

Sixty-Ninth Meeting of the  
**Obstetrics and Gynecology Devices Panel**

*Tuesday, May 17, 2005  
Holiday Inn, Gaithersburg, Maryland*

**MediSpectra LUMA (P040028)**

DRAFT Discussion Questions, 4/29/05

Safety and Effectiveness

1. The two co-primary effectiveness endpoints of Pivotal Study I (PS I) pertained to true positive (TP) and false positive (FP) rates. Individual subjects were TP, FP, or negative as follows.
  - TP subject: one or more biopsies taken, at least one was CIN 2/3+ positive
  - FP subject: one or more biopsies taken, none was CIN 2/3+ positive
  - negative subject: no biopsies taken

TP and FP rates were calculated by dividing the numbers of TP and FP subjects by the total numbers of subjects.

- a. For the original study population (i.e. all per protocol subjects), the FP endpoint was met, but the difference of TP rates was not statistically significant. Please discuss the strength of these findings relative to the proposed indication, i.e. as an adjunct to colposcopy for use in patients referred with ASCUS or LSIL cervical cytology results after a thorough colposcopic evaluation with identification or selection of biopsy sites.

**PS I, Original Population: All Subjects**

	<b>Colpo-only % (n/N)</b>	<b>LUMA+Colpo % (n/N)</b>	<b>Difference (95% CI)</b>	<b>Met Hypothesis?</b>
<b>TP</b>	19.9% (218/1096)	21.8% (238/1090)	1.9% (-1.5%, 5.3%)	<b>No:</b> 95% CI includes 0
<b>FP</b>	57.4% (629/1096)	60.5% (659/1090)	<b>3.1%</b> <b>(-1.0%, 7.2%)</b>	<b>Yes:</b> 95% CI <8%

- b. The original population in the clinical trials was women referred for colposcopy because of an abnormal Pap smear result (first-time ASC-US/-H, repeat ASC-US/-H, LSIL, HSIL, or squamous cell cervical cancer). The proposed indication is for a portion of this population, the ASCUS/LSIL Pap referrals. Please discuss the clinical significance of this proposed population.

- c. For the ASCUS/LSIL sub-population, neither the TP nor the FP endpoint was met in PS I. Please discuss the significance of these findings. Note that the analysis for this sub-population was not pre-specified.

**PS I, Proposed Patient Population: ASCUS/LSIL Subjects**

	<b>Colpo-only % (n/N)</b>	<b>LUMA+Colpo % (n/N)</b>	<b>Difference (95% CI)</b>	<b>Met Hypothesis?</b>
<b>TP</b>	11.4% (99/871)	14.4% (126/876)	3.0% (-0.1%, 6.1%)	<b>No:</b> 95% CI includes 0
<b>FP</b>	61.2% (533/871)	65.2% (571/876)	4.0% (-0.5%, 8.5%)	<b>No:</b> 95% CI includes 8%

2. Please comment on the observed age-related device performance seen in PS I, i.e. the increase in the TP rate was observed primarily among patients in the <21 age group across all Pap strata. What are the clinical implications of this finding?
3. a. In Pivotal Study II (PS II), for the original study population, the TP endpoint was met, but the FP endpoint was not met, i.e. there was 95% confidence that the LUMA increment of TP exceeds 2%, but there was not 95% confidence that the LUMA increment of FP would be less than 15%. Please discuss the strength of these findings relative to the proposed indication, i.e. as an adjunct to colposcopy for use in patients referred with ASCUS or LSIL cervical cytology results after a thorough colposcopic evaluation with identification or selection of biopsy sites.

**PS II, Original Population: All Subjects** (*per protocol definition of LUMA increment*)

	<b>Initial Colposcopy</b>		<b>LUMA Increment</b>		<b>Met Hypothesis?</b>
	<b>Rate (n/N)</b>	<b>95% CI</b>	<b>Rate (n/N)</b>	<b>95% CI</b>	
<b>TP</b>	21.2% (41/193)	15.7%, 27.7%	<b>4.7%</b> (9/193)	<b>2.2%, 8.7%</b>	<b>Yes:</b> 95% CI >2%
<b>FP</b>	51.8% (100/193)	44.5%, 59.0%	18.1% (35/193)	13.0%, 24.3%	<b>No:</b> 95% CI includes 15%

- b. For the ASCUS/LSIL sub-population, neither the TP nor the FP endpoint was met in PS II. Please discuss the significance of these findings. Note that the analysis for this sub-population was not pre-specified.

**PS II, Proposed Patient Population: ASCUS/LSIL Subjects** (*per protocol definition of LUMA increment*)

	<b>Initial Colposcopy</b>		<b>LUMA Increment</b>		<b>Met Hypothesis?</b>
	<b>Rate (n/N)</b>	<b>95% CI</b>	<b>Rate (n/N)</b>	<b>95% CI</b>	
<b>TP</b>	14.4% (24/167)	9.4%, 20.6%	3.6% (6/167)	1.3%, 7.7%	<b>No:</b> 95% CI includes 2%
<b>FP</b>	55.7% (93/167)	47.8%, 63.4%	20.4% (34/167/193)	14.5%, 27.3%	<b>No:</b> 95% CI includes 15%

4. The Sponsor has proposed two changes to the analysis of TP rate for PS II compared to the original protocol:
  - i. changing the success criteria based on observed prevalence, and assigning success criteria to each Pap substrata,
  - ii. changing the denominator for calculating TP rate.

As indicated below, with these changes, the study meets the revised TP requirements for both the overall population and the ASCUS/LSIL sub-population. For analogous changes to the FP rate analysis, the study does not meet the revised FP requirements for either the overall or the ASCUS/LSIL populations. Please discuss the significance of these results.

**PS II TP Results, (1) Different Null Hypothesis Gets Assigned to Each Pap Substratum, and (2) Denominator is Calculated Differently from Original Agreement with FDA**

<i>Stratum</i>	TP Hypothesis	95% CI for LUMA Increment	
		Per protocol, Full Denominator	New Definition, Reduced Denominator
<b>All Subjects</b>	>2%	<b>2.2%, 8.7%</b> <b>(p=0.0164)</b>	<b>2.7%, 10.9%</b> <b>(p=0.0037)</b>
<b>ASCUS/LSIL</b>	>1.5%	1.3%, 7.7% (p=0.0411)	<b>1.6%, 8.9%</b> <b>(p=0.0214)</b>

5. Based on the results of PS I, LUMA's false negative (FN) rate can be estimated to be 23% when colposcopy is used as the gold standard to determine true disease status, i.e. of all CIN 2/3+ patients found by colposcopy, 23% were not be found by LUMA. In PS II, 22% of the TP biopsies identified by colposcopy were not identified by LUMA.

These false negative rates underscore the importance of the "Always-Never" rule. Does the panel believe that this risk of false negatives is adequately mitigated by the indication statement (for use only after a thorough colposcopic evaluation with identification or selection of biopsy sites)?

6. Are there any safety concerns associated with use of this device?
7. Do the planned and unplanned analyses of PS I and PS II demonstrate the safety and effectiveness of this device for the ASCUS/LSIL population, i.e.
  - a. Do the probable benefits to health from use of the device outweigh any probable risks?
  - b. Will use of the device provide clinically significant results?

### Labeling & Training

8. Does the panel have any comments on the labeling and instructions for use provided by the sponsor?
9. Does the panel have any concerns about the training needed to use this device safely and effectively?

### Post-approval Study

10. Does the panel have concerns about any issues that should be addressed in a post-approval study?

*Note: Post-approval studies may provide additional information about an approved device; however, the safety and effectiveness must be demonstrated before approval. The results of a post-approval study should not be expected to change the "approval" status of the device.*