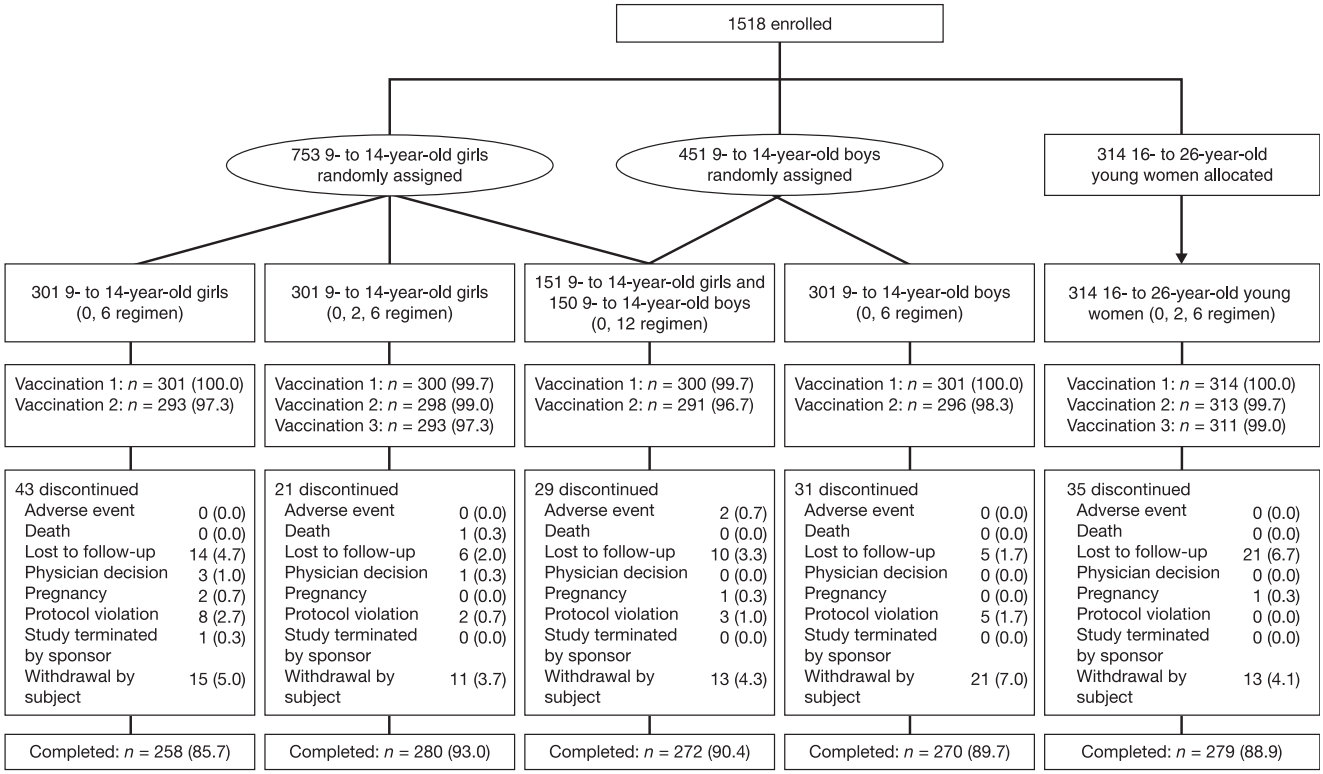

FIGURE 2
Participant disposition.

Immunogenicity

Comparison of 2-Dose Regimens in Girls and Boys With a 3-Dose Regimen in Young Women

Antibody responses at 1 month after the last dose of the assigned regimen were reported previously.[18] Formal statistical testing revealed noninferiority of GMTs at 1 month after the last dose in the 2-dose cohorts versus young women receiving 3 doses (the noninferiority criterion required that the lower bound of the 95% CI of the GMT ratio [2-dose to 3-dose] be >0.67).[18]

Antibody responses (GMTs) over time through month 36 are presented in Fig 3. Throughout the study, anti-HPV cLIA GMTs in girls and boys who received the 2-dose or 3-dose regimen were generally higher or similar compared with those in young women who received the 3-dose regimen (Fig 3). GMTs were the highest at 1 month after the last dose, then generally declined until levels plateaued at ~12 (for the [0, 12] regimen) to 18 months (for all other regimens) after the last dose of the regimen (Fig 3), which corresponded to the month 24 study visit. Analyses to compare GMTs in girls and boys who received the (0, 6) regimen with young women who received 3 doses were conducted at months 7, 12, 24, and 36. GMT ratios (girls and boys to young women) were the highest at month 7 and tended to decrease between months 7 and 24 and then, remained stable between months 24 and 36 (Table 1). Across HPV types, the GMT ratios between girls and boys receiving the (0, 6) regimen and young women receiving the 3-dose regimen ranged from 1.13 to 2.06 at month 24 and 1.05 to 1.93 at month 36. The lower bound of the 95% CI for the GMT ratios remained >0.67 for all HPV types (ranging from 0.97 to 1.79 and 0.90 to 1.66 at month 24 and month 36, respectively; Table 1); thus, the noninferiority criterion that was demonstrated at month 7 (as reported previously[18]) persisted at month 24 and month 36. Similar results were obtained when considering separately girls and boys who received the (0, 6) regimen (Supplemental Table 3).

Although GMTs at study visits beyond 1 month post last dose are not directly comparable between girls and boys who received the (0, 12) regimen and young women who received the 3-dose regimen, the graphical representation of GMT trends at similar time intervals post last dose of the regimen can be compared (Fig 3). For all HPV types, the GMT trends at 12 to 24 months post last dose of the regimen were higher in (0, 12) regimen recipients compared with the corresponding trends in young women who received 3 doses (Fig 3). Similar trends were observed when considering separately girls and boys who received the (0, 12) regimen (Supplemental Table 4).

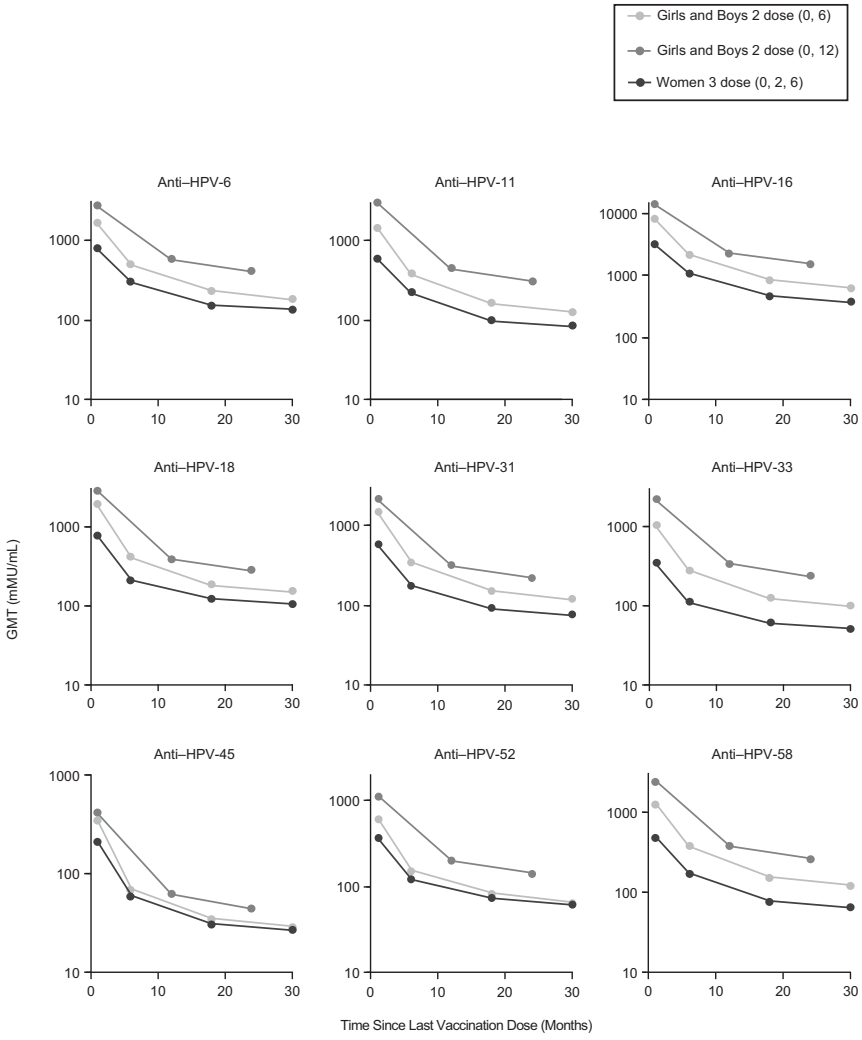

FIGURE 3

Anti-HPV GMTs (based on cLIA) after the last 9vHPV vaccine dose, by vaccination regimen (PPI population). The PPI population includes all participants who (1) received all planned vaccinations within acceptable day ranges, (2) had a 4-week post last dose serum sample collected within an acceptable day range, (3) were seronegative at baseline to the relevant HPV type, and (4) had no other protocol violations that could interfere with immunogenicity evaluation.

Exploratory Analysis of 2-Dose Regimens Versus a 3-Dose Regimen in Girls

We performed exploratory analyses comparing girls who received a 2- or 3-dose regimen to glean insight into the effect of 2- vs 3-dose regimens in participants of the same age group, ie, eliminating the effect of age difference. Generally, 2-dose (0, 12) regimen recipients had higher or similar GMT trends, compared with girls who received 3 doses from 1 to 24 months post last dose of the regimen. This observation applies to all HPV types except HPV-45 (Fig 4). Generally, for all HPV types, 2-dose (0, 6) regimen recipients had lower or similar GMT trends compared with girls who received 3 doses from 1 to 30 months post last dose of the regimen (Fig 4).

Analyses to compare GMTs in girls who received the (0, 6) regimen with girls who received 3 doses were conducted at months 7, 12, 24, and 36. GMT ratios (girls [0, 6] to girls [0, 2, 6]) were the highest at month 7, tended to decrease between months 7 and 24 and, then, remained stable between months 24 and 36 (Table 2). Across HPV types, the GMT ratios between girls receiving the (0, 6) regimen and girls receiving the 3-dose regimen ranged from 0.43 to 1.09 at month 24 and 0.46 to 1.11 at month 36. Similar results were obtained when comparing boys who received the (0, 6) regimen with girls who received 3 doses (Supplemental Table 5).

Persistence of Seropositivity Over Time

Administration of a 2-dose regimen in girls and boys resulted in high seroconversion in all vaccine HPV types at 1 month after the last dose of the regimen on the basis of cLIA (range: >99%–100%; Supplemental Table 6 and previously reported[18]) that persisted through 2 years ([0, 12] regimen) to 2.5 years ([0, 6] regimen) after the last dose of the regimen (range: >81%–100%; Supplemental Table 6). The seropositivity based on IgG-LIA for vaccine HPV types in 2-dose regimen recipients at 2 years ([0, 12] regimen) to 2.5 years ([0, 6] regimen) after the last dose of the regimen ranged from >91% to 100% (Supplemental Table 7).

Subgroup Analysis of Antibody Responses by Participant Age

In age-stratified analyses of immunogenicity in 2-dose regimen recipients, for each vaccination group, the HPV type-specific GMT and seropositivity trends over time that were observed in the overall vaccination group were also observed consistently across the 3 age strata within the vaccination group (Supplemental Tables 8 and 9). Across all age strata, GMTs for the 2-dose recipients were generally similar to or higher than GMTs in young women who received 3 doses (Table 1; Supplemental Tables 8 and 9).

TABLE 1 Comparison of HPV cLIA GMTs Over Time Post Last Vaccination Dose in Girls and Boys Receiving 2 Doses of 9vHPV Vaccine (0, 6 Months) Versus Young Women Receiving 3 Doses (0, 2, 6 Months) (PPI Population)

Assay (HPV Type) Time in Months Post Last Dose[a]	Girls and Boys Aged 9–14 y (0,6) Regimen (*N* = 602)		Young Women Aged 16–26 y (0, 2, 6) Regimen (*N* = 314)		Girls and Boys (0,6) to Young Women (0, 2, 6), GMT Ratio (95% CI)
	n	GMT, mMU/mL (95% CI)	*n*	GMT, mMU/mL (95% CI)	
Anti–HPV-6					
1	522	1603.7 (1484.9–1732.0)	238	770.9 (687.4–864.7)	2.08 (1.81–2.39)
6	517	486.4 (448.2–527.8)	232	294.9 (261.1–333.0)	1.65 (1.42–1.91)
18	512	233.1 (213.8–254.3)	232	153.2 (135.8–172.9)	1.52 (1.31–1.77)
30	490	182.3 (166.4–199.7)	214	133.8 (118.1–151.6)	1.36 (1.16–1.60)
Anti–HPV-11					
1	523	1405.5 (1298.1–1521.8)	238	580.5 (515.6–653.4)	2.42 (2.10–2.79)
6	522	375.1 (344.5–408.4)	236	218.9 (194.9–245.8)	1.71 (1.48–1.99)
18	513	159.8 (146.0–174.8)	232	98.3 (86.9–111.3)	1.63 (1.39–1.90)
30	491	123.8 (112.8–135.8)	214	82.9 (72.7–94.5)	1.49 (1.27–1.76)
Anti–HPV-16					
1	546	8213.1 (7596.1–8880.3)	249	3154.0 (2791.4–3563.7)	2.60 (2.26–3.00)
6	544	2201.6 (2026.9–2391.3)	246	1095.4 (979.8–1224.7)	2.01 (1.74–2.32)
18	535	849.0 (768.7–937.7)	241	461.6 (403.5–528.0)	1.84 (1.55–2.19)
30	511	630.7 (566.4–702.4)	222	368.9 (319.0–426.5)	1.71 (1.42–2.07)
Anti–HPV-18					
1	545	1866.8 (1713.8–2033.6)	267	761.5 (665.3–871.6)	2.45 (2.10–2.86)
6	543	404.5 (368.5–443.9)	265	209.9 (182.8–241.1)	1.93 (1.63–2.27)
18	534	182.7 (168.4–198.1)	259	122.2 (109.8–136.0)	1.50 (1.30–1.72)
30	510	149.8 (138.0–162.6)	239	104.1 (93.5–115.9)	1.44 (1.25–1.66)
Anti–HPV-31					
1	544	1464.7 (1352.3–1586.4)	264	572.1 (498.4–656.8)	2.56 (2.21–2.97)
6	542	344.1 (313.5–377.6)	262	174.8 (152.1–200.9)	1.97 (1.67–2.32)
18	533	149.5 (136.0–164.3)	258	89.6 (78.8–102.0)	1.67 (1.42–1.96)
30	509	116.6 (105.7–128.6)	235	74.6 (65.2–85.3)	1.56 (1.32–1.85)
Anti–HPV-33					
1	545	1034.4 (955.3–1119.9)	279	348.1 (309.2–392.0)	2.97 (2.58–3.42)
6	543	285.1 (260.6–311.9)	276	112.0 (99.2–126.4)	2.55 (2.19–2.97)
18	534	126.3 (116.0–137.5)	269	61.3 (55.2–68.0)	2.06 (1.79–2.37)
30	510	100.6 (92.2–109.8)	246	52.2 (46.7–58.3)	1.93 (1.66–2.23)
Anti–HPV-45					
1	548	355.0 (325.5–387.2)	280	213.6 (185.0–246.7)	1.66 (1.42–1.95)
6	546	70.1 (63.7–77.0)	277	60.3 (52.0–70.0)	1.16 (0.98–1.38)
18	537	34.7 (31.8–37.9)	271	30.7 (27.0–34.9)	1.13 (0.97–1.32)
30	513	28.6 (26.2–31.2)	248	27.3 (24.0–31.0)	1.05 (0.90–1.22)
Anti–HPV-52					
1	546	608.6 (566.6–653.7)	271	364.2 (322.8–410.9)	1.67 (1.46–1.91)
6	544	153.2 (141.1–166.4)	268	121.3 (107.1–137.3)	1.26 (1.09–1.46)
18	535	82.9 (76.7–89.6)	261	73.7 (66.2–82.0)	1.13 (0.98–1.29)
30	511	64.7 (59.8–70.1)	239	61.5 (54.8–69.0)	1.05 (0.92–1.21)
Anti–HPV-58					
1	541	1285.5 (1192.6–1385.6)	261	491.1 (433.5–556.3)	2.62 (2.28–3.01)
6	539	381.5 (352.4–413.0)	259	174.4 (154.3–197.0)	2.19 (1.90–2.52)
18	530	152.6 (140.0–166.3)	253	76.8 (67.6–87.1)	1.99 (1.71–2.31)
30	507	122.4 (111.9–133.8)	231	64.7 (56.5–74.0)	1.89 (1.61–2.22)

The PPI population includes all participants who (1) received all planned vaccinations within acceptable day ranges, (2) had a 4-week post last dose serum sample collected within an acceptable day range; (3) were seronegative at baseline to the relevant HPV type; and (4) had no other protocol violations that could interfere with immunogenicity evaluation. *n*, number of participants contributing to the analysis; *N*, number of randomly assigned participants who received at least 1 injection in the respective vaccination group.

[a] The 1, 6, 18, and 30 mo post last dose time points correspond to study visits at month 7, month 12, month 24, and month 36, respectively.

Exploratory Analysis of Antibody Responses After a Single Vaccine Dose

The study was not designed for the assessment of antibody response to 1-dose administration of the 9vHPV vaccine. However, serum collection in (0, 6) regimen recipients at month 1 and month 6 (predose 2 vaccination) and in (0, 12) regimen recipients at month 12 (predose 2 vaccination), allowed for a short-term analysis of immunogenicity response by cLIA and IgG-LIA after 1-dose administration of the 9vHPV vaccine (Fig 2; Supplemental Tables 10 and 11). Generally, the 1-dose regimen of the 9vHPV vaccine did not result in 100% seropositivity at 1 month postvaccination, and the GMTs at 1 month after 1 dose were lower than GMTs after 2 or 3 doses (12–49-fold lower than the [0, 6] regimen; Table 1; Supplemental Table 10). The antibody levels declined from 1 to 6 months post dose 1 on the basis of cLIA, as shown by the percent seropositivity and GMTs in girls who received the (0, 6) regimen (Supplemental Table 10). The results at 12 months post dose 1 in participants receiving the (0, 12) regimen were consistent with this trend of declining antibody titers after a 1-dose regimen of the 9vHPV vaccine. Only HPV-58 exhibited antibody titers that did not decline rapidly from 1 to 12 months post dose 1. Supportive analyses performed using the IgG-LIA also suggested declines in antibody titers and seropositivity rates over time for some HPV types after a single 9vHPV vaccine dose (Supplemental Table 11).

Safety

A total of 34 participants experienced SAEs during the study (Supplemental Table 12). One participant in the (0, 6) group experienced abdominal pain 15 days after the month 36 dose and fully recovered 11 days later; this SAE was considered vaccine related. One girl in the (0, 2, 6) group experienced autoimmune encephalitis and status epilepticus 353 days after dose 3 and died of cardiac arrest 114 days later; none of these SAEs were considered vaccine related. Narratives for these 2 events are provided in the Supplemental Information. Thirty-two participants experienced SAEs that were not considered vaccine related and resolved (2 participants resolved with sequelae). One participant (a 9-year-old girl) discontinued from study vaccination because of a nonserious vaccine-related adverse event of transient urticaria 1 day after the first dose of the vaccine, which fully resolved.

DISCUSSION

Antibody responses in girls and boys (aged 9–14 years) who received 2 doses of 9vHPV vaccine 6 or 12 months apart were maintained over 2 to 2.5 years after administration of the second dose. GMTs were generally similar to or higher than responses in young women who received 3 doses throughout this time period, indicating that the noninferiority profile of the 2-dose regimens in girls and boys versus a 3-dose schedule in young women[18] persisted through 2 to 2.5 years. The GMT ratios (2-dose [0, 6] to 3-dose) ranged from 1.05 to 1.93 at month 36; the noninferiority criterion persisted throughout the study for all HPV types, including those with the lowest GMT ratios (HPV-45 and HPV-52). Although antibody levels after the (0, 12) regimen were not directly comparable with the other dosing regimens, the GMTs during the 2 years after the last vaccine dose were generally higher than those in young women receiving 3 doses during the 2 years after the last dose. On the basis of this immunogenicity bridging, the efficacy of 2-dose schedules of 9vHPV vaccine in girls and boys 9 to 14 years of age was inferred.

In exploratory analyses, GMTs were generally similar or lower in girls who received 2 doses 6 months apart versus girls who received 3 doses. Lower GMTs have been reported in previous studies of 2-dose regimens of the quadrivalent and bivalent HPV vaccines.[12,14] In contrast, GMTs were generally higher in girls who received 2 doses 12 months apart versus girls who received 3 doses. Results from studies of 3-dose regimens of the qHPV vaccine have indicated that a longer interval between the first 2 doses resulted in higher antibody responses.[23–25] The relevant objective of this study was to compare 2-dose regimens of the 9vHPV vaccine in girls and boys with a 3-dose regimen in young women (the population and dose regimen used to demonstrate 9vHPV vaccine efficacy) to infer effectiveness of 2-dose regimens. Therefore, the clinical significance of these differences in the immunogenicity of 2-dose and 3-dose regimens in girls is unknown. On the basis of these results, the ACIP has recommended a 2-dose schedule in individuals 9 to 14 years of age, with the 2 doses administered 6 to 12 months apart.[20]

The durable immune responses observed after 2 doses of the 9vHPV vaccine are consistent with findings from clinical studies of 2-dose regimens of bivalent HPV and qHPV vaccines.[12,13,15,26,27] In particular, antibody responses at 1 month after the last dose were noninferior in girls receiving 2 qHPV vaccine doses (6 months apart) compared with young women receiving 3 doses.[12] Long-term follow-up data from the qHPV vaccine study revealed a decline in GMTs during the 5 years after vaccination; GMT ratios (2- vs 3-dose) tended to decrease between months 7 and 24 and then remained stable between months 24 and 36 (which is consistent with the results reported here with the 9vHPV vaccine).[26] After month 36, the trend in decline was similar between girls

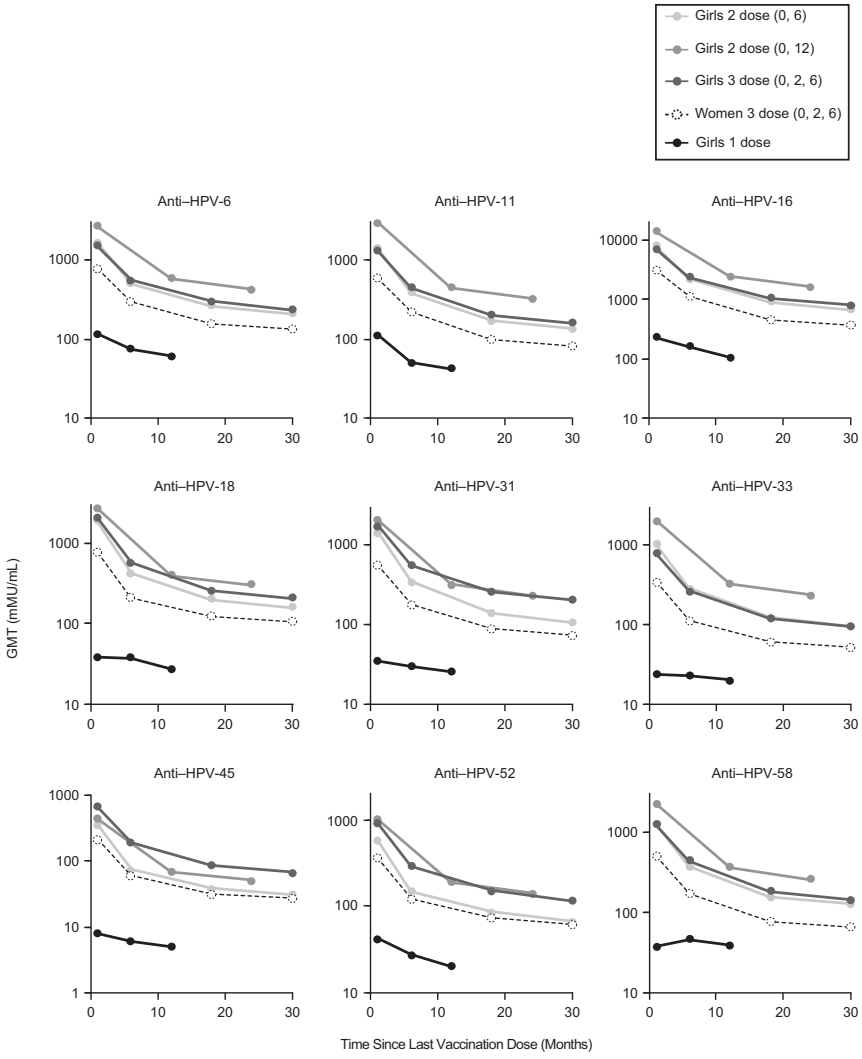

FIGURE 4

Anti-HPV GMTs (based on cLIA) in girls 9 to 14 years of age after the last 9vHPV vaccine dose, by the number of doses (PPI population). The PPI population includes all participants who (1) received all planned vaccinations within acceptable day ranges, (2) had a 4-week post last dose serum sample collected within an acceptable day range, (3) were seronegative at baseline to the relevant HPV type, and (4) had no other protocol violations that could interfere with immunogenicity evaluation.

receiving the 2-dose and 3-dose regimens.[26] Ten years after vaccination, anti-HPV antibody responses in girls receiving either a 2-dose or 3-dose regimen were noninferior to those observed in young women receiving 3 doses.[15] With this result, together with the high (>95%) efficacy and long-term effectiveness of the qHPV vaccine in young women,[28,29] it is suggested 2 doses of the qHPV vaccine would provide similar efficacy in the target population. The similar trajectories of antibody responses up to month 36 between the qHPV and 9vHPV vaccines suggest longer-term immunogenicity may also be similar, in the absence of longer-term follow-up data with the 9vHPV vaccine.

Our findings of durable antibody responses to 9vHPV vaccine in girls and boys for at least 2 to 2.5 years after the last dose of the regimen support the current ACIP and WHO recommendations for the use of 2-dose HPV vaccine schedules in young adolescents (aged 9–14 years), which have been adopted in many countries.[17,19,20,27] For individuals from the ages of 9 to 14 years, the WHO recommends 2 doses 5 to 13 months apart,[17] and the ACIP recommends 2 doses separated by 6 to 12 months.[20] The use of fewer doses may have advantages in terms of cost and improving adherence to HPV vaccination regimens.[30]

An exploratory analysis of antibody responses at 1, 6, and 12 months after a single vaccine dose indicated that not all participants seroconverted to the vaccine HPV types after vaccination, and declines in antibody titers and seropositivity rates were observed over time. Post hoc analyses of observational studies of clinical trial participants who were randomly assigned to receive 2 or 3 doses but did not complete the vaccination series provided the initial suggestion of effectiveness of single-dose HPV vaccination.[31,32] In 2 ongoing randomized trials, researchers are evaluating the short-term efficacy (2–4 years) of a 1-dose schedule to prevent infection with vaccine HPV types: the ESCUDDO (Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano) trial in Costa Rica (NCT03180034) and the KENSHE (KENya Single-dose HPV-vaccine Efficacy) trial in Kenya (NCT03675256). Considering the lower immunogenicity, decrease in GMT over time, and incomplete seroconversion observed after a single dose of the 9vHPV vaccine, it will be important to thoroughly assess the long-term effectiveness of single-dose HPV vaccination in these trials.

In the current study, we included a comprehensive evaluation of several dosing regimens in both girls and boys; however, there are several limitations. The duration of follow-up was limited to 2.5 years after the last dose of the vaccination regimen. However, a durable immune response through at least 10 years has been demonstrated after 2 doses of the

TABLE 2 Comparison of HPV cLIA GMTs Post Last Vaccination Dose in Girls Aged 9–14 Years Receiving 2 Doses (0, 6 Months) Versus Girls Aged 9–14 Years Receiving 3 Doses (0, 2, 6 Months) of 9vHPV Vaccine (PPI Population)

Assay (HPV Type) Time in Months Post Last Dose[a]	Girls Aged 9–14 y (0, 6) Regimen (N = 301)		Girls Aged 9–14 y (0, 2, 6) Regimen (N = 300)		Girls (0, 6) to Girls (0, 2, 6), GMT Ratio (95% CI)
	n	GMT, mMU/mL (95% CI)	n	GMT, mMU/mL (95% CI)	
Anti–HPV-6					
1	258	1657.9 (1483.2–1853.1)	254	1496.1 (1337.3–1673.7)	1.11 (0.95–1.30)
6	256	498.8 (444.6–559.5)	251	545.8 (486.0–613.0)	0.91 (0.78–1.07)
18	253	260.7 (231.5–293.6)	249	300.7 (266.8–339.0)	0.87 (0.73–1.03)
30	236	209.6 (184.9–237.6)	240	232.2 (205.1–263.0)	0.90 (0.75–1.08)
Anti–HPV-11					
1	258	1388.9 (1238.7–1557.4)	254	1306.3 (1163.9–1466.1)	1.06 (0.90–1.25)
6	257	383.2 (340.5–431.2)	253	443.7 (393.9–499.7)	0.86 (0.73–1.03)
18	253	169.8 (150.5–191.7)	249	201.9 (178.7–228.1)	0.84 (0.70–1.00)
30	236	133.7 (117.6–152.1)	240	159.1 (140.0–180.7)	0.84 (0.70–1.01)
Anti–HPV-16					
1	272	8004.9 (7164.2–8944.2)	269	6996.0 (6257.4–7821.7)	1.14 (0.98–1.34)
6	270	2204.9 (1960.9–2479.2)	268	2371.2 (2107.9–2667.4)	0.93 (0.79–1.09)
18	266	900.5 (788.0–1028.9)	264	1041.3 (910.8–1190.4)	0.86 (0.71–1.05)
30	248	673.8 (582.8–779.1)	255	792.4 (686.7–914.4)	0.85 (0.69–1.05)
Anti–HPV-18					
1	272	1872.8 (1652.4–2122.5)	270	2049.3 (1807.3–2323.6)	0.91 (0.77–1.09)
6	270	416.5 (363.8–476.7)	269	569.2 (497.1–651.7)	0.73 (0.61–0.88)
18	266	196.8 (174.9–221.6)	265	255.8 (227.2–288.0)	0.77 (0.65–0.91)
30	248	158.9 (140.8–179.4)	256	206.5 (183.3–232.7)	0.77 (0.65–0.91)
Anti–HPV-31					
1	272	1436.3 (1272.5–1621.2)	271	1748.3 (1548.6–1973.9)	0.82 (0.70–0.97)
6	270	345.2 (301.8–394.8)	270	559.4 (489.1–639.7)	0.62 (0.51–0.74)
18	266	160.6 (140.8–183.3)	266	260.6 (228.4–297.3)	0.62 (0.51–0.74)
30	248	127.8 (111.4–146.5)	258	205.9 (180.0–235.5)	0.62 (0.51–0.75)
Anti–HPV-33					
1	273	1030.0 (920.2–1153.0)	275	796.4 (711.8–891.2)	1.29 (1.11–1.51)
6	271	285.5 (252.0–323.5)	274	262.0 (231.4–296.7)	1.09 (0.92–1.30)
18	267	131.2 (116.9–147.2)	270	120.8 (107.7–135.4)	1.09 (0.92–1.28)
30	249	106.0 (94.1–119.5)	261	95.5 (85.0–107.3)	1.11 (0.94–1.31)
Anti–HPV-45					
1	274	357.6 (313.4–408.0)	275	661.7 (580.0–754.9)	0.54 (0.45–0.65)
6	272	72.7 (63.3–83.6)	274	189.2 (164.7–217.4)	0.38 (0.32–0.47)
18	268	37.8 (33.2–43.0)	270	86.9 (76.4–98.9)	0.43 (0.36–0.52)
30	250	30.6 (26.9–35.0)	261	66.1 (58.1–75.2)	0.46 (0.39–0.56)
Anti–HPV-52					
1	272	581.1 (520.9–648.2)	275	909.9 (816.1–1014.4)	0.64 (0.55–0.74)
6	270	148.6 (131.0–168.4)	274	291.8 (257.6–330.5)	0.51 (0.43–0.60)
18	266	85.1 (76.4–94.7)	270	150.4 (135.2–167.4)	0.57 (0.48–0.66)
30	248	66.2 (59.1–74.0)	261	115.9 (103.9–129.3)	0.57 (0.49–0.67)
Anti–HPV-58					
1	270	1251.2 (1117.7–1400.8)	273	1229.3 (1098.8–1375.4)	1.02 (0.87–1.19)
6	268	370.3 (329.7–415.9)	272	442.5 (394.3–496.5)	0.84 (0.71–0.98)
18	264	155.4 (138.0–175.1)	268	183.7 (163.3–206.7)	0.85 (0.71–1.00)
30	246	125.8 (111.1–142.5)	259	143.0 (126.7–161.5)	0.88 (0.74–1.05)

The PPI population includes all participants who (1) received all planned vaccinations within acceptable day ranges, (2) had a 4-week post last dose serum sample collected within an acceptable day range, (3) were seronegative at baseline to the relevant HPV type, and (4) had no other protocol violations that could interfere with immunogenicity evaluation. *n*, number of participants contributing to the analysis; *N*, number of randomly assigned participants who received at least 1 injection in the respective vaccination group.

[a] The 1, 6, 18, and 30 mo post last dose time points correspond to study visits at month 7, month 12, month 24, and month 36, respectively.

qHPV vaccine.[15] Together with the similarity of the immunogenicity profiles of the qHPV and 9vHPV vaccines,[1] these results provide reassurance that a 2-dose regimen of the 9vHPV vaccine can provide durable protection. In addition, this noninferiority immunobridging study was not designed to assess the efficacy of 2- versus 3-dose regimens against HPV infection and disease, given the low potential for young adolescents to be exposed to HPV. The effectiveness of the 2-dose regimens was inferred on the basis of

the demonstration of noninferior immunogenicity in young women from ages 16 to 26 years who received a 3-dose regimen. Two-dose regimens were not evaluated in participants aged >14 years. This could be an area for future research because, in some studies, researchers have suggested that a 2-dose regimen of HPV vaccine may be suitable in individuals aged >14 years.[33]

In this study, we assessed regimens with 2 doses administered either 6 or 12 months apart. Intervals longer than 6 months may have logistic advantages in some settings (eg, in school-based immunization programs or during periods of vaccine shortages), and preliminary evidence suggests longer intervals between 2 doses of HPV vaccine may still provide protective antibody levels.[34] Studies in which researchers rigorously validate regimens with longer than 12 months between doses remain to be conducted.

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ABBREVIATIONS

9vHPV: 9-valent human papillomavirus
ACIP: Advisory Committee on Immunization Practices
CI: confidence interval
cLIA: competitive Luminex immunoassay
GMT: geometric mean titer
HPV: human papillomavirus
IgG-LIA: immunoglobulin G-Luminex immunoassay
mMU: milli-Merck units
PPI: per-protocol immunogenicity
qHPV: quadrivalent human papillomavirus
SAE: serious adverse event
WHO: World Health Organization

Dr Bornstein contributed to the conception, design, and planning of the study, data analysis, data acquisition, interpretation of the results, drafting of the manuscript and critical review and revision of the manuscript for important intellectual content; Drs Roux, Petersen, Tytus, Rupp, Senders, Engel, Ferris, Y-J Kim, YT Kim, Kurugol, and Nolan acquired data and critically reviewed and revised the manuscript for important intellectual content; Dr Huang contributed to data analysis, data acquisition, interpretation of the results, drafting of the manuscript, and critical review and revision of the manuscript for important intellectual content; Drs Dobson, Diez-Domingo, Schilling, and Ariffin acquired data, interpreted results, and critically reviewed and revised the manuscript for important intellectual content; Dr Pitisuttithum interpreted results and critically reviewed and revised the manuscript for important intellectual content; Dr Bautista analyzed data, interpreted results, and critically reviewed and revised the manuscript for important intellectual content; Dr Sankaranarayanan contributed to the conception, design, and planning of the study, data acquisition, and drafting of the manuscript; Dr Saah contributed to the conception, design, and planning of the study, data analysis, interpretation of the results, and critical review and revision of the manuscript for important intellectual content; Dr Luxembourg analyzed data, interpreted results, drafted the manuscript, and critically reviewed and revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

The data-sharing policy, including restrictions, of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via e-mail to dataaccess@merck.com.

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