

EBCOG, Lisbon, March 4-8, 2008

Posters with Discussion

0518 Continued efficacy of quadrivalent hpv (types 6/11/16/18)L1 VLP vaccine in preventing cervical or external genital disease: 4 years of follow-up

Charles JN Lacey for the GARDASIL Phase II/III Investigators, Hull York Medical School, University of York, UK

Objectives: HPV16 and 18 cause approximately ~75% of cervical cancers, ~70% of vulvar and vaginal cancers, as well as cervical, vulvar, and vaginal precancerous lesions. HPV6 and 11 cause ~90% of genital warts cases. Quadrivalent HPV6/11/16/18 vaccine (GARDASIL™/SILGARD™, Merck & Co., Inc.) was licensed in 2006 based on prophylactic vaccine efficacy against HPV16/18-related cervical cancer (via surrogates). However, phase III studies continued to provide further data on the duration of vaccine efficacy. Here we present an end-of-study update (4 years of follow-up) on the efficacy of the quadrivalent HPV vaccine against HPV6/11/16/18-related CIN and EGL (VIN/VaIN/condyloma)

Methods : Combined data presented are representative of 18,150 women enrolled in 1 of 3 large clinical studies (Protocols 007, 013, and 015). In each study, subjects were randomized in a 1:1 ratio to receive quadrivalent HPV vaccine or placebo at day 1, month 2 and month 6. Procedures performed for efficacy data evaluation included detailed genital examination, Pap testing, and collection of cervicovaginal specimens. Colposcopy referral was per a Pap triage algorithm (except Protocol 007). All specimens were HPV typed and given histologic diagnoses by a gynecologic pathology panel. Follow-up for the current analysis was 4 years post-dose 1. Analyses were carried out in a per protocol population that included subjects who received all 3 vaccinations, were sero- and PCR-negative at day 1 and PCR-negative through month 7 to the appropriate vaccine HPV types. Protocol violators were not included.

Results: The efficacy of quadrivalent HPV vaccine against HPV6/11/16/18-related CIN was 96.0% (95% CI: 92.3 to 98.2). The efficacy of the vaccine against HPV6/11/16/18-related EGL was 99.1% (95% CI: 96.8 to 99.9%). The estimated efficacy of the vaccine against HPV6/11-related CIN and EGL was 100.0% (95% CI: 93.4 to 100.0%) and 99.0% (95% CI: 96.5 to 99.9%), respectively.

Conclusions: Vaccination with quadrivalent HPV vaccine is highly efficacious in preventing the incidence of HPV6/11/16/18-related CIN and EGL among 16- to 26-year old women naïve to vaccine HPV types prior to vaccination.

CONTINUED EFFICACY OF QUADRIVALENT HPV (TYPES 6/11/16/18) L1 VLP VACCINE IN PREVENTING CERVICAL OR EXTERNAL GENITAL DISEASE: 4 YEARS OF FOLLOW-UP

Charles JN Lacey, for the GARDASIL Phase III Investigators

ABSTRACT

OBJECTIVES: HPV 16 and 18 cause approximately ~70% of cervical cancers, ~70% of vulvar and vaginal cancers, as well as cervical, vulvar, and vaginal precancerous lesions. HPV 6 and 11 cause ~90% of genital warts cases. Quadrivalent HPV 6/11/16/18 vaccine (GARDASIL™/SILGARD™, Merck & Co., Inc.) was licensed in 2006 based on prophylactic vaccine efficacy against HPV 16/18-related cervical cancer (via surrogates). However, phase III studies continued to provide further data on the duration of vaccine efficacy. Here we present an end-of-study update (4 years of follow-up) on the efficacy of the quadrivalent HPV vaccine against HPV 6/11/16/18-related CIN and EGL (VIN/VaIN/condyloma).

METHODS: Combined data presented are representative of 18,150 women enrolled in 1 of 3 large clinical studies (protocols 007, 013, and 015). In each study, subjects were randomized in a 1:1 ratio to receive quadrivalent HPV vaccine or placebo at day 1, month 2 and month 6. Procedures performed for efficacy data evaluation included detailed genital examination, Pap testing, and collection of cervicovaginal specimens. Colposcopy referral was per a Pap triage algorithm (except protocol 007). All specimens were HPV typed and given histologic diagnoses by a gynecologic pathology panel. Follow-up for the current analysis was 4 years post-dose 1. Analyses were carried out in a per-protocol population that included subjects who received all 3 vaccinations, were sero- and PCR-negative at day 1 and PCR-negative through month 7 to the appropriate vaccine HPV types. Protocol violators were not included.

RESULTS: The efficacy of quadrivalent HPV vaccine against HPV 6/11/16/18-related CIN was 96.0% (95% CI: 92.3 to 98.2). The efficacy of the vaccine against HPV 6/11/16/18-related EGL was 99.1% (95% CI: 96.8 to 99.9%). The estimated efficacy of the vaccine against HPV 6/11-related CIN and EGL was 100.0% (95% CI: 93.4 to 100.0%) and 99.0% (95% CI: 96.5 to 99.9%), respectively.

CONCLUSIONS: Vaccination with quadrivalent HPV vaccine is highly efficacious in preventing the incidence of HPV 6/11/16/18-related CIN and EGL among 16- to 26-year old women naive to vaccine HPV types prior to vaccination.

BACKGROUND

GARDASIL™/SILGARD™ (QUADRIVALENT HPV [TYPES 6, 11, 16, 18] VACCINE [qHPV])

- Key Product Features
 - Broad spectrum vaccine to prevent more disease
 - Manufactured in yeast: yeast-derived vaccines given to millions of infants and adults
 - Proprietary adjuvant (aluminum hydroxyphosphate sulfate)
- Now licensed in >90 countries for prevention of HPV 6/11/16/18-related:
 - Cervical cancer, cervical pre-cancers, vulvar pre-cancers, vaginal pre-cancers, genital warts

FOUR YEARS OF FOLLOW-UP

- In September 2006, qHPV vaccine was licensed in the E.U.
- Included in the application for licensure were efficacy summaries which integrated data from 3 separate efficacy/immunogenicity trials (protocols 007, 013, and 015) which were similar in design and infrastructure and which mandated similar rigorous procedures for the collection of cervical intraepithelial neoplasia (CIN) and cervical cancer data and external genital lesion (EGL) data
 - Protocol 007 was complete at the time the initial BLA for qHPV was submitted to regulatory agencies. Protocols 013 and 015 were ongoing
 - Thus, the integrated summaries and analyses included in the initial BLA were based on the full 3 years of post-vaccination follow-up in protocol 007 and ~2 years of post vaccination follow-up in protocols 013 and 015
- A supplemental application was prepared in early 2007 based on extra follow-up in protocols 013 and 015 plus the final follow-up for protocol 007

Design Feature	Protocol 007	Protocol 013	Protocol 015
General			
Phase	IIb	III	III
Trial registry number/reference	NA ¹	NCT00092521 ²	NCT00092534 ³
Total number of enrolled women	1,106	5,759	12,167
Study dates	2000 to 2004	2001 to 2007	2002 to 2007
Study sites	International, Multicenter		
Blinding	Double-blind		
Study vaccine	Quadrivalent vaccine (one of three formulations) or placebo	Quadrivalent vaccine, monovalent vaccine, or placebo	Quadrivalent vaccine or placebo
Vaccination regimen	0, 2, 6 months		
Visit schedule for efficacy analyses (months)	0, 7, 12, 18, 24, 30, and 36	0, 3, 7, 12, 18, 24, 30, 36, and 48	0, 7, 12, 24, 36 and 48
Inclusion/Exclusion Criteria			
Age	16 to 23 years	16 to 23 years	16 to 26 years
Lifetime number of male sexual partners	0 to 4	0 to 4	0 to 4
Cervical Cancer Screening			
Timing of Pap screening	Every 6 months	Every 6 months	Every 12 months
Screening triage strategy	Discretionary	Standardized	Standardized
Minimal Pap test abnormality for referral	ASC-US, HPV (+) on HC-II	ASC-US, HPV (+) on HC-II	ASC-US, HPV (+) on HC-II
External Lesion Screening (warts, VIN or VaIN)			
Timing of screening	Every 6 months	Every 6 months	Every 12 months
Requirement for biopsy	All lesions that in the opinion of the investigator were possibly, probably, or definitely HPV-related, or whose diagnosis could not be ascertained		

METHODS

OBJECTIVE AND ENDPOINTS

OBJECTIVE

- To demonstrate that qHPV vaccine reduces the incidence of HPV 6/11/16/18-related CIN or cervical cancer and HPV 6/11/16/18-related external genital lesions among vaccine HPV type-naïve women.

ENDPOINTS

- A case of disease was defined from a tissue sample that was:
 - (a) diagnosed by a panel of pathologists as CIN1-3, AIS, cervical cancer, or any EGL (vulvar/vaginal intraepithelial neoplasia or cancer, condyloma), and (b) positive for type-specific HPV DNA

STUDIES AND POPULATIONS

- Integrated summaries of vaccine efficacy were obtained by pooling all data from protocols 007, 013, and 015 and then computing vaccine efficacy as done in each of the individual protocols
- Protocol 013 and 015 data included in this report reflect study information collected through (at least) the month 48 follow-up visit for 88% of protocol 013 subjects, and for 94% of protocol 015 subjects
 - It is important to note that 013 and 015 were closed early in order to vaccinate the placebo population
 - For many subjects their month 48 measurements were taken before 48 months after day 1 (incidence data truncated at month 42)

CURRENT ANALYSIS: EFFICACY IN PER-PROTOCOL POPULATION

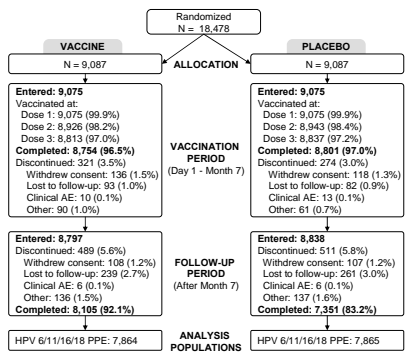
Per-Protocol Efficacy (PPE) population: data are considered for all subjects who received (1) all three vaccinations; (2) were seronegative at day 1, and PCR negative at day 1 and month 7 to the relevant HPV type; and (3) did not deviate from the protocol. Endpoints are counted after month 7.

Relevance: Assessment of efficacy in an HPV-naïve population of 16-26 year old girls/women.

Additionally: time-to-event curve is conducted on intention-to-treat (ITT) population that included subjects who (1) received at least 1 vaccination and (2) had any follow-up visit after 1 month following the first injection

RESULTS

SUBJECT ACCOUNTING



EFFICACY AGAINST HPV 6/11/16/18-RELATED DISEASE (PPE)

CIN1 OR WORSE	qHPV Vaccine			Placebo			Efficacy (%)	95% CI
	n	Cases	Rate	n	Cases	Rate		
HPV 6/11/16/18	7,864	9	0.0	7,865	225	1.0	96.0	(92.3, 98.2)
by Severity								
CIN 1	7,864	7	0.0	7,865	170	0.7	95.9	(91.4, 98.4)
CIN 2 or Worse	7,864	2	0.0	7,865	110	0.5	98.2	(93.3, 99.8)
CIN 2	7,864	0	0.0	7,865	71	0.3	100.0	(94.7, 100.0)
CIN 3 or Worse	7,864	2	0.0	7,865	66	0.3	97.0	(88.7, 99.6)
CIN 3	7,864	2	0.0	7,865	63	0.3	96.8	(88.1, 99.6)
AIS	7,864	0	0.0	7,865	7	0.0	100.0	(30.9, 100.0)
EGL								
HPV 6/11/16/18	7,900	2	0.0	7,902	227	1.0	99.1	(96.8, 99.9)
by Severity								
Condyloma	7,900	2	0.0	7,902	193	0.8	99.0	(96.2, 99.9)
VIN 1 or VaIN 1	7,900	0	0.0	7,902	28	0.1	100.0	(85.9, 100.0)
VIN 2/3 or VaIN 2/3 (or worse)	7,900	0	0.0	7,902	23	0.1	100.0	(82.6, 100.0)

qHPV = quadrivalent HPV; CI = confidence interval; rate = incidence rate per 100 person years; CIN = cervical intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia; n = number of subjects evaluable, i.e., number of subjects in the given population who also had at least one follow-up visit.

SYNOPSIS OF CIN 2/3 CASES IN VACCINEES

- Both cases were read as CIN3 related to HPV 16
 - Case 1: HPV 51 positive at enrollment**
- Pap test revealed ASC-US at month 49 (+ high-risk probe). Biopsy specimen was HPV 16 DNA positive only. Definitive therapy specimen (month 52) was HPV 56 DNA positive and HPV 16 DNA negative
 - Case 2: HPV 52 positive at enrollment**
- Sequential Pap test revealed ASC-US and LSIL at month 32.5. Biopsy specimen was positive for HPV 52 and HPV 16. All definitive therapy specimens were HPV 52 DNA positive and HPV 16 DNA negative

SUMMARY

THROUGH 4 YEARS POST DAY 1:

- The efficacy of qHPV vaccine against HPV 6/11/16/18-related CIN or worse was 96.0% (95% CI: 92.3 to 98.2) in the per-protocol population
 - Efficacy against CIN2 or worse was 98.2% (95% CI: 93.3, 99.8)
- Efficacy against HPV 6/11/16/18-related EGL was 99.1% (95% CI: 96.8 to 99.9) in the per-protocol population
 - Efficacy against VIN 2/3, VaIN 2/3 or worse was 100% (95% CI: 82.6, 100.0)
- The estimated efficacy of qHPV vaccine against HPV 6/11-related CIN and EGL was 100.0% (95% CI: 93.4 to 100.0) and 99.0% (95% CI: 96.5 to 99.9) respectively in the per-protocol population

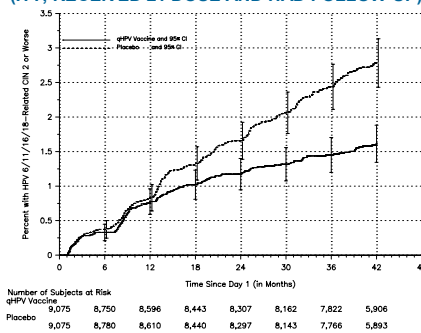
ACKNOWLEDGEMENTS

Phase III Steering Committee: K. Ault, USA, X. Bosch, Spain, D. Brown, USA, J. Diller, Sweden, D. Ferris, USA, P. Garcia, Peru, M. Hernandez, Mexico, O.E. Iversen, Norway, L. Koutsky, USA, S. Kruger-Kjaer, Denmark, R. Kurman, USA, S. Majewski, Poland, E. Myers, USA, N. Munoz, France, S.E. Olsson, Sweden, J. Paavonen, Finland, G. Perez, Colombia, E. Tay, Singapore, S. Thoresen, Norway, K. Sigurdsson, Iceland, L. Villa, Brazil, **Data Safety Monitoring Board:** J. Modin, M. Boulos, Brazil, J.T. Cox, U.S.A., F. Langmark, Norway, A. Munoz, USA, V. Odind, Sweden, E. Wilkinson, U.S.A. **Coordinating Center - Merck & Co.:** E. Barr, Program Head, T. Hesley, Clinical Monitor, K. Giacometti, L. Lupinacci-Statisticians, A. Thornton-Project Manager, K. Conway-Data Management, D. Aversa-IT Clinical Operations, J. Bryan/M. Esser/F. Taddeo/PCR and serology labs, S. Vuocolo-Medical Communications.

REFERENCES

- Villa LL, et al. *Lancet Oncology*. 2005;5:271-278.
- Garland S, et al. *New Eng J Med*. 2007;356:1928-1943.
- The FUTURE II Study Group. *New Eng J Med*. 2007; 356:1915-1927

TIME TO EVENT CURVE FOR CIN2 OR WORSE (ITT; RECEIVED ≥1 DOSE AND HAD FOLLOW-UP)



TIME TO EVENT CURVE FOR ANY EXTERNAL GENITAL LESION (ITT; RECEIVED ≥1 DOSE AND HAD FOLLOW-UP)

