LUMA™ Cervical Imaging System

Mridulika Virmani, Ph.D.

Joyce M. Whang, Ph.D.

lead reviewers

CDRH/ODE/DRARD

History of FDA Review

- **513(a) determination** August 2000
  - Class III, PMA (pre-market approval)
  - possible indications:
    - triage following an abnormal Pap smear
    - adjunct to colposcopy
  - randomized controlled trial with histopathology results
  - algorithm locked before study begins

History of FDA Review

- **non-significant risk (NSR)**

  February 2001

  – device characteristics

  – study design

  Investigational Device Exemption (IDE) approval not needed.

History of FDA Review

- **510(g)(7) agreement letter (PS II)**
  February 2003

  proposed indication: as an adjunct to colposcopy in identifying regions of the ectocervix that most likely represent CIN 2/3+ for colposcopically directed biopsy

History of FDA Review

- **PMA submitted** June 2004

  Expedited Status

  proposed indication: as an adjunct to colposcopy for the identification of high-grade disease (CIN 2/3+) in patients referred to colposcopy with an ASCUS or LSIL cervical cytology result. LUMA is not intended to replace colposcopy. A thorough colposcopic evaluation with an identification or selection of biopsy sites must be performed independently and prior to the viewing of the LUMA results.

Device Description

FDA Review Team

- Mridulika Virmani, Ph.D -- lead reviewer and biocompatibility
- Joyce M. Whang, Ph.D. -- lead reviewer
- Julia A. Carey-Corrado, M.D. -- clinical safety & efficacy
- Danica Marinac-Dabic, M.D., Ph.D. -- epidemiology
- Gene Pennello, Ph.D. -- statistics
- Anant Agrawal, M.S. -- electro-optics
- Brandon D. Gallas, Ph.D. -- algorithm
- Joseph Jorgens III -- software
- Donald Witters -- electromagnetic compatibility (EMC)
- Wolfgang Kainz, Ph.D. -- electromagnetic compatibility (EMC)
- Ray L. Walchle -- electrical safety
- J. Michael Kuchinski -- disinfection & cleaning
- Veronica A. Price -- mechanical design and performance
- Sharon Murrain-Ellerbe -- manufacturing
- Kevin M. Hopson -- bioresearch monitoring

Major Review Topics

- Electro-optics
- Algorithm Development
- Bioresearch Monitoring
- Manufacturing
- Clinical
- Statistical

Major Review Topics

- **Electro-optics**
  - exposure to UV and visible light
  - optical performance
  - calibration methods
  - medications
  - cervicitis
  - interactions between UV light and HPV

Major Review Topics

- **Algorithm Development**
  - how it was developed
  - how it works
  - changes between PS I and PS II

Major Review Topics

- Electro-optics
- Algorithm Development
- **Bioresearch Monitoring**
- Manufacturing
- Clinical
- Statistical

Major Review Topics

- Electro-optics
- Algorithm Development
- Bioresearch Monitoring
- **Manufacturing**
- Clinical
- Statistical

Major Review Topics

- Electro-optics
- Algorithm Development
- Bioresearch Monitoring
- Manufacturing
- **Clinical**: Dr. Carey-Corrado
- **Statistical**: Dr. Pennello

FDA Clinical Review of LUMA Cervical Imaging System

Julia Carey-Corrado, MD
CDRH/ODE/OGDB

FDA Clinical Presentation

- Proposed Indication for Use
- Design and Results of Pivotal Study 1 (PS1)
- Design and Results of Pivotal Study 2 (PS2)
- Panel Discussion Questions

LUMA Indication for Use

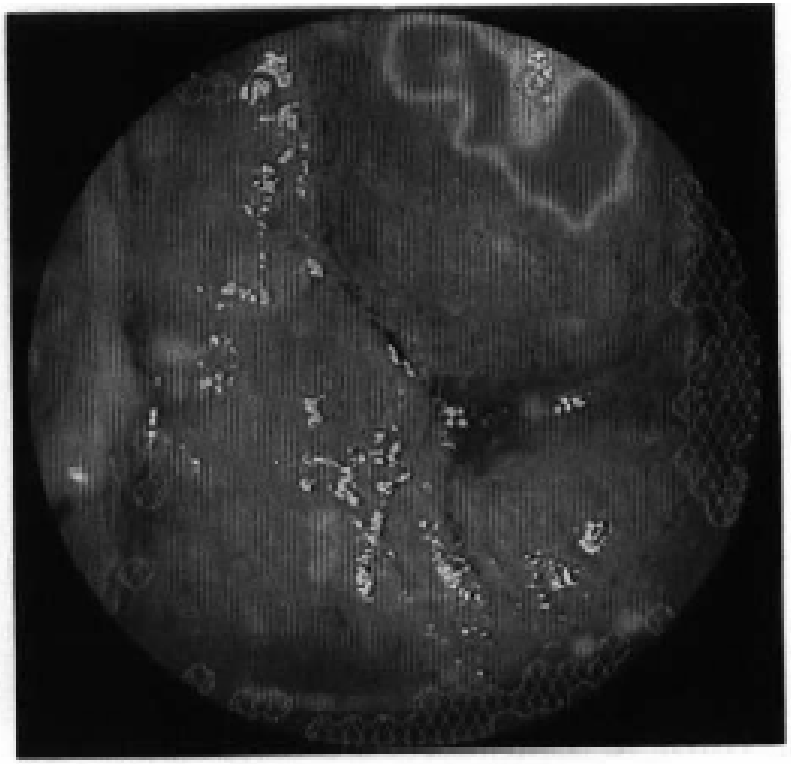
- Adjunct to colposcopy in identifying high grade disease (CIN 2/3+) in patients referred to colposcopy with an ASCUS or LSIL cytology test result. LUMA is not intended to replace colposcopy. A thorough colposcopic evaluation with identification and selection of biopsy sites must be performed independently of and prior to viewing the LUMA result.

Indication for Use

- Commitment to colposcopy-directed biopsy sites prior to identification of LUMA-directed biopsy sites
- Breast CAD precedent
  - “Always/Never Rule”

Sample LUMA Image

Original Cervix



Cervix with Overlay

Comparison of PSI and PSII

	PSI	PSII
Study Design	Randomized, controlled	Single arm, pt as own control
Sample Size	2299	228 (788 planned)
Treatment Arm	Simultaneous (LUMA and colpo)	Sequential (first colpo then LUMA)
Primary Endpoints	TP increase>0% FP increase<8%	TP increment >2% FP increment<15%

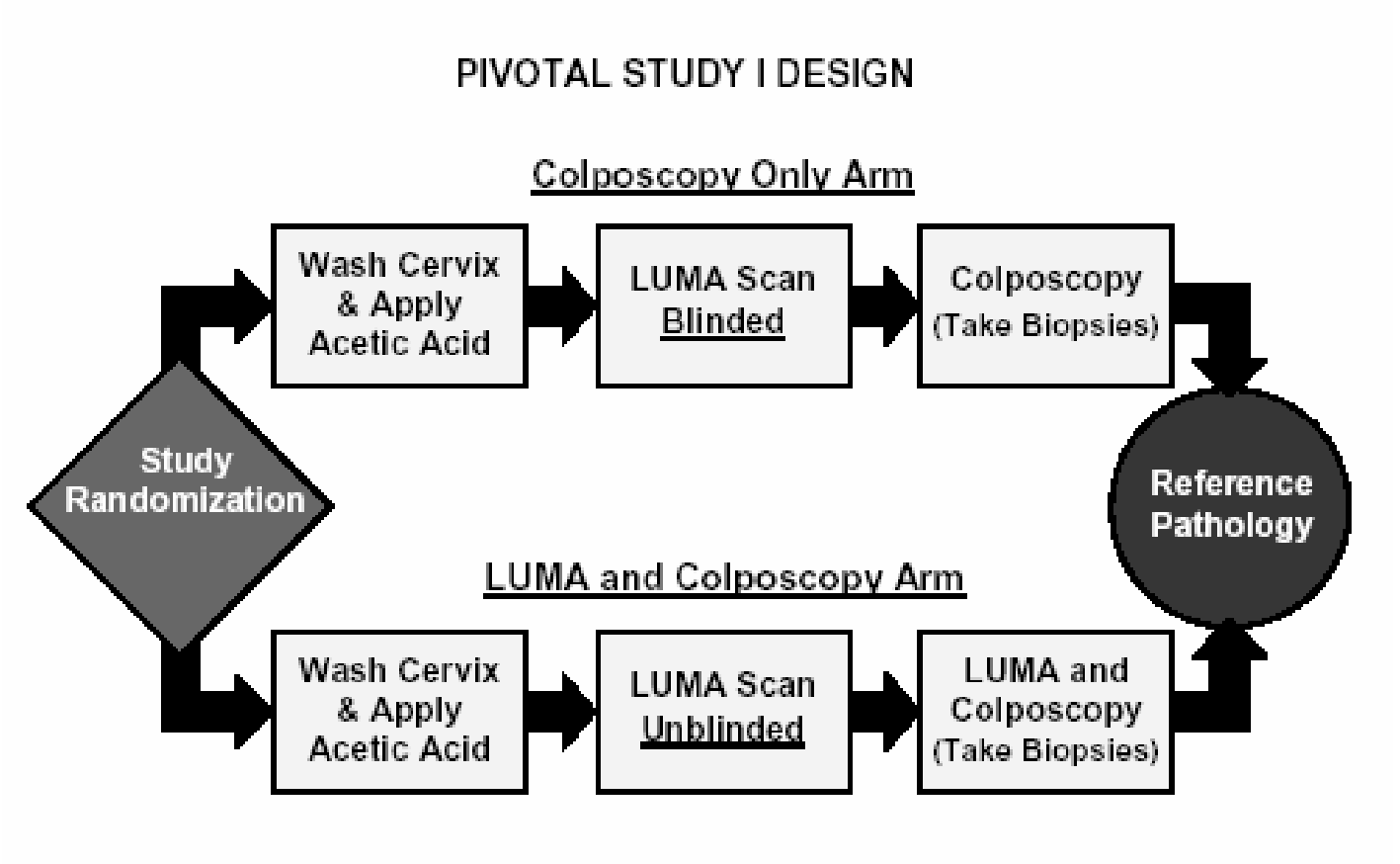
LUMA System PS1 – Study Definitions

- Definitions
  - “TP rate”: number of TP subjects divided by total number of subjects
  - “FP rate”: number of FP subjects divided by the total number of subjects

LUMA System PS1 – Study Endpoints

- PS1 not designed to determine "sensitivity" of LUMA to detect CIN 2/3+

Pivotal Study 1 – Study Steps



PS1 Primary Endpoints

- Subject level TP rate greater in LUMA+colpo arm
- Increase in subject level FP rate in LUMA+colpo arm compared to colpo only arm <8%

PS1 Results – Overall

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

PS1 Results –ASCUS/-H, LSIL subjects (post hoc analysis)

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

PS1 False Negative Analysis

- LUMA alone would have missed some CIN 2/3+ lesions found by colposcopy;
- Colposcopy alone would have missed some CIN 2/3+ lesions found by LUMA:

Panel Discussion Question 5

LUMA PS1 - Conclusions

Panel Discussion Question 1a

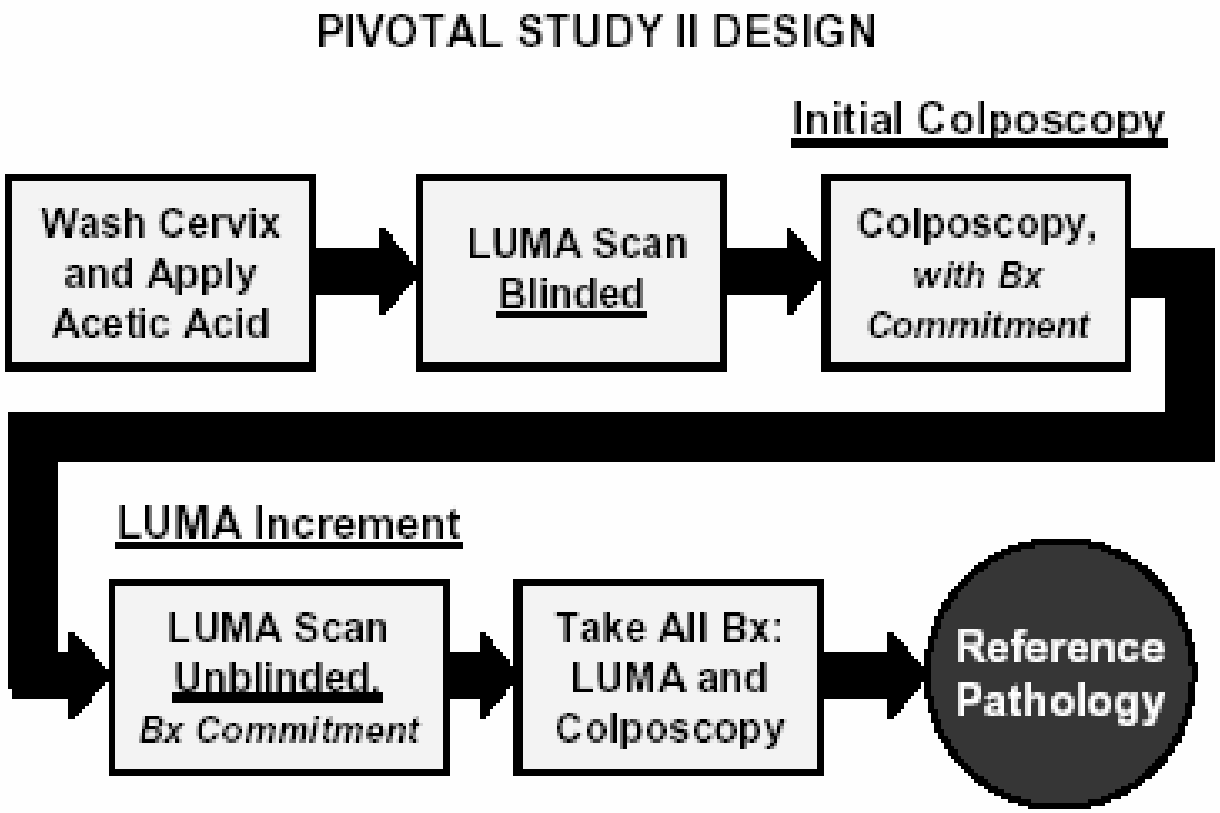
Panel Discussion Question 1b and 1c

Panel Discussion Question 2

LUMA PS2

- Prospective, non-randomized, multi-center, subject as own control
- 228 subjects (powered for 788)
- Primary endpoints:
  - LUMA TP rate increment >2%
  - LUMA FP rate increment <15%

PS2 – Study Steps



LUMA PSII

- In PSII, LUMA overlay was reviewed only after thorough colposcopy and selection of biopsy sites was done
- This study design allows for assessment of diagnostic capability of LUMA for identifying patients with CIN2/3+ above what colposcopy can accomplish

PS2 Results – Overall Study Population

	Initial colpo % (N=193) (95% CI)	LUMA increment % (N=193) (95% CI)	Met Hyp?
TP	21.2 (15.7, 27.7)	4.7 (2.2, 8.7)	Yes
FP	51.8 (44.5, 59.0)	18.1 (13.0, 24.3)	No

PS2 Results – ASCUS / -H, LSIL Subjects (post-hoc analysis)

	Initial Colpo % (N=167) (95% CI)	LUMA increment % (N=167) (95% CI)	Met Hyp?
TP	14.4 (9.4, 20.6)	3.6 (1.3, 7.7)	No
FP	55.7 (47.8, 63.4)	20.4 (14.5, 27.3)	No

Panel Discussion Question 3

PS2 Results – ASCUS/-H, LSIL Subjects (post hoc, eligible population definition)

- Hypothesis for TP success lowered from 2.5% to 2.0% (in overall population) to 1.5% within ASCUS/-H, LSIL stratum based on lower than assumed disease prevalence
- Definition of denominator in TP rate calculation changed from “all subjects” to “all subjects minus those already detected by colpo”

PS2 Results – ASCUS / -H, LSIL Subjects (post hoc, eligible population definition)

- Example:
  - Original study endpoint definition of TP
    - 6/167 X 100 = 3.6% (95% CI 1.3, 7.7)
  - Eligible population definition of TP
    - 6/143 X 100% = 4.2% (95% CI 1.6, 8.9)

Panel Discussion Question 4

Safety Issues - PS1 and PS2 Adverse Event Reports

- Cramping (2)
- Vomiting (1)
- Weakness (1)
- Vaginal bleeding (1)
- Fainting (3)
- Abdominal pain (1)
- Dysuria (1)

Safety Issues

- Increase in FP biopsies
- Higher rate of FN compared to colposcopy

Safety Issues - Risk to Patient From UV Exposure

- Theoretical
  - HPV activation
  - Cellular damage
- Risk assessment based on pre-clinical data

Panel Discussion Question 6

Conclusion

- Results of PS1 and PS2 planned and post hoc analyses
- Benefits vs. risks of LUMA
- Patient population (ASCUS/-H, LSIL)
- Strictly adjunctive (to colposcopy) role for LUMA

Panel Discussion Question 8

Medispectra LUMA:

Statistical Design and Analysis of Pivotal Studies I and II

Gene Pennello, Ph. D.

Division of Biostatistics

Center for Devices and Radiological Health

Outline

- **Endpoint definitions**
- **PS I**
  Study design, accountability, analysis
- **PS II**
  Study design, accountability, analysis
- **Summary**

ENDPOINTS

Evaluating Diagnostics

Diagnostic Test Has Two Outcomes:
Test is + for disease
Test is – for disease

Evaluate trade-off between

detecting disease	***falsely* detecting disease**
test + when disease is present	test + when disease is absent

Evaluating Diagnostics

EX. LEEP every subject

All subjects are test + regardless.

All subjects with CIN 2/3+ detected,

but at the expense of

all subjects without CIN 2/3+ undergoing LEEP.

LUMA Adjunct to Colposcopy

Subject level:

Subject is test + if biopsies taken

test – if no biopsies taken.

Biopsy level:

Biopsies are all test +

Regions not biopsied are test –

Clinically, more important to detect disease at subject level than at biopsy level.

Subject TPs, FPs, Negatives

TP subject: biopsies taken,
some are CIN2/3+ positive

FP subject: biopsies taken,
none are CIN2/3+ positive

Negative: no biopsies taken

Limitations

Biopsy location matters: FP subject could be FN (have CIN 2/3+ elsewhere)!

Accuracy of negatives unavailable.

Endpoint Pair, PS I and PS II

Subject

TP Rate =

$$\frac{\text{\# TP subjects}}{\text{total \# subjects}}$$

Subject

FP Rate =

$$\frac{\text{\# FP subjects}}{\text{total \# subjects}}$$

LUMA+colpo and colpo only compared on TP, FP rate trade-off.

More Common Endpoint Pair (1)

Subject sensitivity =

$$\frac{\text{\# TP subjects}}{\text{\# with CIN 2/3+}}$$

Subject 1 – specificity =

$$\frac{\text{\# FP subjects}}{\text{\# w/o CIN2/3+}}$$

Denominators not available in PS I, PS II.

Better than TP, FP rate pair because sensitivity, specificity measure accuracy.

More Common Endpoint Pair (2)

Positive, Negative Predictive Values:

PPV =

$$\frac{\#\ \text{TP's}}{\#\ \text{test +'s}}$$

1 – NPV =

$$\frac{\#\ \text{FN's}}{\#\ \text{test –'s}}$$

In PS I, PS II,
PPV estimable at subject and biopsy level.
NPV not estimable at either level.

Later, will discuss PPV at biopsy level.

Comparison of PS I and PS II

	PS I	PS II
Agreement Letter	No	Yes
Study Design	Two-arm, randomized controlled trial	one-arm, paired design
Sample Size	2299	227 (788 planned, stopped early)
Treatment Group	simultaneous LUMA + colpo evaluation	colpo followed by LUMA increment
Primary Endpoints	TP rate increase > 0% FP rate increase < 8%	TP rate increment > 2% FP rate increment < 15%

PIVOTAL STUDY I (PS I)

Study Design

Randomized Controlled Study

***Arms*:** LUMA+Colpo simultaneous evaluation
Colpo-only evaluation

Randomization stratified by

Colposcopist

PAP Stratum: 1st-time ASC-US/-H
repeat ASC-US/-H
LSIL
HSIL

Study Design Limitation

Colposcopist not blinded to arm to which subject was randomized.

Differential in level of colposcopy possible
Colposcopy could have been better in
LUMA+colpo arm ("placebo" effect),
colpo only arm (due to reliance on LUMA)

TP & FP rate comparisons between arms
confound LUMA effect with
any differential in colposcopy.

Subject Accountability

	All			ASCUS/LSIL		
	LUMA +Colpo Arm	**Colpo-Only Arm**	**Both Arms**	**LUMA +Colpo Arm**	**Colpo-Only Arm**	**Both Arms**
Intent to Diagnose	NA	NA	2299	NA	NA	1830
Not Randomized	NA	NA	27	NA	NA	22
Randomized	1139	1133	2272	911	897	1808
Excluded	49	37	86	35	26	61
-Due to Pathology*	21	20	41 (1.8%)	14	13	27 (1.5%)
Per Protocol	1090	1096	2186	876	871	1747

*Subjects excluded because of “no majority pathology” <u>for all</u> biopsies.

Subject TP and FP Rates, All Subjects (Primary Analysis)

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

For all subjects, study
failed to show TP rate difference > 0%.
demonstrated FP rate difference < 8%

Subject TP and FP Rates by Individual Pap Stratum

Secondary analyses were pre-specified for ASCUS, LSIL, and HSIL,
but ***not*** for combinations of these groups.

Seven possible groupings:

ASCUS	ASCUS/LSIL	All
LSIL	ASCUS/HSIL	
HSIL	LSIL/HSIL	

Statistical Procedures to Test Multiple Subgroups

Adjust significance level to control overall chance of a falsely significant result.

Bonferroni: test 7 groupings at 5%/7= 0.7%

Gatekeeper:

If all subjects significant at 5%

then test 6 PAP subgroups at 5%/6 = 0.8%

Gatekeeper more likely to have been pre-specified.

Subject TP and FP Rates, ASCUS/LSIL Subgroup (Post Hoc)

PS I

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

For post hoc ASCUS/LSIL subgroup, study failed to show TP rate difference > 0%, failed to show FP rate difference < 8%

Per Biopsy Analysis: Positive Predictive Value, LUMA+Colpo Arm

PS I

Per Biopsy PPV a Secondary Endpoint

PPV: % biopsies confirmed to be CIN 2/3+

PPV in LUMA+colpo arm stratified by biopsy reason:

Colpo-only
LUMA-only
Both

Biopsy PPV, LUMA+Colpo Arm

Colpo-indicated biopsies

PAP Stratum	LUMA + Colpo Arm Reason Given for Biopsy		p Value for Difference
	Colpo-only	Both	
All	17.5%	28.8%	0.0005

LUMA selections better than random otherwise PPVs would be the same.

Not directly relevant to adjunctive use of LUMA.

Biopsy PPV, LUMA+Colpo Arm

LUMA-only indicated biopsies (PS I) vs. random biopsies (literature control).

PAP Stratum	Reason for Biopsy		p Value for Difference
	LUMA-only	Random*	
ASCUS	11.3%	3.6%	0.0001
LSIL	8.6%	1.7%	

*Based on Shanxi Province Cervical Cancer Screening Study II (SPCCSS II). Pretorius et al. *Am J Obstet Gynecol* 2004, **191**: 430-434.

LUMA-only selections appear to be better than random.

Biopsy PPV, LUMA+Colpo Arm

Results only suggest that LUMA selections are better than random.

LUMA PPVs are based on
colposcopist choices of LUMA regions,
where to biopsy within those regions.

Even if LUMA PPVs are better than random, may not translate to detection of additional subjects with CIN 2/3+.

Joint Analyses (Post Hoc)

Consider TP, FP, Negative rates jointly.

Test for heterogeneity between arms.

End-point	All Subjects (p=.013)		ASCUS/LSIL (p=.001)	
	LUMA+ Colpo % (n/N)	Colpo-only % (n/N)	LUMA+ Colpo % (n/N)	Colpo-only % (n/N)
TP	21.8% (238/1090)	19.9% (218/1096)	14.4% (126/876)	11.4% (99/871)
FP	60.5% (659/1090)	57.4% (629/1096)	65.2% (571/876)	61.2% (533/871)
Neg-ative	17.7% (193/1090)	22.7% (249/1096)	20.4% (179/876)	27.4% (239/871)

Joint Analyses (Post Hoc)

1. Fisher Exact Test

Gatekeeper procedure used.

TP, FP, and negative rates shown to be heterogeneous for ASCUS/LSIL as well as all subjects (p = 0.013, 0.001).

Fisher test not specific on primary hypotheses (TP difference > 0%,
FP difference < 8%).

Joint Analyses (Post Hoc)

2. Grizzle-Starmer-Koch (GSK)

Multinomial regression model built in steps

HSIL excluded because of arm by PAP stratum interaction

Rates heterogeneous for ASCUS/LSIL ($p = 0.002$)

Joint Analyses (Post Hoc)

2. Grizzle-Starmer-Koch (GSK)

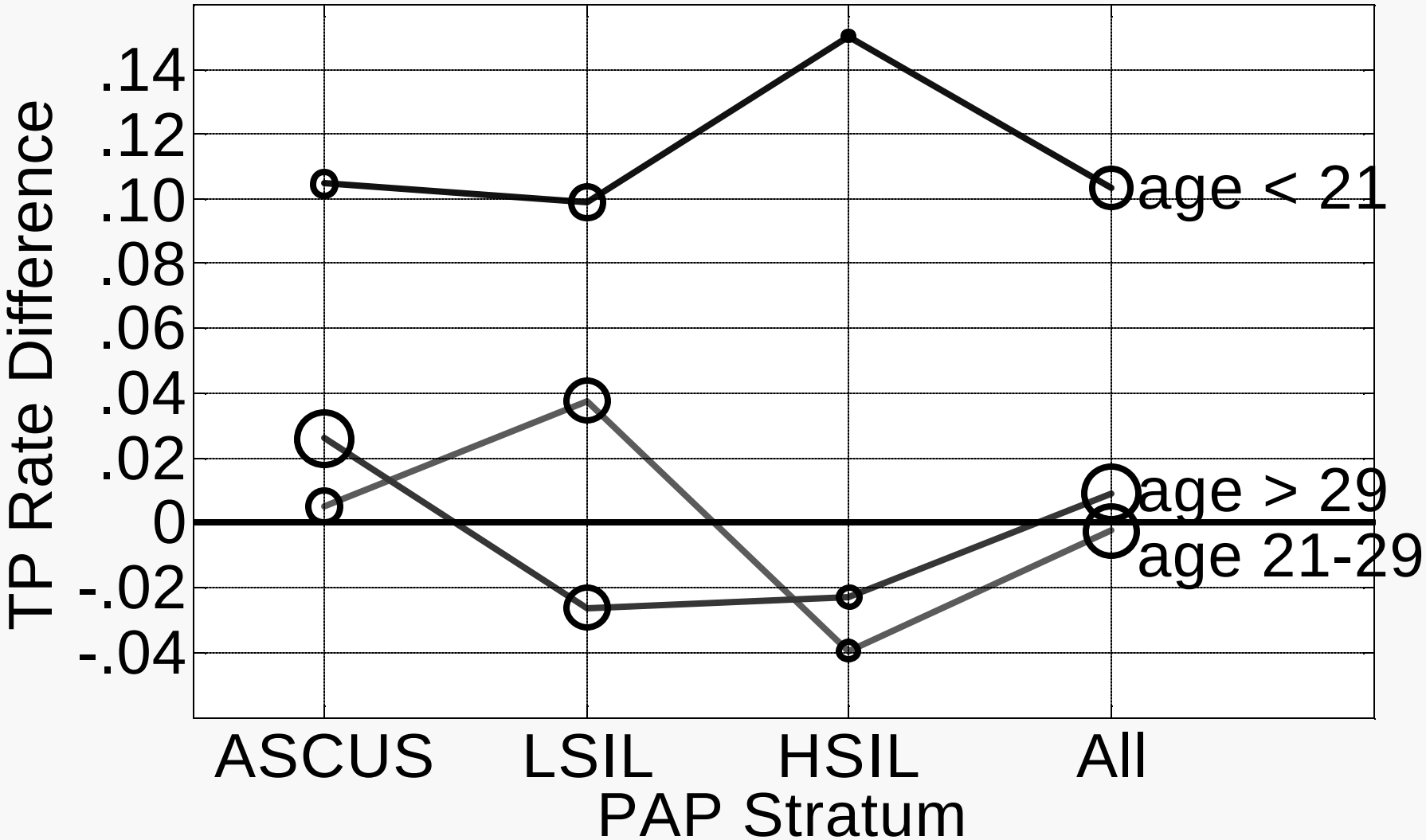
95% confidence region on TP, FP rate differences contains success criteria boundary point (0%, 8%).

TP rate difference > 0% not shown (p>0.025)
FP rate difference < 8% not tested.

Clinically, multinomial model is inadequate: TP, FP rate difference negatively, not positively correlated.

Age Effect (Post Hoc)

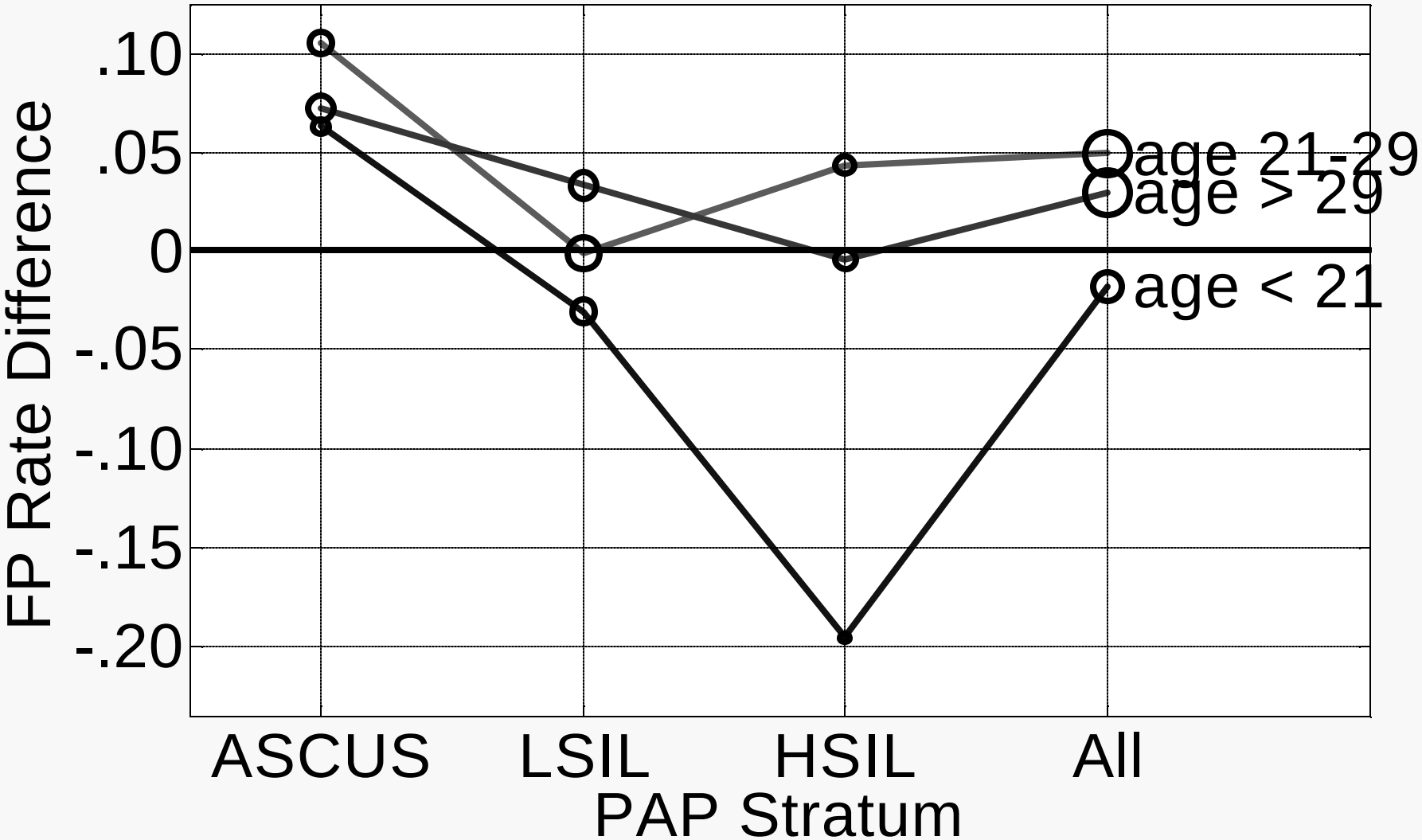
TP Rate Arm Difference by Age, PAP Stratum



Age Effect (Post Hoc)

PS I

FP Rate Arm Difference by Age, PAP Stratum



Age Effect (Post Hoc)

FDA Bayesian multinomial logistic model:

Effects Included: Arm, Age Group, PAP stratum, Arm by Age Interaction

Bayesian probability that subject rate > for LUMA+colpo arm than colpo-only arm:

	TP			FP		
	Age (years)			Age (years)		
	<21	21-29	> 29	<21	21-29	> 29
LSIL	1.00	0.79	0.54	0.62	0.96	0.90
ASCUS	1.00	0.74	0.49	0.42	0.93	0.90
HSIL	1.00	0.64	0.41	0.01	0.49	0.70

NOTE: Disagrees with Sponsor Analysis

Sponsor Age Effect Analyses

Age effect not significant for age group cuts other than < 21, 21-29, > 29 years.

Grizzle-Starmer-Koch (GSK)

HSIL excluded because of arm by PAP stratum interaction

Age by Arm interaction insignificant, but plots of observed vs. fitted values suggest lack of fit.

Sponsor Age Effect Analyses

Logistic Analysis

Age assumed to be continuous, ***linear*** predictor of TP, FP rates.

Arm by linear age interaction insignificant

Quadratic age term not included.

Other Possible Analyses:

Change point analysis.

Subject False Negative Rate

In LUMA+colpo arm, 126 TP subjects detected
26 detected by colpo
85 detected by colpo & LUMA
15 detected by LUMA .

Based on colpo-detected subjects,
LUMA false negative rate = 23% (26/111)

Based on LUMA-detected subjects,
Colpo false negative rate = 15% (15/100)

Suggests that adjunctive use of LUMA is needed to ensure FN rate is not increased.

Site/Colposcopist Variability

Site variability, ASCUS/LSIL:
significant in FP rate difference (p=0.0376),
insignificant in TP rate difference (p=0.4570)

Colposcopist Variability
Colposcopists considered fixed,
not a random sample from population.

Treating colposcopists as random
generalizes analysis to their population,
increases confidence interval widths.

PIVOTAL STUDY II (PS II)

Study Design

Single-Arm Study

Initial Colposcopy blinded to LUMA output.

Colposcopist commits to selections for biopsy

LUMA output revealed.

Additional LUMA-based biopsies can be taken.

Study Design

Planned Sample Size: 788 subjects.

Study terminated early at 227 subjects enrolled (29%).

Early stopping may not warrant a statistical penalty because sponsor blinded to data when decision to stop made, made a one-time test of data at that time.

Study Design Limitation

Undercall of initial colposcopy biases study in favor of finding a LUMA effect.

Undercall appears unlikely. Initial colposcopy similar to PS I colpo-only arm in

Mean # biopsies (0.9 vs. 1.0)
TP rate (21.2% vs. 19.9%)
Biopsy-level PPV (26.2% vs. 24.0%)

(Comparisons not adjusted for colposcopist, PAP strata.)

Study Design

By design, TP & FP rates cannot decrease.

Additional biopsies cannot decrease number of TP and FP subjects detected.

Formal agreement on success criteria:

incremental TP rate > 2% (not just 0%)

incremental FP rate < 15%

Subject Accountability

	All	ASCUS/LSIL
Intent to Diagnose	227	193
Excluded	34	26
Incomplete Pathology*	16 (7.0%)	12 (6.2%)
Per Protocol	193	167

*Subjects excluded because of incomplete pathology <u>for at least one</u> biopsy.

Incremental TP, FP Rates

Initial Colpo	Colpo + LUMA Increment			
	TP	FP	Negative	Total
TP	41	0	0	41
FP	**7**	93	0	100
Negative	**2**	**35**	15	52
Total	50	128	15	193

Incremental TP rate = 9/193 (4.7%)
Incremental FP rate = 35/193 (18.1%)

Incremental TP and FP Rates, All Subjects (Primary Analysis)

PS II

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

For all subjects, study
demonstrated incremental TP rate > 2%.
failed to show incremental FP rate < 15%

Subject Incremental TP & FP Rates by Pap Stratum

Secondary analyses were pre-specified for ASCUS, LSIL, and HSIL,
but ***not*** for combinations of these groups.

Seven possible groupings:

ASCUS	ASCUS/LSIL	All
LSIL	ASCUS/HSIL	Subjects
HSIL	LSIL/HSIL	

Statistical Procedures to Test Multiple Subgroups

Adjust significance level to control overall chance of a falsely significant result.

Bonferroni: test 7 groupings at 5%/7= 0.7%

Gatekeeper:

If all subjects significant at 5%

then test 6 PAP subgroups at 5%/6 = 0.8%

Gatekeeper more likely to have been pre-specified.

Incremental TP and FP Rates, ASCUS /LSIL Subgroup (Post Hoc)

PS II

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

For post hoc ASCUS/LSIL subgroup, study failed to show incremental TP rate > 2%. failed to show incremental FP rate < 15%.

Incremental TP and FP Rates, ASCUS /LSIL Subgroup (Post Hoc)

PS II

CIN 2/3+ prevalence expected to be lower for ASCUS/LSIL than all subjects.

In proportion to prevalence ratio,

TP target value changed from 2% to 1.5%

FP target value changed from 15% to 16.1%

Incremental TP and FP Rates, ASCUS/ LSIL Subgroup (Post Hoc)

PS II

	Subject-Level Rate		
	Initial Colposcopy (n/N)	LUMA Increment (n/N) 95% CI	Met Hypothesis?
TP	14.4% (24/167) (9.4%, 20.6%)	3.6% (6/167) (1.3%, 7.7%)	No: 1.5% in 95% CI
FP	55.7% (93/167) (47.8%, 63.4%)	20.4% (34/167) 14.5%, 27.3%	No:16.1% in 95% CI

For post hoc ASCUS/LSIL subgroup, study
failed to show incremental TP rate > 1.5%
failed to show incremental FP rate < 16.1%

Incremental TP Rate, Reduced Denominator (Post Hoc)

PS II

New Denominator: All subjects ***minus*** TP's based on initial colposcopy biopsies.

Rationale: only consider those subjects for which an incremental TP is possible.

FDA does not believe this analysis is valid: FDA/sponsor agreement on TP/FP rate target values was based on the full denominator, not a reduced denominator.

Exclusions Due to Pathology

16 subjects excluded if pathology was incomplete for at least one biopsy.

For some of these subjects, incremental TP, FP status can be inferred.

In worst case scenario, these subjects do not change conclusions.

Site/Colposcopist Variability

Site Variability, All Subjects. Significant in incremental FP rate ($p = 0.0025$), not in incremental TP rate ($p = 0.1890$).
(CMH test controlling for PAP strata).

Colposcopist Variability

Treating colposcopists as random, not fixed generalizes analysis to their population, increases confidence interval widths.

PS II Compared with PS I

Mean # biopsies

1.80 (0.99 LUMA-based) in PS II

1.24 for LUMA+colpo arm in PS I.

% of subjects biopsied

92.2% (178/193) in PS II

82.3% (897/1090) for LUMA+colpo arm, PS I

TP, FP rate increases larger in PS II than PS I largely because of more biopsies and more biopsied subjects than in PS I.

SUMMARY OF PS I AND PS II

Summary of Both Studies

PS I and PS II study success defined by success in both TP and FP rate endpoints.

Neither PS I nor PS II was successful for all subjects (Primary Analysis), ASCUS/LSIL (Post Hoc Subgroup).

	PS I		**PS II**	
	TP	FP	TP	FP
All Subjects	fail	pass	pass	fail
ASCUS/LSIL	fail	fail	fail	fail

Summary of Both Studies

Combining PS I and PS II results is difficult: Different study designs lead to different operating characteristics for colposcopists**.**

Age Effect

PS I: TP rate difference large for < 21 years age group.

PS II: Result not replicated.

Summary of Both Studies

LUMA false negative rate
23% based on colpo-detected subjects (PS I).

LUMA-indicated biopsies could be better than random. Does not necessarily translate to detection of additional CIN 2/3+ subjects.

Design limitations:

PS I, PS II are potentially biased.

TP, FP rate trade-off a surrogate for sensitivity, specificity trade-off.