PLEASE NOTE: *This trial has been registered retrospectively.*

Trial Description

Title

Clinical Evaluation of the CINtec® Cytology Dual Stain Kit as a Screening Test as well as a Reflex Test in the Triage of Women with a Pap Cytology Result of ASC-US or LSIL

Trial Acronym

The PALMS- Trial - "Primary, ASC-US, LSIL Marker Study"

URL of the trial

[---]*

Brief Summary in Lay Language

The PALMS study is a multinational, diagnostic study for evaluation a new biomarker test (CINtec® Cytology Dual Stain) in the prevention of cervical cancer disease.
In the course of the general gynecological cancer screening, the gynecologists perform a Pap test to examine the cells of the cervix for changes. The aim of this trial is to determine whether the new test can more reliably detect women with cytological abnormalities of the cervix and distinguish them from those that do not require further treatment.
In the course of a gynecological examination a smear will be taken from all participants. The smear is then evaluated with the Pap method. Next, another smear is taken for the HPV test that detects the virus responsible for cervical cancer. The rest of the Pap smear is used for an evaluation with the new test method. If one or more of the tests (Pap, HPV or the new test) show an abnormality, the gynecologist will make an appointment for a special consultation (dysplasia consultation). In the course of this consultation a colposcopy will be performed. If the colposcopy indicates an abnormality, a tissue sample from the area will be taken, as per standard procedure. This sample is then examined for premalignant and malignant lesions. At the end of the study a statistical analysis will be performed to evaluate which test was more reliable in identifying women with cytological abnormalities of the cervix and in distinguishing them from those that do not require further treatment.
The trial will be performed in Europe and approximately 27.000 women will be recruited.

Brief Summary in Scientific Language

Study Device:
CINtec Cytology Dual Stain is an immunochemistry based biomarker combination of two biomarkers, p16 and Ki-67, provided in a single test

Study Rationale:
The purpose of this study was to evaluate the performance characteristics of the

CINtec Cytology Dual Stain Kit for the identification of women with established high-grade cervical intra-epithelial lesions (HGCIN).
The overall aim of the study was to investigate the clinical utility of CINtec Cytology Dual Stain as a screening test as well as a reflex test to the routine Pap cytology.

Study Objectives:
Main objective:
To evaluate the sensitivity and specificity of CINtec Cytology Dual Stain for identifying HGCIN (CIN2+/CIN3+)
in a primary cervical cancer screening setting,
in women with a Pap cytology result of ASC-US,
in women with a Pap cytology result of LSIL.
Additional major objectives:
To compare the sensitivity and specificity of the CINtec Cytology Dual Stain for identifying HGCIN (CIN2+/CIN3+) in a primary cancer screening setting with the sensitivity and specificity of the following tests or test combinations:
Pap cytology,
Combined Pap cytology and CINtec Cytology Dual Stain testing,
HPV-testing using High-Risk HPV hc2 Test® (in women aged 30 years or older only).
To compare the sensitivity and specificity of CINtec Cytology Dual Stain for detecting HGCIN (CIN2+/CIN3+) with the sensitivity and specificity of the High-Risk HPV hc2 Test for women with a Pap cytology result of ASC-US or LSIL (combined evaluation of the ASC-US and LSIL group as well as evaluation of the ASC-US and LSIL group separately).

Study Design:
Multinational, multicenter, prospective diagnostic study

Study Subjects:
Enrolment of women undergoing a routine cervical cancer screening based on Pap cytology testing and evaluated according to the Bethesda classification system, aged 18 to 65, with signed written informed consent.

Tests performed:
- CINtec Cytology Dual Stain Kit (mtm laboratories)
- Pap cytology test: Conventional Pap smear, or ThinPrep® Pap Test or SurePath® Pap Test
- HPV test: digene High-risk HPV hc2 Test®

Study Samples:
First cervical sample collected using either spatula/brush or broom-type sampling device:
-Conventional smear: first slide prepared for Pap staining; second glass slide prepared from left-over material on the sampling device (split sample technique) and used for CINtec Cytology Dual Stain

**HPV testing performed in centralized laboratories in France, Italy, and Germany
CINtec Cytology Dual Stain cytology testing: Slide preparation and immunostaining performed centrally at the sponsor´s laboratories; slide interpretation performed by individual members of a team of cytotechnologists in Germany (independent cytotechnologists, specifically contracted for Dual stained Cytology reading in the course of the PALMS trial), as well as by European pathologists**

Women were referred to colposcopy based on a positive test result for either Pap cytology (ASC-US or higher), and/or CINtec Cytology Dual Stain dual stained cytology, and/or a positive High-risk HPV test. In case the HPV test was the only positive test result, then only women aged 30 or higher were referred to colposcopy.

**Gold standard:
Histology diagnoses on biopsy materials served as clinical endpoints.
All local histology results were verified by members of an independent QC review board of five European pathologists, masked to the clinical center interpretation and all other test results.
-The QC review of each histological diagnosis was assigned to one member of the QC review board and was based on the review of the H&E stained slide. In case the result of the QC review was concordant with the local center diagnosis, this diagnosis was regarded as final study diagnosis, unless HGCIN was diagnosed by the local pathologist. All HGCIN cases as well as all cases with discrepant results between the local pathologist and the first QC reviewer were subjected to an extended QC review. At least one additional QC pathologist reviewed these cases. In case of concordant results for both QC reviewers, the QC review result was regarded as final study result. In case of a discrepancy in the diagnosis of these two expert pathologists, the slides were reviewed by at least a third independent expert pathologist. The majority consensus diagnosis of the QC reviewers was regarded as final study diagnosis (adjudication in cases where no majority consensus diagnosis was achieved).**

-For all tissue specimens, a parallel section stained for p16 was evaluated regarding its staining pattern (i.e. diffuse positive, vs. focal or no staining, considered as negative). For all cases with diffuse staining pattern, but no CIN diagnosed per final H&E result, as well as all cases with focal or negative staining pattern, but CIN2+ diagnosed per final H&E result, a separate conjunctive analysis of the H&E and p16 stained slides was performed by three QC review pathologists during an adjudication meeting.

**Sample size/Statistics:
Sample size calculation for the main objective (comparison of sensitivities between Pap cytology and CINtec Cytology Dual Stain testing for the identification of CIN2+) based on a disease prevalence estimate of 0.8% and alpha =0.05, Power of 90% revealed a sample size of > 25,500 subjects, assuming a drop-out rate of 25%.
For the evaluation of the triage performance, sample size considerations were based on estimation of sensitivity and specificity rates with confidence intervals of**

Organizational Data

- DRKS-ID: **DRKS00000408**
- Date of Registration in DRKS: **2010/05/14**
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Date of Registration in DRKS: **2010/05/14**
Date of Registration in Partner Registry or other Primary Registry: **[---]***

- Investigator Sponsored/Initiated Trial (IST/IIT): **no**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **2008394 , Ethikkommission der Ärztekammer Nordrhein**

Secondary IDs

- Universal Trial Number (UTN): **U1111-1114-8436**
- Sponsor-ID: **9522-08-REG-EP-001 (mtm laboratories AG)**

Health condition or Problem studied

- Free text: **cervical cancer, High-grade lesion of cervix uteri**
- ICD10: **N87.2 - Severe cervical dysplasia, not elsewhere classified**

Interventions/Observational Groups

- Arm 1: **Pap cytology**
- Arm 2: **CINtec Cytology Dual Stain**
- Arm 3: **HR-HPV test**

Characteristics

- Study Type: **Non-interventional**
- Study Type Non-Interventional: **Other**
- Allocation: **Other**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Other**
- Purpose: **Screening**
- Assignment: **Other**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

Evaluation of the senitivity and specificity of CINtec cytology Dual Stain for identifying HGCIN (CIN2+/CIN3+) employing the quality-controlled histology diagnosis of cervical biopsies as gold standard.

Secondary Outcome

Comparison of the sensitivity and specificity of CINtec Cytology Dual Staining for identifying HGCIN with the sensitivity and specificity of the follwing tests:
- Pap cytology
- HR-HPV test

Countries of recruitment

- BE **Belgium**
- DE **Germany**
- IT **Italy**
- ES **Spain**
- FR **France**

Locations of Recruitment

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2009/02/09**
- Target Sample Size: **27000**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Female**
- Minimum Age: **18 Years**
- Maximum Age: **65 Years**

Additional Inclusion Criteria

Women undergoing a routine cervical cancer screening based on Pap cytology testing or women with a Pap cytology result of ASC-US or LSIL based on liquid-based cytology and evaluated according to the Bethesda classification system,

Signed, written informed consent.

Exclusion criteria

Women who are pregnant,

Women with a history of hysterectomy (except a supracervical hysterectomy),

Women who are unwilling or unable to provide informed consent and/or to adhere to study requirements.

Addresses

- **Primary Sponsor**

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Sources of Monetary or Material Support

- **Commercial (pharmaceutical industry, medical engineering industry, etc.)**

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Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2010/01/13**

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*
**** This entry means that data is not displayed due to insufficient data privacy clearing.*