Merck’s Investigational 9-valent HPV Vaccine, V503, Prevented 97 Percent of Cervical, Vaginal and Vulvar Pre-cancers Caused by Five Additional HPV Types, in Phase III Study

Release Date:
Monday, November 4, 2013 7:30 am EST

Terms:
Research and Development News  Corporate News  Latest News

Dateline City:
WHITEHOUSE STATION, N.J.

- **Immunogenicity non-inferior to GARDASIL® for original four HPV types**
- **Merck expects to file Biologics License Application with U.S. FDA in 2013**

WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that in the pivotal Phase III efficacy study, its investigational 9-valent HPV vaccine (V503) prevented approximately 97 percent of cervical, vaginal and vulvar pre-cancers caused by HPV types 31, 33, 45, 52, and 58. V503 also generated immune responses to HPV types 6, 11, 16, and 18 that were non-inferior to those generated by GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]. V503 includes five more HPV types (31, 33, 45, 52, 58) in addition to the four original HPV types (6, 11, 16, 18) in GARDASIL. These data, along with results of two other Phase III studies, will be presented for the first time at the European Research Organisation on Genital Infection and Neoplasia (EUROGIN) Congress during a late-breaker oral session on Tuesday, November 5.

**Results from the pivotal Phase III efficacy study (abstract #SS 8-4)**

The pivotal Phase III study (Protocol 001) evaluated the efficacy, safety and immunogenicity of V503 (n=7,099) compared to GARDASIL (n=7,105) in 16-26-year old females. The primary efficacy analysis was conducted in those who received all three doses of vaccine within one year, who were not infected with the relevant HPV types at enrollment and who remained free of infection with the relevant HPV types through Month 7 (per-protocol population). The results were as follows:

- 96.7 percent reduction (95% CI; 80.9, 99.8) in the combined incidence of high-grade cervical/vulvar/vaginal disease [CIN (cervical intraepithelial neoplasia) 2/3+, VIN (vulvar intraepithelial neoplasia) 2/3+, and VaIN (vaginal intraepithelial neoplasia) 2/3+] caused by HPV types 31, 33, 45, 52, 58 (1 case in the group that received V503 vs. 30 cases in the group that received GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]).
- 97.1 percent reduction (95% CI; 91.8, 99.2) in the combined incidence of cervical/vulvar/vaginal disease of any grade (all CIN, VIN, VaIN) caused by HPV types 31, 33, 45, 52, 58 (3 cases in the group that received V503 vs. 103 cases in the group that received GARDASIL).
- 96.0 percent efficacy (95% CI; 94.4, 97.2) against six-month persistent HPV infection with HPV types 31, 33, 45, 52, 58 (35 cases in the group that received V503 vs. 810 cases in the group that received GARDASIL).

Because GARDASIL does not contain the five additional HPV types in V503, cases of disease caused by these five types in the study group that received GARDASIL were expected.

“In the Phase III studies being presented for the first time, V503 prevented approximately 97 percent of high-grade cervical, vulvar and vaginal diseases caused by five additional HPV types,” said Elmar Joura, M.D., Associate Professor of Gynecology and Obstetrics, Medical University of Vienna and Comprehensive Cancer Center, Vienna, Austria, and study investigator who will present these results at EUROGIN.

Non-inferior immunogenicity for the four HPV types (6, 11, 16, 18) also in GARDASIL was a second primary endpoint in this study. Because GARDASIL has been shown in clinical studies to be highly effective against certain diseases caused by HPV types 6, 11, 16, and 18, few disease endpoints caused by these HPV types were expected, making it difficult to directly assess efficacy of V503 for these four types. Therefore, antibody levels were evaluated for these four HPV types common to both vaccines. V503 generated immune responses for HPV 6, 11, 16, and 18 (measured by geometric mean titers (GMTs) and seroconversion rates at Month 7) that were non-inferior to those generated by GARDASIL. In the study, the
Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after

**Safety of V503 in pivotal efficacy study (abstract #SS 8-7)**

In this study, the frequencies of adverse event (AE) reports were generally comparable between V503 and GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]; however, there was a higher frequency of injection-site AEs (90.8 percent vs. 85.1 percent), including swelling, pain and erythema in the V503 group. Injection-site pain was mostly reported as mild or moderate in intensity with both vaccines. The majority of injection-site swelling and erythema cases were of small size (less than or equal to one inch). The most frequently reported vaccine-related systemic AEs (frequency greater than or equal to 2 percent) for V503 compared to GARDASIL, respectively, were: headache (14.6 percent vs. 13.7 percent), pyrexia (5.0 percent vs. 4.3 percent), nausea (4.4 percent vs. 3.7 percent), dizziness (3.0 percent vs. 2.8 percent), and fatigue (2.3 percent vs. 2.1 percent).

“Our investigational vaccine V503 reduced HPV-associated precancerous lesions in young women,” said Roger M. Perlmutter, M.D., Ph.D., president of Merck Research Laboratories. “With our ongoing commitment to research, we are building upon the success obtained with GARDASIL, and we expect to submit a Biologics License Application for V503 to the U.S. Food and Drug Administration before the end of 2013.”

**Results of adolescent immunobridging studies for V503 also presented (abstracts #SS 8-5 and #SS 8-6)**

Also presented at EUROGIN were results from two open-label immunobridging studies for V503 in adolescents.

Immunobridging studies were used for the adolescent population because adolescents are not likely to have been exposed to HPV, and therefore, efficacy against disease endpoints cannot be studied directly. Immunogenicity ‘bridging data’ is an accepted surrogate for efficacy and is an approach that is accepted by major regulatory agencies.

In Protocol 002, which is aimed at extending the pivotal efficacy study findings in females 16-26 years of age to males and females 9-15 years of age (adolescents), 3,074 subjects were divided into three groups – 669 male 9-15-year olds, 1,935 female 9-15-year olds and 470 female 16-26-year olds. Immune responses to V503 were compared among the groups. All study participants in the per-protocol population received three doses of V503 over a six-month period and were evaluated at month 7 for GMTs and seroconversion rates. Results from this study showed non-inferior immunogenicity of V503 in adolescent males and females compared with females 16-26 years old for all nine vaccine HPV types: 99.8-100 percent of adolescent females and 99.8-100 percent of adolescent males seroconverted, or developed antibodies, against the nine HPV types at month 7 compared to 99.5-100 percent of 16-26-year old females. The safety profile of V503 was similar or slightly more favorable in adolescent males compared to adolescent females and females 16-26 years old; the overall safety and tolerability findings were consistent with those reported in previous studies with GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant].

In Protocol 009, 600 adolescent females who had not yet received a prophylactic HPV vaccine were randomized into two groups – 300 who received V503 and 300 who received GARDASIL – to compare the immune responses in adolescent girls for HPV types 6, 11, 16 and 18. All study participants in the per-protocol population received three doses of GARDASIL or V503 over a six-month period and were evaluated at month 7 for GMTs and seroconversion rates. In this study, immunogenicity of V503 was non-inferior compared to GARDASIL in adolescent females for HPV types 6, 11, 16 and 18: 100 percent of adolescent females and 99.8-100 percent of adolescent males seroconverted, or developed antibodies, against the nine HPV types at month 7 compared to 99.5-100 percent of 16-26-year old females. The safety profile of V503 was similar or slightly more favorable in adolescent males compared to adolescent females and females 16-26 years old; the overall safety and tolerability findings were generally similar to those reported with GARDASIL, with higher frequency of injection-site swelling with V503.

**About GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]**

GARDASIL is indicated in the United States for use in girls and young women 9 through 26 years of age for the prevention of cervical, vulvar, vaginal and anal cancers caused by HPV types 16 and 18; genital warts caused by HPV types 6 and 11; and precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18. GARDASIL is also approved for use in boys and men 9 through 26 years of age for the prevention of anal cancer caused by HPV types 16 and 18; genital warts caused by HPV types 6 and 11; and precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18.

**Important information about GARDASIL**

GARDASIL does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Recipients of GARDASIL should not discontinue anal cancer screening if it has been recommended by a health care provider.

GARDASIL has not been demonstrated to provide protection against diseases from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.

GARDASIL is not intended to be used for protection of active external genital lesions; cervical, vulvar, vaginal and anal cancers; cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia, or anal intraepithelial neoplasia.

GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] has not been demonstrated to protect against disease due to HPV types not contained in the vaccine.

Not all vulvar, vaginal and anal cancers are caused by HPV, and GARDASIL protects only against those vulvar, vaginal and anal cancers caused by HPV Types 16 and 18.

**Select safety information for GARDASIL**

GARDASIL is contraindicated in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of GARDASIL.

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after
administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion.

GARDASIL is not recommended for use in pregnant women.

The most common adverse reaction was headache. Common adverse reactions that were observed among recipients of GARDASIL at a frequency of at least 1.0 percent and greater than placebo were: fever, nausea, dizziness; and injection-site pain, swelling, erythema, pruritus and bruising.

Dosage and administration for GARDASIL

GARDASIL is a ready-to-use, three-dose, intramuscular vaccine. GARDASIL should be administered in three separate intramuscular injections in the deltoid region of the upper arm or in the higher anterolateral area of the thigh. The following dosage schedule is recommended: first dose at elected date, second dose two months after the first dose and the third dose six months after the first dose.

About HPV and cancer

Human papillomavirus (HPV) causes virtually all cervical cancer cases and also causes some cases of vulvar and vaginal cancer in females, and anal cancers and genital warts in both females and males. Cervical cancer is the third most common type of cancer among women worldwide. It is estimated that approximately 530,000 women develop cervical cancer annually around the world, with about 85 percent of cases occurring in developing countries.

The seven cancer-causing HPV types in V503 (16, 18, 31, 33, 45, 52 and 58) cause approximately 90 percent of cervical cancer cases, approximately 80 percent of high-grade cervical dysplasias (cervical precancers) worldwide, and approximately 50-60 percent of cases of low-grade cervical dysplasias. These seven HPV types also can cause vaginal, vulvar and anal cancers and pre-cancers. After HPV types 16 and 18, the five additional HPV types in V503 are the most common cervical cancer-causing types worldwide. HPV types 6 and 11 cause approximately 90 percent of genital warts cases.

About Merck

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook, and YouTube.

Merck Forward-Looking Statement

This news release includes “forward-looking statements” within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck’s management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck’s 2012 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).


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