Brief Summary of the Microbiology Devices Panel Meeting – March 12, 2014

Introduction:

On March 12, 2014, the Panel discussed, made recommendations, and voted regarding a premarket approval application for a new indication for the **cobas**® HPV (human papillomavirus) Test, sponsored by Roche Molecular Systems, Inc (RMS). The **cobas**® HPV Test is a qualitative in vitro test for the detection of Human Papillomavirus (HPV) that is currently approved for use in conjunction with cervical cytology. RMS is seeking a claim whereby the **cobas**® HPV Test can be used as a first-line primary cervical cancer screening test. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies types HPV 16 and HPV 18 while concurrently detecting the rest of the HR types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). Per the proposed indication, women who test negative for high risk HPV types by the **cobas**® HPV Test would be followed up in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the **cobas**® HPV Test would be referred to colposcopy. Women who test high risk HPV positive and 16/18 negative by the **cobas**® HPV Test (12 other HR HPV positive) would be evaluated by cervical cytology to determine the need for referral to colposcopy.

Guest Presentation:

Francisco García, MD, MPH, Director and CMO, Distinguished Outreach Professor of Public Health, at Pima County Health Department in Arizona, attended as a guest speaker on behalf of FDA. His presentation included the following: a review of the current understanding of the epidemiology and natural history of HPV infection and cervical cancer precursors as well as a discussion of the evolution of screening guidelines and their application to the public health setting. Dr. Garcia offered the following conclusions in his presentation: cervical cancer prevention efforts must balance safety and potential benefit, new guidelines should be based on improved understanding of the disease process; screening and policy decisions must be made from a societal perspective, while clinical choices reflect individual preferences and perception of risk.

Sponsor Presentation:

Representatives from RMS presented including Christoph Majewski, PhD Lifecycle Leader, HPV & Microbiology, RMS; Thomas C. Wright, Jr., MD Professor Emeritus, Columbia University; Abha Sharma, PhD, Director Biostatistics, RMS; and Catherine Behrens, MD, PhD, FACOG, Director, Clinical Research, RMS. In their presentation, RMS reviewed the technical aspects of the **cobas**® HPV Test, the ATHENA (Addressing THE Need for Advanced HPV Diagnostics) clinical study design and patient flow, the demographics of the ATHENA study and the distribution of cytology results and **cobas**® HPV Test results in ATHENA. RMS also described the proposed new indication for use (IU) and provided a summary of

the performance data generated to support this IU. They concluded that using HPV primary screening will not adversely impact women with other gynecological cancers or sexually transmitted infections, and although no screening test with acceptable specificity will detect all cervical cancers or precursors, HPV primary screening offers greater protection against CIN (cervical intraepithelial neoplasia) 3 and invasive cervical cancer than cytology alone and provides similar protection against CIN3 and invasive cervical cancer as cytology and HPV co-testing.

FDA Presentation:

Kate Simon, PhD and Marina Kondratovich, PhD presented for the FDA. The FDA provided the regulatory history of the device, the FDA perspective on the published literature on HPV primary screening, the unique aspects of the ATHENA study design and analysis, appropriate comparators for establishing safety and effectiveness for HPV primary screening, the influence of screening age range on performance as well as performance in women subsequently diagnosed with cancer. Also discussed was the issue of women with unsatisfactory cytology results, the influence of a cytologist's prior knowledge of HPV status on performance, the benefit vs. risk of the proposed new indication, and the limitations in evaluating the future risk of disease. FDA requested the panel's input on the safety and effectiveness of the proposed new indication for use of the device considering the data presented by both FDA and the sponsor.

Discussion

The panel generally agreed that the clinical study results support the proposed indication for use of this device; however, the effectiveness data is stronger than the safety data. The following were further considered regarding the proposed indication for use.

The panel generally discussed whether the indicated age range (25 years of age and older) was appropriate for the proposed indication or if a more appropriate age range would be 30 years of age or older. Several panel members expressed concerns about the possibility of overtreatment in the 25 to 29 age year old group and the possible impact it may have on their future reproductive health, noting that the data on the impact of treatment on preterm labor remain inconclusive. Given that there is significant prevalence of CIN3 in this age range and that over-screening could be mitigated with proper screening intervals, the panel agreed that the benefits outweigh the risks.

As a result of the discussion about the appropriate age range, the panel emphasized the need for physician and patient education, training, and clear guidelines to ensure correct usage of the test.

The panel agreed that the triage testing proposed for the candidate algorithm (cytology and **cobas**® HPV Test 16/18 genotyping) are acceptable for determining which high risk **cobas**® HPV Test positive patients need immediate referral to colposcopy.

Generally, the panel indicated that the benefit vs. risk in using the device for the proposed indication for use was acceptable, particularly in terms of the number of tests and colposcopies performed per 10,000 patients in relation to the proportion of disease diagnosed.

The panel discussed whether they anticipated any changes in clinical performance due to recent changes in recommended screening intervals or HPV vaccination. The panel did not anticipate, but could not definitively rule out changes in performance for the candidate algorithm, with the possible exception that HPV 16 and 18 would be less prevalent due to vaccination, which could affect the positive predictive value of screening tests. Several panelists indicated that any changes would likely also impact the comparator algorithm (cytology alone).

The Bethesda System for Classifying Cervical/Vaginal Diagnoses from cytology tests includes non-cancer related diagnostic categories such as the ability to detect microscopically certain organisms and abnormal endometrial cells. The device is not designed to screen for these additional diagnostic categories. Based on their clinical experience, the panel discussed the potential impact on patients if this additional diagnostic information is lost. The panel generally agreed that patients would not be adversely impacted by loss of these cytology categories since other better testing methods exist for these conditions that clinicians would utilize over cytology.

The panel also discussed what specific warnings and/or limitations could mitigate the risk that this test will be misused or used inappropriately for the proposed indication in patient management. Suggestions included that the warnings and/or limitations cover women who have undergone hysterectomy, non-indicated collection methods, non-indicated colposcopies and HPV negative cancers.

Voting Questions and Discussion:

The panel unanimously agreed that there a reasonable assurance that the **cobas**® HPV Test is safe for the proposed indication for use. Total Yes: 13 (thirteen). Total No: 0 (zero). Total Abstain: 0 (zero).

The panel unanimously agreed that there a reasonable assurance that the **cobas**® HPV Test is effective for the proposed indication for use. Total Yes: 13 (thirteen). Total No: 0 (zero). Total Abstain: 0 (zero).

The panel unanimously agreed that the benefits of the **cobas**® HPV Test for the proposed indication for use outweigh the risks of the **cobas**® HPV Test for the proposed indication. Total Yes: 13 (thirteen). Total No: 0 (zero). Total Abstain: 0 (zero).

Public Speakers

Multiple Open Public Speakers attended the meeting. These included: Warner Huh, MD, Society of Gynecologic Oncology, Foundation for Gynecologic Oncology; Walter Kinney MD, Division of Gynecologic Oncology; the Permanente Medical Group; Mark Schiffman, MD, MPH, Division of Cancer Epidemiology and Genetics National Cancer Institute, NIH; Dorothy Rosenthal, MD, Johns Hopkins University; Jennifer S. Smith, PhD, MPH, Cervical Cancer-Free Coalition; Heather Banks on behalf of herself; R. Marshall Austin, MD, PhD Magee-Women's Hospital of University of Pittsburgh Medical Center; Anna Mazzucco, PhD, Cancer Prevention and Treatment Fund; Michele Prigo on behalf of herself; Deborah Arrindell, American Sexual Health Association; Lee P. Shulman MD, Northwestern University; Keith Gantner, Women's Health Diagnostics and Patricia Wasserman, MD, American Society of Cytopathology.

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