LeuTech® BLA # 99-1407
Review Team

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THE PRODUCT

LeuTech™ is a kit for the preparation of Technetium Tc 99m labeled RB5 anti-CD15 monoclonal antibody, intended for intravenous administration after reconstitution and radiolabeling.

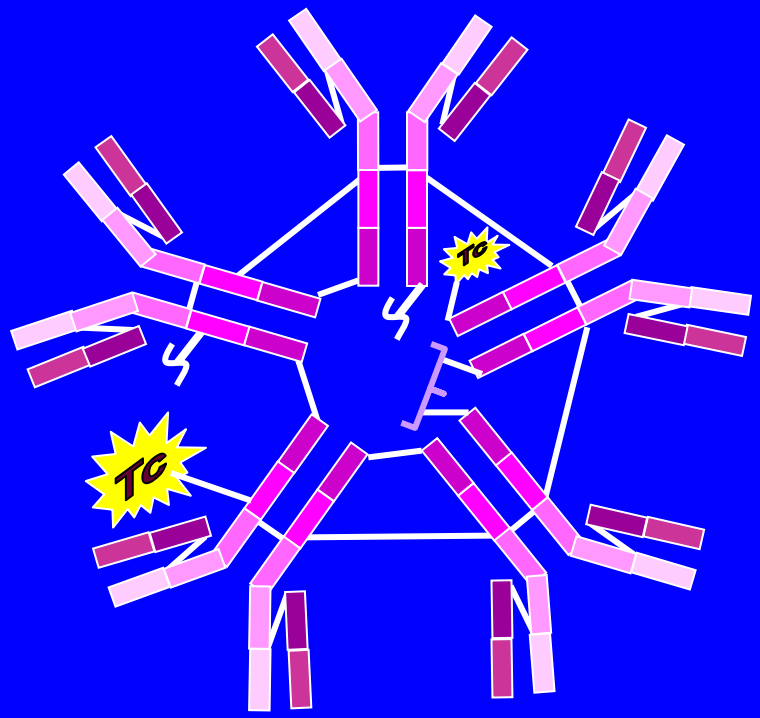
Each kit contains one reagent vial with 0.25 mg lyophilized, partially reduced RB5 murine IgM antibody and excipients, and a 2mL ampule of 500mg/mL ascorbic acid for injection (Abbott) as a diluent.

THE PROPOSED INDICATION

- **LeuTech "is indicated for the diagnosis of appendicitis in patients with equivocal signs and symptoms. It is useful to rule out appendicitis in patients presenting with equivocal diagnostic evidence."**

THE Tc 99m LABELED ANTIBODY

- **RB5 anti-CD15 IgM is a murine mAb.**
- **General structure of a partially reduced, labeled IgM:**



THE TARGET ANTIGEN

- **CD15**
- **A branched oligosaccharide, Lacto-N-neo-fucopentaose III, that can be found on glycolipids and glycoproteins expressed on cell membranes**

Gal β1 → 4GlcNAcβ1 →R

3

↑

Fucα1

- **CD15 is an adhesive carbohydrate moiety that can bind to itself and to other carbohydrates. It is important in cell-cell recognition and migration.**

THE TARGET ANTIGEN

- CD15 is reported to be strongly expressed by neutrophils, eosinophils, monocytes and normal myeloid precursor cells. Activated T cells and Reed-Sternberg cells have also been reported to express CD15.

- ALTERNATE NAMES
    - 3-FAL
    - LNFP III
    - Lewis X (Le^x)
    - SSEA-1 epitope

THE RATIONALE

- **Appendicitis is associated with a neutrophilic infiltration of the muscularis and, usually, the appendix mucosa.**

- **The technetium Tc 99m labeled Rb5 IgM antibody binds the CD15 epitopes on the polymorphonuclear neutrophils found at sites of infection/ inflammation, allowing imaging of the site.**

MANUFACTURING

- Palatin controls all steps in the manufacturing process, is responsible for release of the product at each stage in the manufacturing process, and performs QC release testing.
- One contract manufacturer makes the Rb5 IgM drug substance.
- A second contract manufacturer then prepares the final drug product.

A number of significant outstanding manufacturing issues remain to be resolved.

LeuTech®
Primary Clinical Trials

Trial #	N	Phase	Design
98-004	203 patients	3	Open label
97-003	56 patients	2	Open label

TECHNETIUM ^{99M}Tc LEUTECH™

Dose Antibody (Anti-CD 15 IgM):

75 - 125 μg

Radiolabel Dose:

Standard Adult: 10-20 mCi ^{99m}Tc

< 17 y/o: 0.21 mCi/Kg up to a maximum of 20 mCi

IMAGING PROTOCOL
(Standardized Across All Sites)

- Total Imaging Time = 90 Minutes
- Immediate Dynamic Acquisition: 10 frames at 4 minute each
- Ambulate x 10-15 minutes, void
- Static Planar Images: Supine Anterior
  Posterior
  RAO, LAO
  Standing Anterior Image
- Acquisition: Anterior Image 1 million counts then all subsequent images for same time

BLINDED READING PROTOCOL

- Independent Blinded Readers
- Aggregate Read(Majority Rules: 2/3)
- Provided with Demographics Only
  (Age, Sex, Height and Weight)
- Image Set Randomized
- Standard Format on Computer Database
- Independent Evaluation
- Electronic CRF

BLINDED IMAGE EVALUATION REPORT

Result

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Negative or **Positive**

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Uptake Pattern

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Location Uptake **Intensity Uptake**

(Appendicitis Zone) (Low, Moderate, High)

BLINDED IMAGE EVALUATION REPORT

- Time Scan Positive (Minutes Into Study)
- Uptake persists throughout study (Y/N)
- Technical Quality
- LeuTech™ Diagnosis → Negative

→ Positive - Acute Appendicitis

- Other Infection

READER TRAINING

- Same Training for Principal Investigators and Blinded Readers
- Utilized 8 Cases from Phase 2 Trial
  - Presentation of 6 (+) Cases, (2) Negative Cases
  - Specified Criteria for Image Interpretation
  - Image Pitfalls
- Followed by Practice Blinded Reads
  (15 Phase 2 Cases)
- Joint Review with Dr. Kipper

INSTRUCTIONS TO ALL READERS

- **Read for Highest Sensitivity and Negative Predictive Value**
- **Read with mindset of being afraid to miss the diagnosis of appendicitis**
- **Search carefully for appendicitis; do not give equivocal readings**

SUBMITTED IMAGE DATABASE

203 Patients Enrolled

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200 Digital Image Data

3 Films Scanned In

Submitted Database - Organized by Site and Patient Number

CBER IMAGE ASSESSMENT

- Adherence to Protocol
- Completeness Dynamic and Planar Dataset
- Time Of Positive Images

IMAGE QUALITY ASSESSMENT

- Image Contrast and Color Display
- Patient Information Redacted (Name, Site #)
- Complete Data Set
  - Evaluable at 30 minutes: 202/203
  - Dynamic: Complete Set 196/203 (97%) Patients
  - Static: Complete Set 164/203 (81%) Patients
- 6/203 Images Technically Unevaluable

TIME TO POSITIVE SCAN TP/READER (N=59)

IMAGE INTERPRETATION	TOTAL	PROPORTION OF PATIENTS WITH POSITIVE IMAGES READ AS POSITIVE		
		By 30 min. N (%)	By 60 min N (%)	By 90 min N (%)
Blinded Reader 1	48	38/48 (79%)	46/48 (96%)	48/48 (100%)
Blinded Reader 2	39	32/39 (82%)	39/39 (100%)	
Blinded Reader 3	45	30/45 (67%)	44/45 (98%)	45/45 (100%)

Clinical Review Outline

- Phase 2 trial
- Phase 3 trial
  - trial design
  - trial results
    - equivocal appendicitis population
  - performance phase 3
    - pooled phase 2 and 3
  - management phase 3
- Safety

Phase 2 Trial Design

- **Eligibility criteria**
  - **Right lower quadrant pain**
  - **Signs, symptoms or laboratory findings suggestive of atypical appendicitis**
  - **PID not excluded**
- **Management questionnaire: pre and post-scan**
  - **Disposition: home, admit for observation, surgery**
  - **likelihood of appendicitis**

Phase 2 Trial Design

- **Performance assessment**
  - **Offsite Blinded Readers**
  - **Onsite Readers**
- **Safety**
  - **Vital signs**
  - **Laboratory data**

Phase 2 Trial Results

- 2 sites ; 56 subjects
  - 49 patients - site A
  - 7 patients - site B
- 45% male ; 55% female
- Age 9-77y ; Median = 27
- 50% incidence of appendicitis

Phase 2 Performance

Comparison of aggregate blind read (Offsite-white) to Onsite reads (yellow)

		LeuTech®		
	Offsite Onsite	Positive (N=34) (N=33)	Negative (N=22) (N=23)	
Appendicitis (N=28)	Offsite Onsite	25 27	3 1	Sensitivity 89% 96%
No Appendicitis (N=28)	Offsite Onsite	9 6	19 22	Specificity 68% 79%
Predictive Value	Offsite Onsite	74% 82%	86% 95%	

Phase 3 Trial

- Eligibility criteria
- Management questionnaire
- Phase 3 trial results
  - equivocal appendicitis patient population
    - eligibility criteria
    - surgeon's pre-scan disposition plan
    - surgeon's pre-scan likelihood estimate
- Performance
  - evaluable subjects
  - subgroups
- Management

Phase 3 Trial Design

- **Eligibility Criteria :RLQ Pain Plus**
  - **Atypical history**
    - **no gradual onset, no increasing intensity,not aggravated by movement, non migrating**
  - **Atypical physical exam**
    - **no McBurney's point tenderness,no referred tenderness, no abdominal wall spasm**
  - **Temperature less than 101^0F**
  - **WBC <10,500/mm^3**
- **Only one criteria need be present to qualify for the study**
- **Women with PID excluded**

Phase 3 Trial Design

- **Management Questionnaire**
  - **Used to assess clinical utility of LeuTech**
  - **Surgeons were asked to assess the following:**
    - **Anticipated disposition of patient pre and post scan**
    - **likelihood of appendicitis pre and post scan**

Phase 3 Trial Design

- **Management Questionnaire**
  - **Surgeon's likelihood estimate**
    - **0-19% - almost definitely not appendicitis**
    - **20-39% - probably not appendicitis**
    - **40-59% - indeterminate appendicitis**
    - **60-79% - probably appendicitis**
    - **80-100% - almost definitely appendicitis**

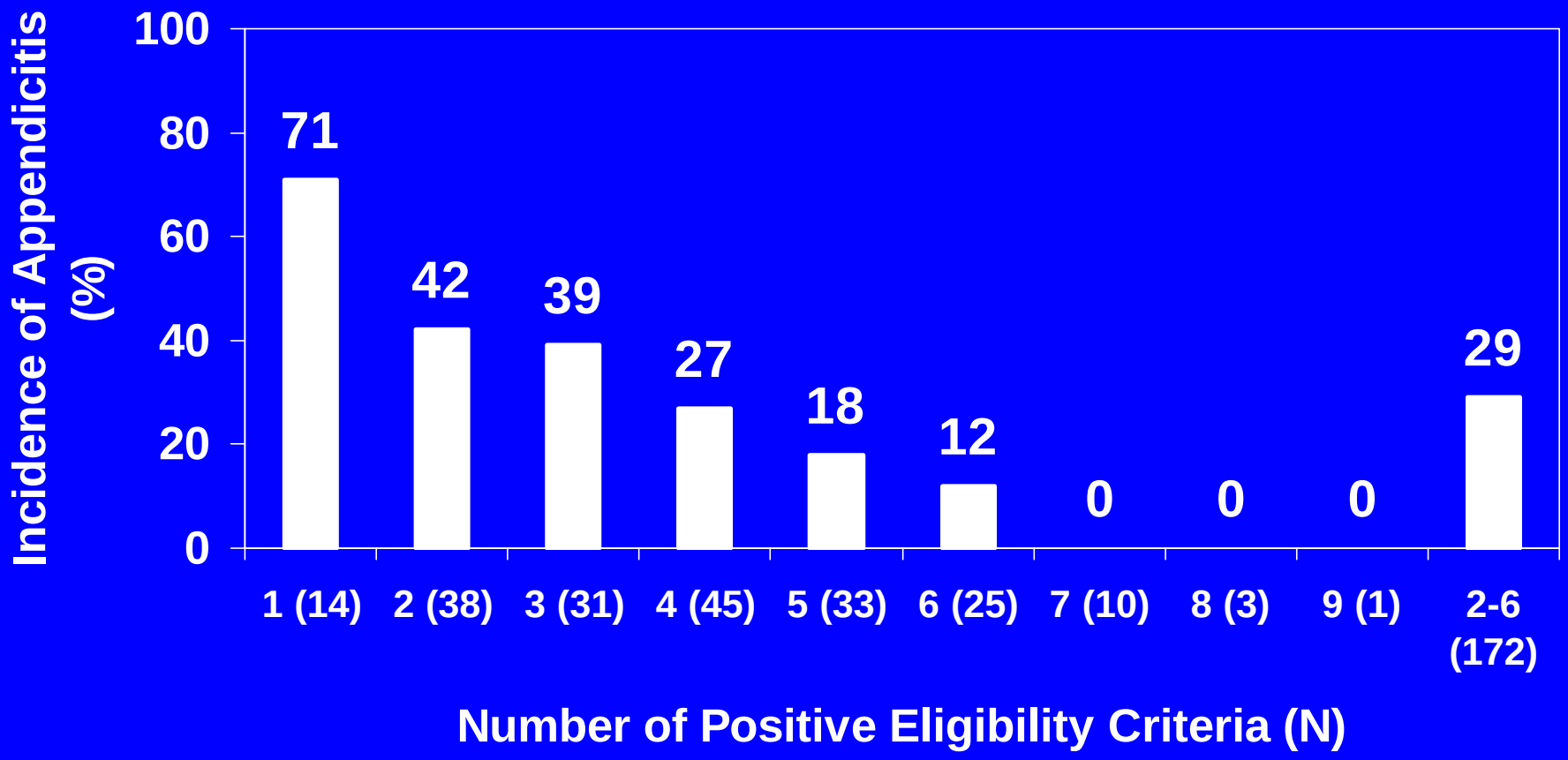
Phase 3 Trial Results

- 10 sites
  - 6 sites 19-39 subjects per site
  - 4 sites ≤ 11 subjects per site
- 60% Male ; 40% Female
- Age 5-85 ; Median = 26
- 30% Incidence of Appendicitis
  - Incidence per site ranged from 0 - 75%

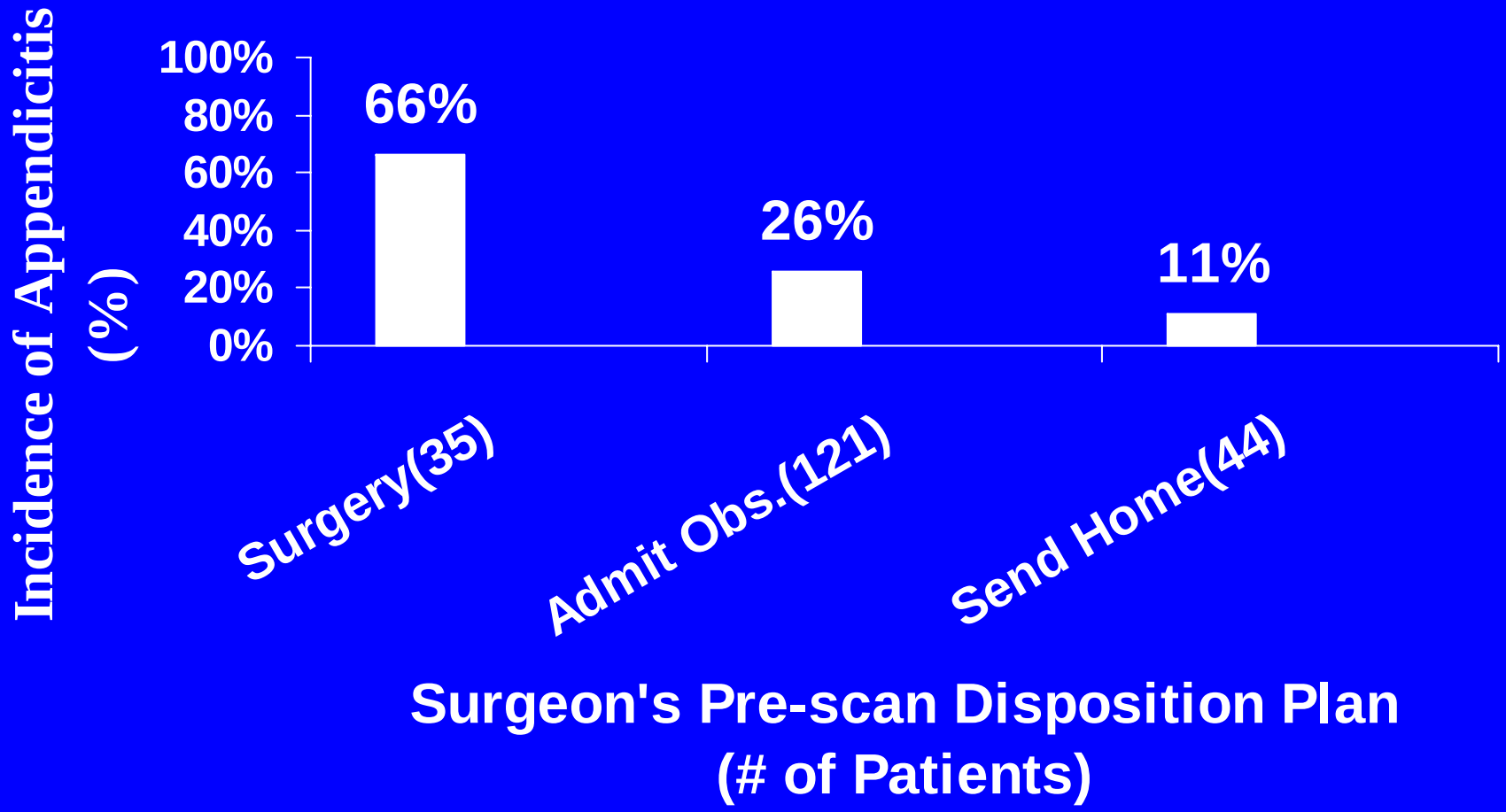
Phase 3 Trial Results

- **Equivocal appendicitis population**
  - **Based on absent classic signs and symptoms**
  - **Surgeon's pre-scan disposition plan**
  - **Surgeon's pre-scan likelihood estimate**

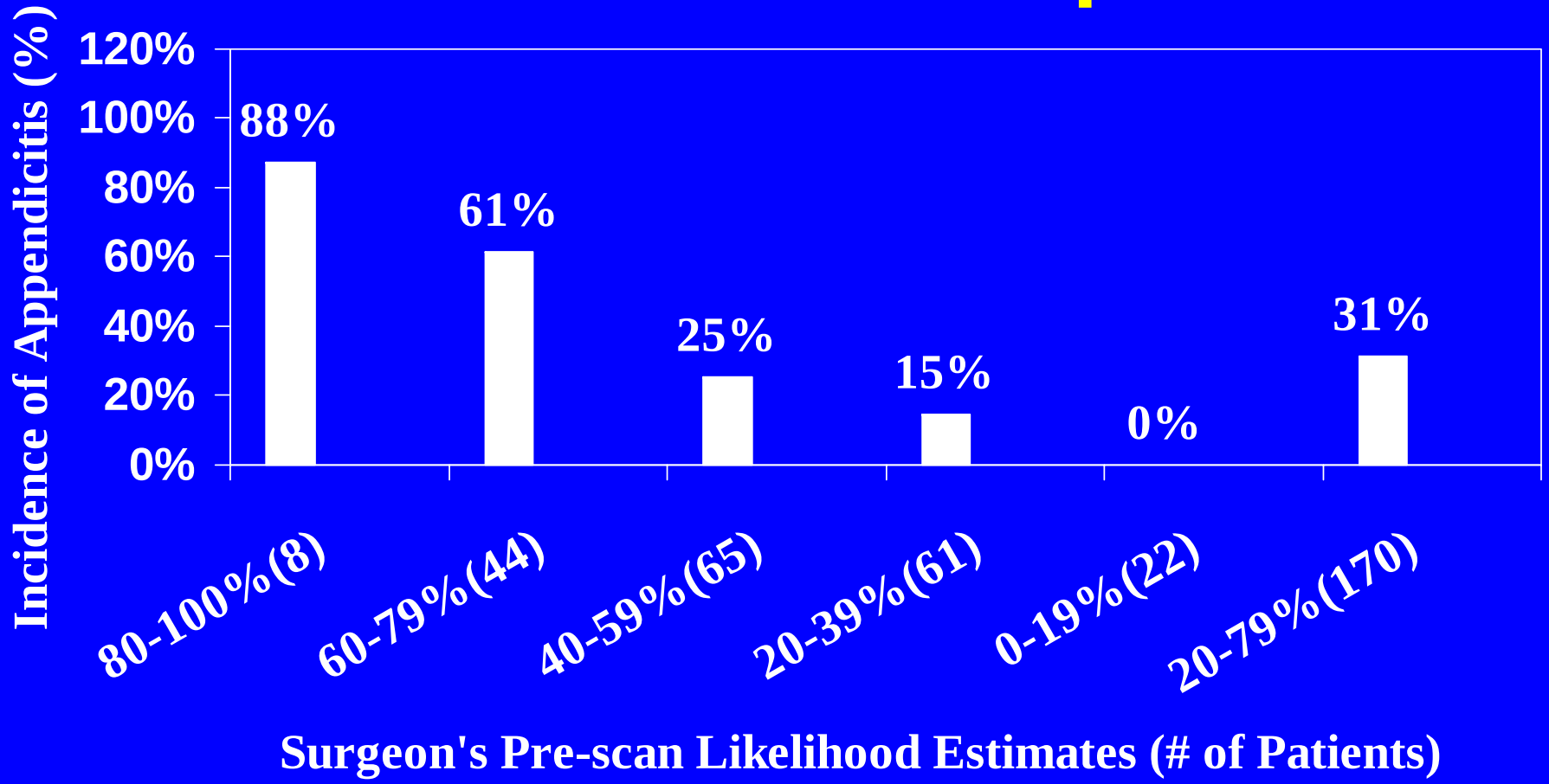
Incidence of Appendicitis Based on Number of Positive Entry Criteria



Incidence of Appendicitis within Surgeon's Pre-scan Disposition Plan



Incidence of Appendicitis within Surgeon's Pre-scan Likelihood Groups



Phase 3 Performance

Comparison of aggregate blind read (Offsite-white) to Onsite reads (Onsite-yellow)

		LeuTech®		
	Offsite / Onsite	Positive (N=53) (N=72)	Negative (N=147) (N=128)	
Appendicitis (N=59)	Offsite	44	15	Sensitivity
	Onsite	53	6	75% / 90%
No Appendicitis (N=141)	Offsite	10	131	Specificity
	Onsite	19	122	93% / 87%
Predictive Value	Offsite	82%	90%	
	Onsite	74%	95%	

Phase 3 Performance

Aggregate Blinded Read (N=172)

Based on 2 - 6 Positive Entry Criteria

Aggregate Blind Read	LeuTech®		Sensitivity / Specificity
	Positive (N=45)	Negative (N=127)	
Appendicitis (N=49)	36	13	73%
No Appendicitis (N=123)	9	114	93%
Predictive Value	80%	90%	

Phase 3 Performance

Aggregate Blinded Read (N=121)
Based on Pre-scan Admit for Observation Disposition Plan

Aggregate Blind Read	LeuTech®		Sensitivity / Specificity
	Positive (N=27)	Negative (N=94)	
Appendicitis (N=31)	21	10	68%
No Appendicitis (N=90)	6	84	93%
Predictive Value	78%	89%	

Phase 3 Performance

Aggregate Blinded Read (N=200)

Surgeon's Pre-scan Likelihood Estimates

Surgeon's pre-scan Likelihood Estimate (N)	Incidence of Appendicitis			Sensi-tivity	Speci-ficity
	Total	If scan + (PPV)	If scan – (100%-NPV)		
0-19% (22)	0%	-	-	-	100%
20-39% (61)	15%	86%	6%	67%	98%
40-59% (65)	25%	67%	8%	75%	88%
60-79% (44)	61%	86%	33%	74%	82%
80-100% (8)	88%	100%	50%	86%	100%
20-79% (170)	31%	79%	11%	73%	92%

Percent of Patients with a Given Eligibility Criteria and Surgeon's Pre-scan Likelihood Estimates

% likelihood	Atyp. Hx	Atyp. PE	Temp. $<101^0$F	WBC $<10{,}500 mm^3$
0-19%	68%	73%	91%	82%
20-39%	80%	69%	92%	72%
40-59%	73%	70%	97%	57%
60-79%	67%	67%	87%	27%
80-100%	63%	38%	67%	38%

Phase 3 - WBC < 10,500/mm^3
Incidence of Appendicitis = 13%
N = 114

Aggregate Blind Read	LeuTech®		Sensitivity / Specificity
	Positive (N=15)	Negative (N=99)	
Appendicitis (N=15)	9	6	60%
No Appendicitis (N=99)	6	93	94%
Predictive Value	60%	94%	

Phase 3 - WBC > 10,500/mm^3
Incidence of Appendicitis = 51%
N = 86

Aggregate Blind Read	LeuTech®		Sensitivity / Specificity
	Positive (N=39)	Negative (N=47)	
Appendicitis (N=44)	35	9	80%
No Appendicitis (N=42)	4	38	90%
Predictive Value	90%	81%	

Women 14-35y Phase 3

Pre-scan likelihood estimate of appendicitis 20-79%
Incidence of Appendicitis 19%

Aggregate Blind Read	LeuTech®		Sensitivity / Specificity
	Positive (N=10)	Negative (N=42)	
Appendicitis (N=10)	8	2	80%
No Appendicitis (N=42)	2	40	95%
Predictive Value	80%	95%	

Pediatrics Pooled Phase 2 and 3

5-9y - N=15 : Incidence=47%

Aggregate Blind Read	LeuTech®		Sensitivity / Specificity
	Positive (N=6)	Negative (N=9)	
Appendicitis (N=7)	6	1	86%
No Appendicitis (N=8)	0	8	100%
Predictive Value	100%	89%	

Pediatrics Pooled Phase 2 and 3

10-17y - N= 48 Incidence=27%

Aggregate Blind Read	LeuTech®		Sensitivity / Specificity
	Positive (N=14)	Negative (N=34)	
Appendicitis (N=13)	11	2	85%
No Appendicitis (N=35)	3	32	92%
Predictive Value	82%	93%	

Geriatric >65

Pooled phase 2 and 3

N=12 Incidence- 50%

Aggregate Blind Read	LeuTech®		Sensitivity / Specificity
	Positive (N=7)	Negative (N=5)	
Appendicitis (N=6)	6	0	100%
No Appendicitis (N=6)	1	5	83%
Predictive Value	86%	100%	

Performance in Subjects with "Other Infections"

Pooled Phase 2 and 3

	FP Readings/ Subjects (%)	
	Other Infections	Negative
Aggregate Blind Read	13/30 (43%)	6/139 (4%)
Onsite	10/30 (33%)	18/139 (13%)

- Phase 3 trial aggregate blind read - all FPs occurred in subjects with "other Infections"

Management-Disposition Phase 3

Pre-scan Disposition	N	Post-scan Disposition	N	Patients with Appendicitis # (%)
Home	43	Home	36	2/36 (6%)
		Admit Obs.	2	0/2 (0%)
		Surgery	5	3/5 (60%)
Admit Obs.	113	Home	39	0/39 (0%)
		Admit Obs.	43	4/43 (9%)
		Surgery	31	25/31 (81%)
Surgery	33	Home	5	0/5 (0%)
		Admit Obs.	2	0/2 (0%)
		Surgery	26	21/26 (81%)

Safety data

- HAMA - 54 subjects
  - No HAMA response
    - defined as a 4 fold rise in titer
  - 30 normal subjects re-exposed
    - 5 positive titers
      - 2 mild
      - 3 moderate

Safety Data

- No serious adverse events (439 subjects)
- Vasodilatation- most common event (2.5%)
  - all others less than 1%
- Vital signs
  - no clinically significant changes noted
- Laboratory parameters
  - No clinically significant changes noted