

**Medical Enterprises, Ltd.
Synergo SB-TS 101.1 Device
+ Mitomycin C
FDA Review of P010045**

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Division of Reproductive, Abdominal, and
Radiological Devices
Office of Device Evaluation / CDRH
June 25, 2008

Device/Drug Description

- Combination Product
- Synergo Hyperthermia Device
- Synergo Kit
 - Disposable catheter-tubing set
 - Mitomycin C (2 vials, 20 mg each)

Proposed Indications for Use

The Synergo device delivers heat transurethrally by means of radio frequency (RF) energy to the urinary bladder walls for the treatment of superficial transitional cell carcinoma of the bladder (STCCB), concomitant with intravesical instillation of Mitomycin for Injection, USP. The combination of Synergo and mitomycin C is intended for prophylactic treatment of recurrence in patients following endoscopic removal of Ta-T1 and G1-3 superficial transitional cell carcinoma of the bladder (STCCB). Synergo and mitomycin C treatment is clinically indicated for STCCB patients of intermediate and high risk.

FDA Review Team

- Center for Devices & Radiological Health (CDRH)
 - Office of Device Evaluation (ODE)
 - Office of Surveillance & Biometrics (OSB)
 - Office of Science & Engineering Laboratories (OSEL)
 - Office of Communication, Education, & Radiation (OCER)
 - Office of Compliance (OC)
- Center for Drug Evaluation & Research (CDER)
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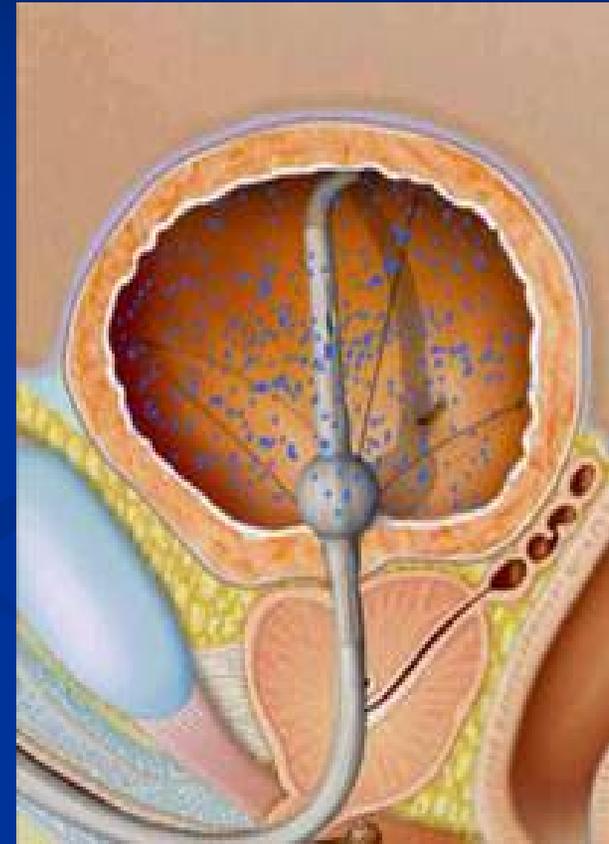
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Principle of Operation



Treatment

- Initiated post-TUR
- 8 weekly + 4 monthly sessions
- Sessions are 60 minutes each
- Bladder temperature range = $42 \pm 2^{\circ}\text{C}$
- 2 consecutive mitomycin C instillations
 - Each 20 mg in 50 mL H₂O
 - 30-minute indwell periods

Preclinical Review

- Mechanical & Functional Testing
- RF Output Testing
- Electrical Safety & Electromagnetic Compatibility (EMC) Testing
- Software Testing
- Biocompatibility
- Animal Studies
- Chemistry, Manufacturing, and Controls (CMC)
- Sterilization, Packaging & Shelf-Life Testing

Clinical Data Sources

	Enrollment	Planned Follow-up
Human Pharmacokinetic Study	Synergo: 29 MMC: 22	N/A
Study 101.1	Synergo: 42 MMC: 41	2 yrs
Study 102.1	Synergo: 51 BCG: 53	2 yrs
Study 101.4	Synergo: 42	1 yr

**Comparison to historical MMC & BCG data,
European Prophylactic Study, Bladder Salvage Patients &
European Ablation Patients**

Study 101.1 Chronology

- 1993 – Protocol finalized
- 1997
 - Study sponsorship transferred to MEL
 - Initial monitoring visits conducted
 - Case report forms created/transcribed
- 2001 – PMA submitted to FDA
- 2001, 2002, 2004 – In-depth review cycles
- 2005 – FDA conducted bioresearch monitoring inspections

FDA Presentation

- **Clinical Overview**

Hector Herrera, MD, MPH

- **Clinical Review**

Robert Kane, MD

- **Statistical Review**

Xuefeng Li, PhD

- **Postapproval Considerations**

Shaokui Wei, MD, MPH

FDA Clinical Overview

Synergo SB-TS 101.1 Device + Mitomycin C

Hector Herrera, MD, MPH

Division of Reproductive, Abdominal, and
Radiological Devices

Office of Device Evaluation / CDRH

June 25, 2008

BLADDER CANCER

Prevalence and Causes

- 60,000+ cases annually diagnosed in the U.S.
- Main causes:
 - Tobacco
 - Industrial carcinogens
 - Age

Transitional Cell Carcinoma TCC

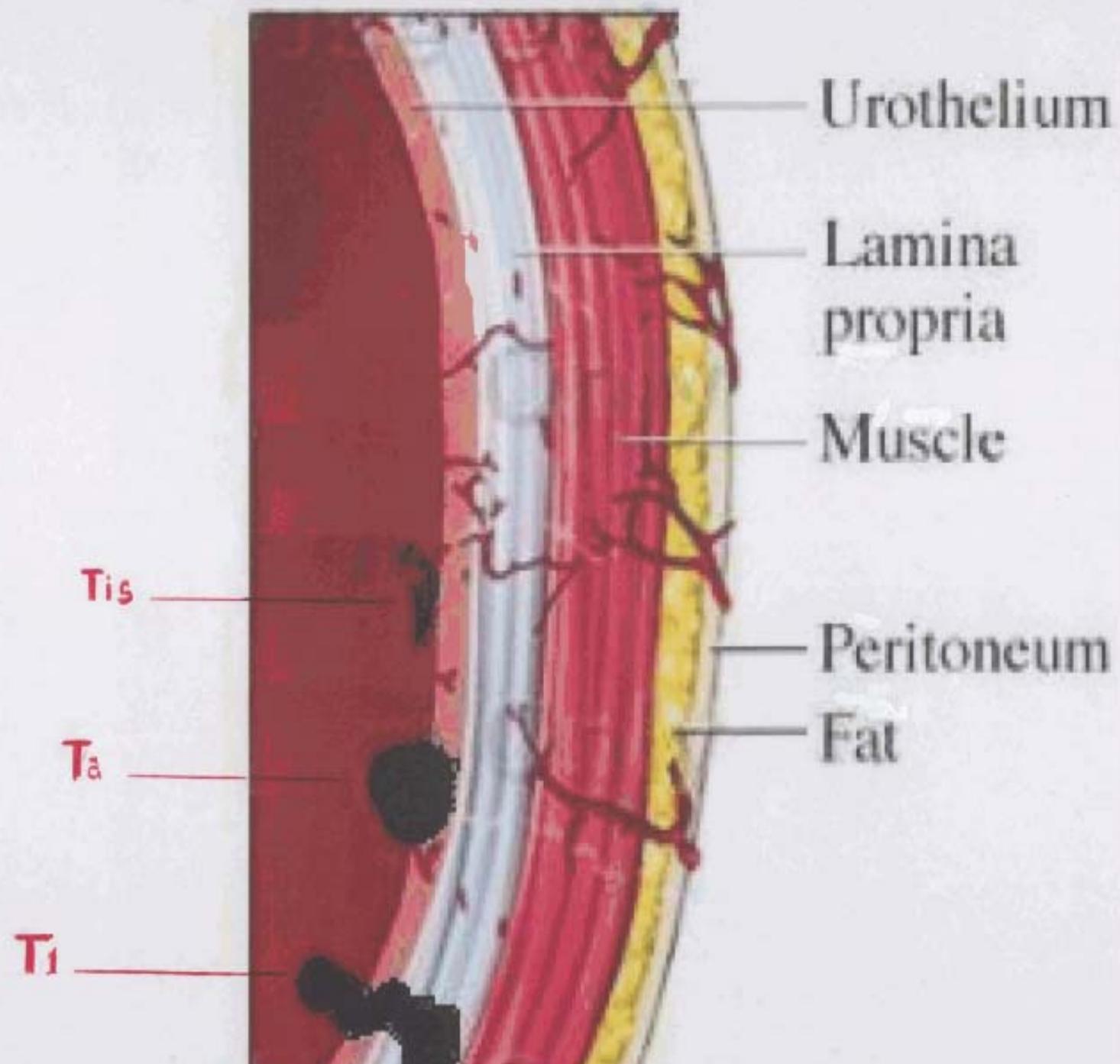
- TCC Most common pathologic subtype
 - Observed in over 90% of tumors
 - Squamous cell carcinoma 5%
 - Adenocarcinomas approximately 1%

Prognostic Factors

- For non-invasive urothelial neoplasms
 - STAGE how far the disease has spread
 - GRADE appearance cells to the microscopic examination.

Tumor Staging

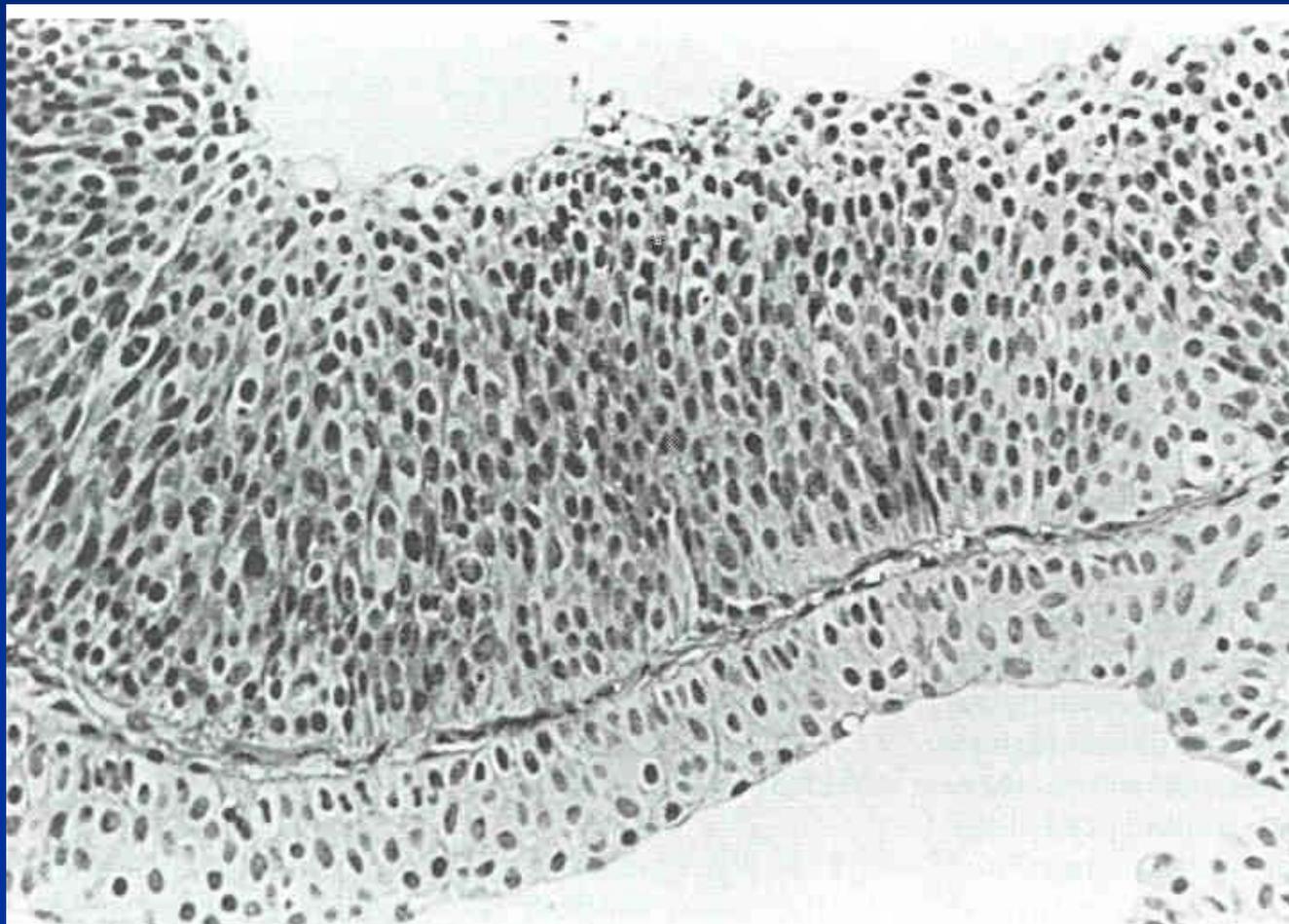
- The three non-muscle invasive stages of bladder cancer
 - **Ta = Invading Urothelium**
 - **T1 = Invading Urothelium and Lamina Propria**
 - **Tis = Confined to mucosa, is highly malignant and aggressive, is also called Cis.**



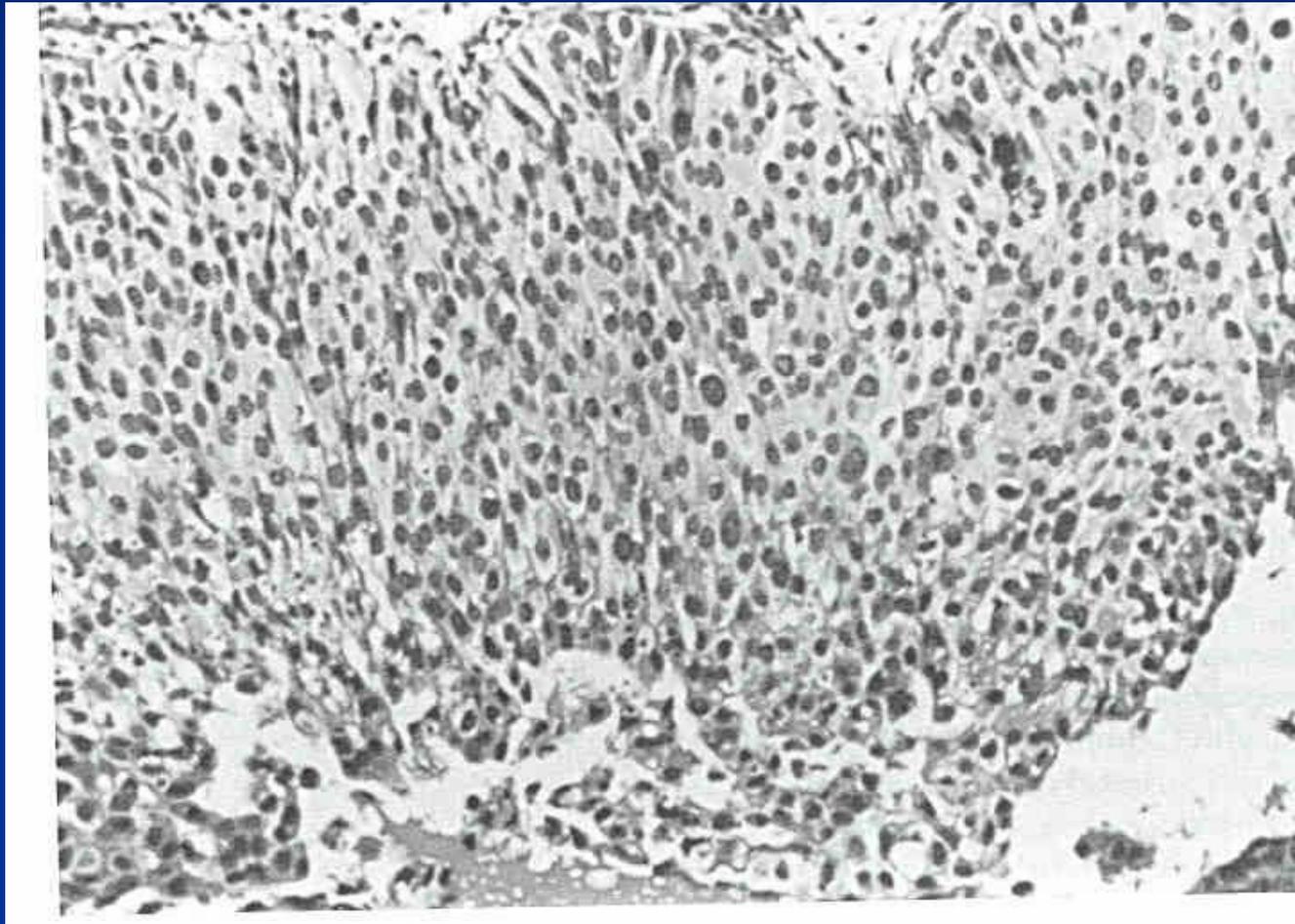
Tumor Grading

- Grade 1 - Well differentiated
- Grade 2 - Moderately differentiated
- Grade 3 - Poorly differentiated

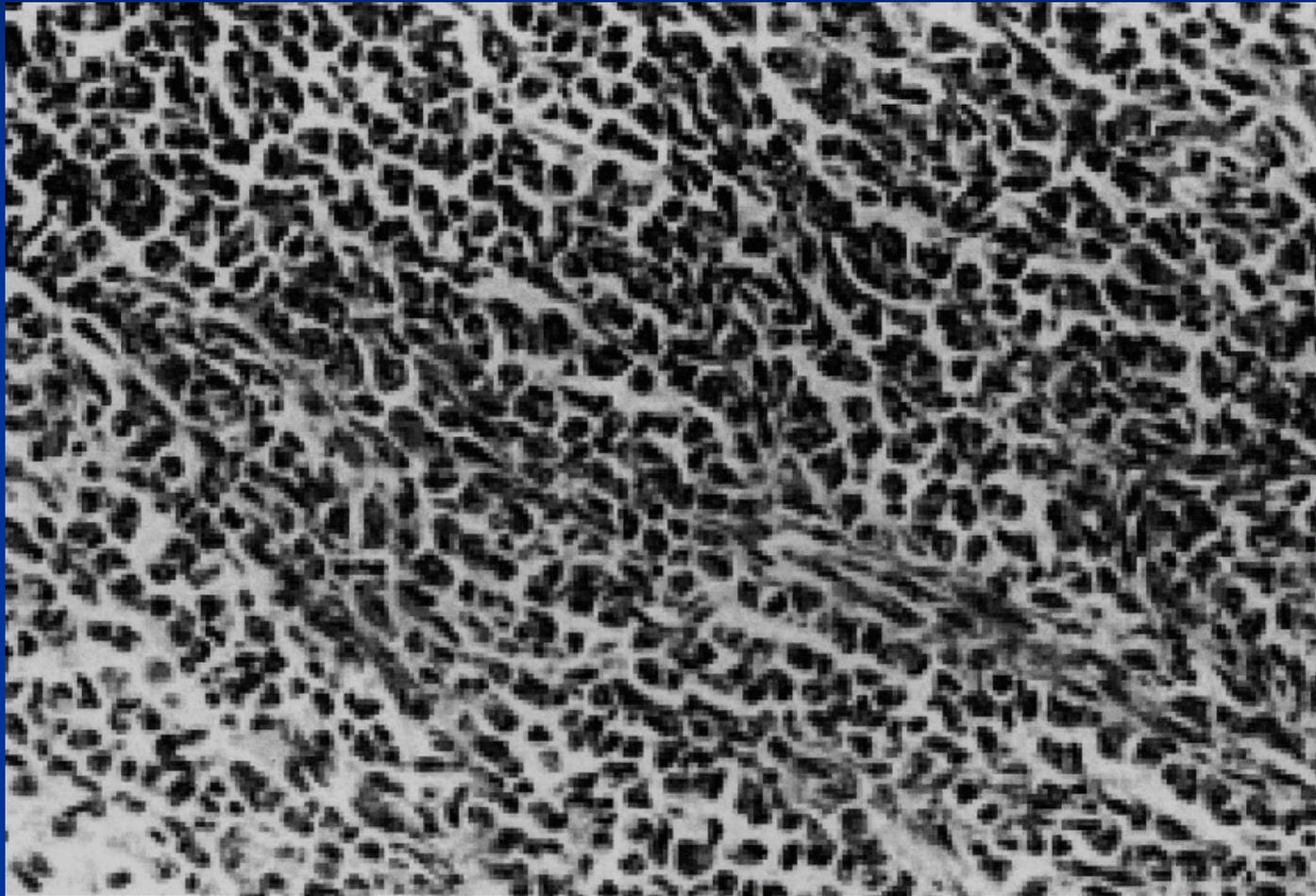
Grade 1 - Well differentiated



Grade 2 - Moderately differentiated

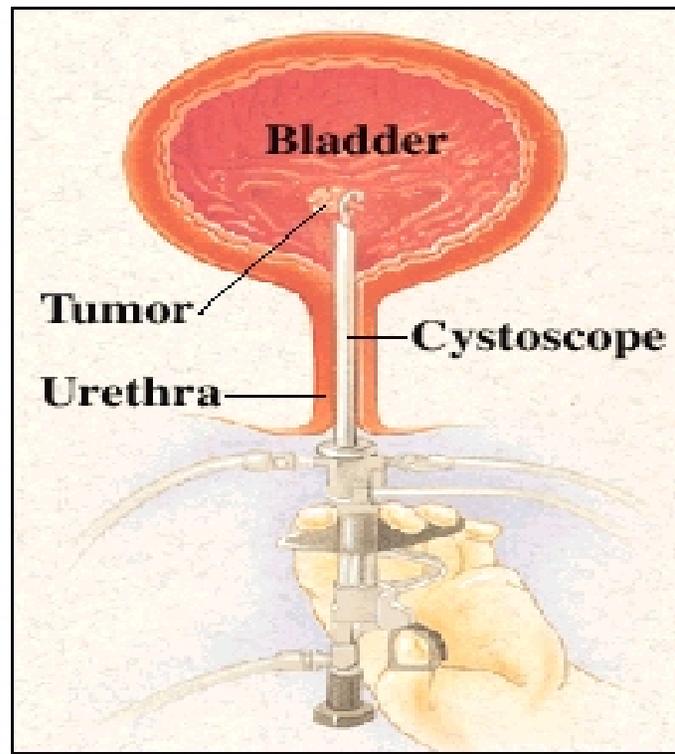


Grade 3 - Poorly differentiated



Treatment Options

- Transurethral resection of bladder tumor
TURBT
- Intravesical chemotherapy and immunotherapy
- Intravesical laser ablation therapy
- Photodynamic Therapy



TURBT

- Transurethral resection of bladder tumor provides essential histopathologic information, and need to provide a deep enough resection sampling of the muscularis propria

Most commonly employed intravesical agents in the US

- **Bacillus Calmette-Guérin (BCG)**
- **Mitomycin C**

Mechanism of Action

- **Bacillus Calmette-Guérin (BCG)**

Inflammatory host response; release of special proteins: cytokines

- **Mitomycin C**

Antineoplastic; inhibits DNA synthesis

- Used both in an adjuvant or maintenance fashion

Mitomycin C

- 20-60 mg instillation
(40mg in 40 mL distilled water most commonly),

Bacillus Calmette-Guérin (BCG)

- First line of treatment for Tis.
 - Effective as prophylaxis for recurrences
 - Optimal dosing not yet established

Side Effects

■ Mitomycin C

- Rate of 22-24% with multiple dose with or without maintenance
- Urgency, frequency, urethral infections and bladder contracture.

■ BCG

- 38% with induction and 57% with induction plus maintenance
- Fever, chills, malaise, altered liver functions, and sepsis

Recurrence, Progression Rates after TURBT

- Recurrences are decreased by 31% with BCG maintenance, and by 18% with and Mitomycin C.
- The progression rate estimate in all patient risk groups is 8% for BCG, and 4% for Mitomycin C.

Predicting Recurrence and Progression

- Risk according to EAU, based on # of tumors, tumor size, prior recurrence rate, T category, tumor grade and presence of Tis.
 - Low-risk
 - Intermediate-risk
 - High-risk

FDA Clinical Review

Synergo SB-TS 101.1 Device + Mitomycin C

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Division of Drug Oncology Products
Office of Oncology Drug Products / CDER
June 25, 2008

SYNERGO PMA

Outline

- Superficial Bladder Cancer re: Synergo
 - Current therapy options
 - Endpoints for study
- Regulatory considerations for marketing
- Synergo studies 101.1 and 102.1
- Regulatory concerns

“Superficial” bladder cancer (STCCB) Non-muscle invasive bladder cancer

- Primary therapy – cystoscopic complete removal resection - TURBT, cautery, laser
- Pathologic staging and grading
 - Ta and T1; Grades 1-3
- “Adjuvant” drug therapy into the bladder via catheter if risk of recurrence elevated
 - BCG (FDA approved)
 - Mitomycin C (MMC)
 - IFN α

STCCB

- Heterogeneous population, thus outcomes vary:
 - Recurrence - COMMON
 - Progression LESS COMMON, not altered by therapy
- Prognostic factors affect outcomes:
 - Grade 3, Cis, recurrent tumors, multifocal, large size; T1 versus Ta
- Standard of care:
 - Complete TURBT, observation, repeated TURBT
 - Recurrence after TURBT alone: 10-70% by 2 yrs
 - Adjuvant MMC or BCG for “higher risk” patients to reduce recurrence

Mitomycin C

- MMC after TURBT: intravesical Rx weekly for 6-8 weeks, may also be used as maintenance
- AUA meta-analysis (2007) reports reduction in probability of recurrence by ~18%
 - (95% CI 8%, 28%) over TURBT alone
 - Considerable variation among studies
- Mitomycin C is not FDA approved for treatment or “prophylaxis” of superficial bladder carcinoma but has wide usage.

Adjuvant therapy

FDA approved adjuvant Rx:

- BCG intravesical therapy is approved for:
 - treatment & prophylaxis of carcinoma in situ (CIS)
 - and for the prophylaxis of
 - primary or
 - recurrent stage Ta and/or T1 papillary tumors
 - following transurethral resection (TUR)
 - BCG is not recommended for stage TaG1 papillary tumors, unless they are judged to be at high risk of tumor recurrence

STCCB Usual Study Endpoints

- Recurrence = more of the same tumor
 - Recurrence rate by 2 years- common
- Progression = advancement of T stage
 - Progression of Stage is unusual unless high grade
- Recurrence-free interval / Time to recurrence
- Long term outcomes- not systematically studied

Requirements for Marketing Approval

Reasonable assurance -

- based on valid scientific evidence
- demonstrating effectiveness with acceptable safety

Sources of evidence -

- Adequate and controlled investigations
- Other studies can provide evidence

Ideal characteristics for a single study to support effectiveness

- a. Multicenter study, adequately powered
- b. Consistent efficacy across multiple endpoints and key study subsets
- c. Statistically very persuasive – “low” p-value
- d. Clinically compelling for the benefit-to-risk assessment

SYNERGO PMA

- Device-drug combination product:
 - Microwave hyperthermia system
 - Kit: disposable catheter plus Mitomycin C vials for intravesical chemotherapy treatment

SYNERGO PMA

- Sponsor's Proposed Indication:
 - Synergo with Mitomycin C is indicated for use for prophylactic treatment of recurrence in patients following endoscopic removal of Ta-T1 and G1-3 superficial transitional cell carcinoma of the bladder (STCCB). Synergo and Mitomycin C treatment is clinically indicated for STCCB patients of intermediate and high risk.

Synergo Studies

- 101.1 – Pivotal study
- 101.4 – Tumor ablation study
- 102.1 – Synergo+MMC versus BCG
- EPP – European prophylactic (commercial use)

Synergo Studies

- 101.4 Tumor ablation study
 - patients not fully resectable by TURBTSingle arm study of Synergo + MMC
- 102.1 - Randomized comparison of Synergo+MMC versus BCG alone without Synergo after definitive TURBT – began in 2002
 - 6 weekly induction/ 6 maint. ; 4 types of BCG used
 - Planned enrollment N = 300
 - n=90 evaluable / 5 years / 10 sites (4/2007)
 - Synergo + MMC arm of interest for safety

SYNERGO Pivotal Study

- Study 101.1: “A comparative study of intravesical Mitomycin C instillation or Mitomycin C and local hyperthermia for prophylaxis of recurrences of superficial transitional bladder tumors”
- 3 sites, research collaboration
- Enrollment 1994 – 1999 during which time 83 patients accrued
- Case report forms initiated in 1997

Study Plan 101.1

- Patients (pts) were randomized 1:1 between Synergo - hyperthermia at 42°C - plus MMC pre-heated (43-45°C) versus MMC alone (room temp)
- MMC given as 2 successive instillations of 20 mg in 50 mL distilled water, each with dwell time of 30 minutes in the bladder, thus a total exposure time of 60 minutes of MMC with each treatment
- All pts: 8 weekly sessions then monthly times 4
- Cystoscopy after initial 8 weeks and quarterly

Study Plan 101.1

- Pts on Synergo-MMC - bladder drained via catheter after 1 hour hyperthermia (40 – 75 min)
- Pts on MMC alone- instructed to void after 1 hour
- Treatment began 20-40 days after TURBT
- Followup quarterly: cysto, cytology and biopsy of any suspicious areas until 2 years or recurrence – off study

Study 101.1

- Stated study endpoints: 1993 protocol
 - Disease-free interval
 - Tumor recurrence rate, including evaluation of the number of recurrent tumors at 2 years post-treatment
 - Progression of stage and grade
 - Occurrence of Cis
 - Occurrence of distant metastases
 - Recurrence-free survival (2001)
- PMA Amdt 16 January 2008:
 - primary – time to recurrence

101.1

■ Inclusion Criteria:

- Resected Stage Ta or T1 and Grade G1 - G3, superficial transitional cell carcinoma of the bladder
- Complete tumor eradication must be possible - cysto
- Life expectancy > 24 months

■ Exclusion Criteria:

- Subjects with Ta, Grade1 single transitional tumors at first episode of disease
- Subjects with tumor stage >T1
- Subjects with positive cytology after complete cysto eradication of tumors
- Subjects with residual tumor after attempted complete eradication of tumors

Demographics 101.1

	N (%)	MMC + Synergono	MMC Control
Number of pts (ITT)	83	42	41
Age < 65	41	25	16
Age ≥ 66	42	17	25
First episode	31 (37%)	15	16
Recurrent (1 or more)	52 (63%)	25	27
Prior therapy	18 (42%)	18	17
Ta	33 (40%)	15	17
T1	50 (60%)	26	24
Grade 1	5 (6%)	4	1
Grade 2	60 (72%)	27	33
Grade 3	18 (22%)	11	7

Study 101.1 Results

	N	MMC + Synergo	MMC
Number of pts randomized	83	42	41
Discontinued before first cystoscopy followup (< 3 mo)	8	7	1
MEL “valid for analysis” “per protocol”	75	35	40
Completed all therapy (8 induction + 4 maintenance)	54 (65%)	29	25

Early Discontinuations: 8 patients

Pt ID:	Reason	Treatment group	Rx courses received
-001-022	Skin allergy to MMC	MMC	2
-001-029	Skin allergy to MMC	Synergo	1
-002-003	"deteriorating health"	Synergo	0
-002-013	Consent withdrawn	Synergo	0
-003-023	Consent withdrawn	Synergo	0
-001-015	Consent withdrawn	Synergo	3
-003-027	Consent withdrawn * (pain, anxiety)	Synergo	1
-003-032	Consent withdrawn * (pain, severe spasms)	Synergo	2

* 2 "Protocol deviations" (patients received MMC alone)
 6 early withdrawals – drop-outs
 8 total (7 on Synergo)

K-M estimated 2 year recurrence rate (Applicant Table 101.1)

Patient Populations		MMC+ Synergo n = 42	MMC n = 41	Log- Rank P
Study 101.1	N = 83 - 8			
“Per-Protocol”	75	17.1% (n=35)	61.6% (n=40)	0.0002

Per-Protocol: (8 early discontinuation patients removed)

- 6 early withdrawals
- 2 “protocol deviations” – patients declined Synergo; received MMC

K-M estimated 2 year recurrence rate (Applicant Table 101.1)

Analyses adjust for randomization errors and also add back the 2 “protocol deviation” patients but not the 6 early drop-outs

Patient Populations		MMC+ Synergo n = 42	MMC n = 41	Log- Rank P
Study 101.1	N = 83			
Minus early withdraw	-6			
Evaluable: “Randomized As Intended” * (should have)	77	25.0% (n=36)	54.4% (n=41)	0.0097
Evaluable: “Randomized As Treated” *	77	18.9% (n=37)	61.6% (n=40)	0.0002

10 patients (12%) randomization assignments were switched.
One patient randomized to Synergo who discontinued early (-022) actually received control arm MMC

K-M estimated 2 year recurrence rate (Applicant Table 101.1)

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Evaluable: "Randomized As Treated"	77	18.9% (n=37)	61.6% (n=40)	0.0002
"Per-Protocol" (-8)	75	17.1% (n=35)	61.6% (n=40)	0.0002



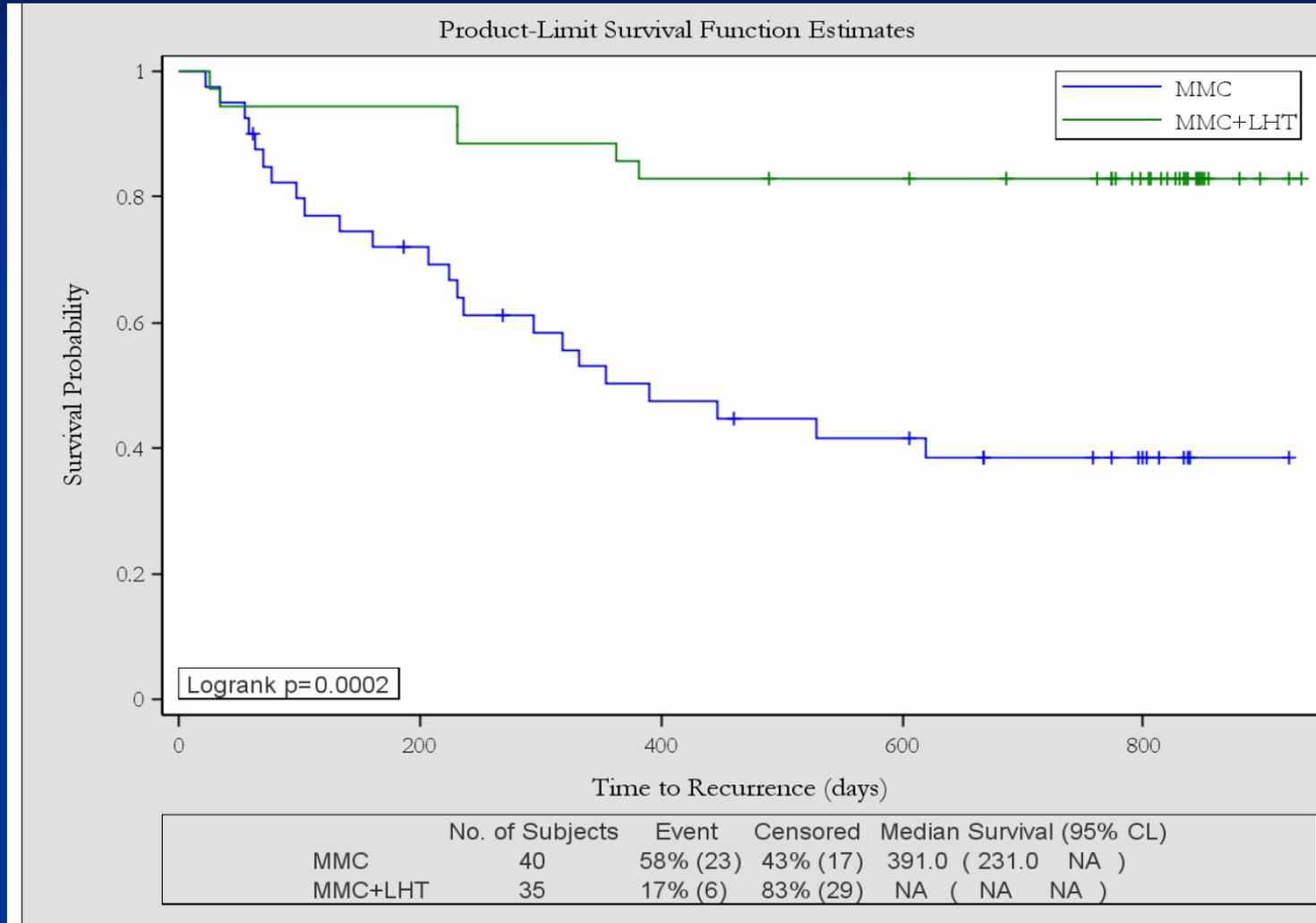
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Evaluable: “Randomized As Treated” 77	18.9% (n=37)	61.6% (n=40)	0.0002
“Per-Protocol” 75	17.1% (n=35)	61.6% (n=40)	0.0002
All pts, as assigned (intended), with “worst-case” censoring* 83	38% (n=42)	51% (n=41)	0.23

*Adds back 6 drop-outs; assumes 1 control patient was recurrence-free and 5 Synergo patients had disease-recurrence at follow-up

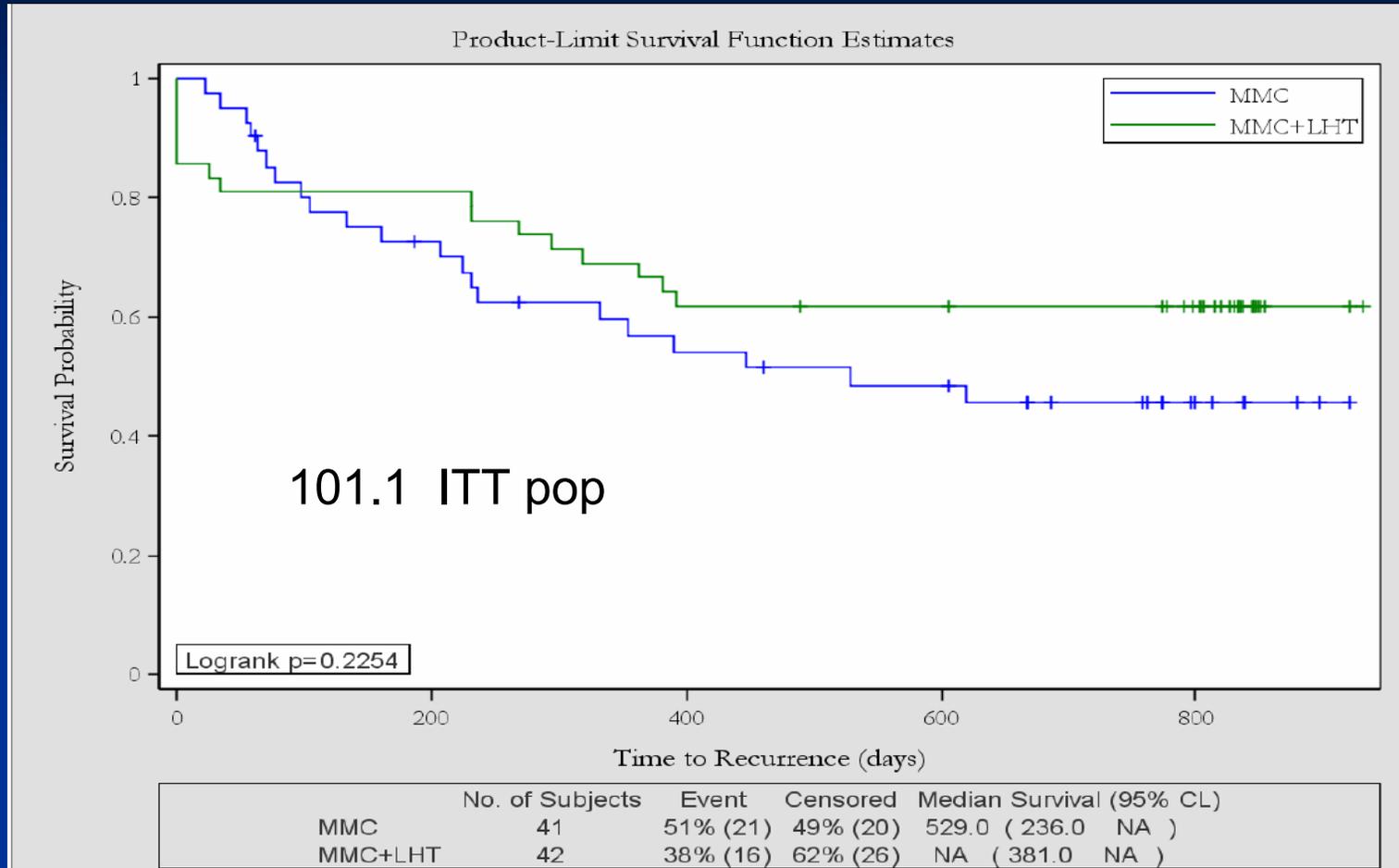
Applicant K-M time to recurrence

“Valid for analysis-Per Protocol” group (N = 75 of 83)



Applicant K-M time to recurrence

All patients with “worst case” censoring (N=83)

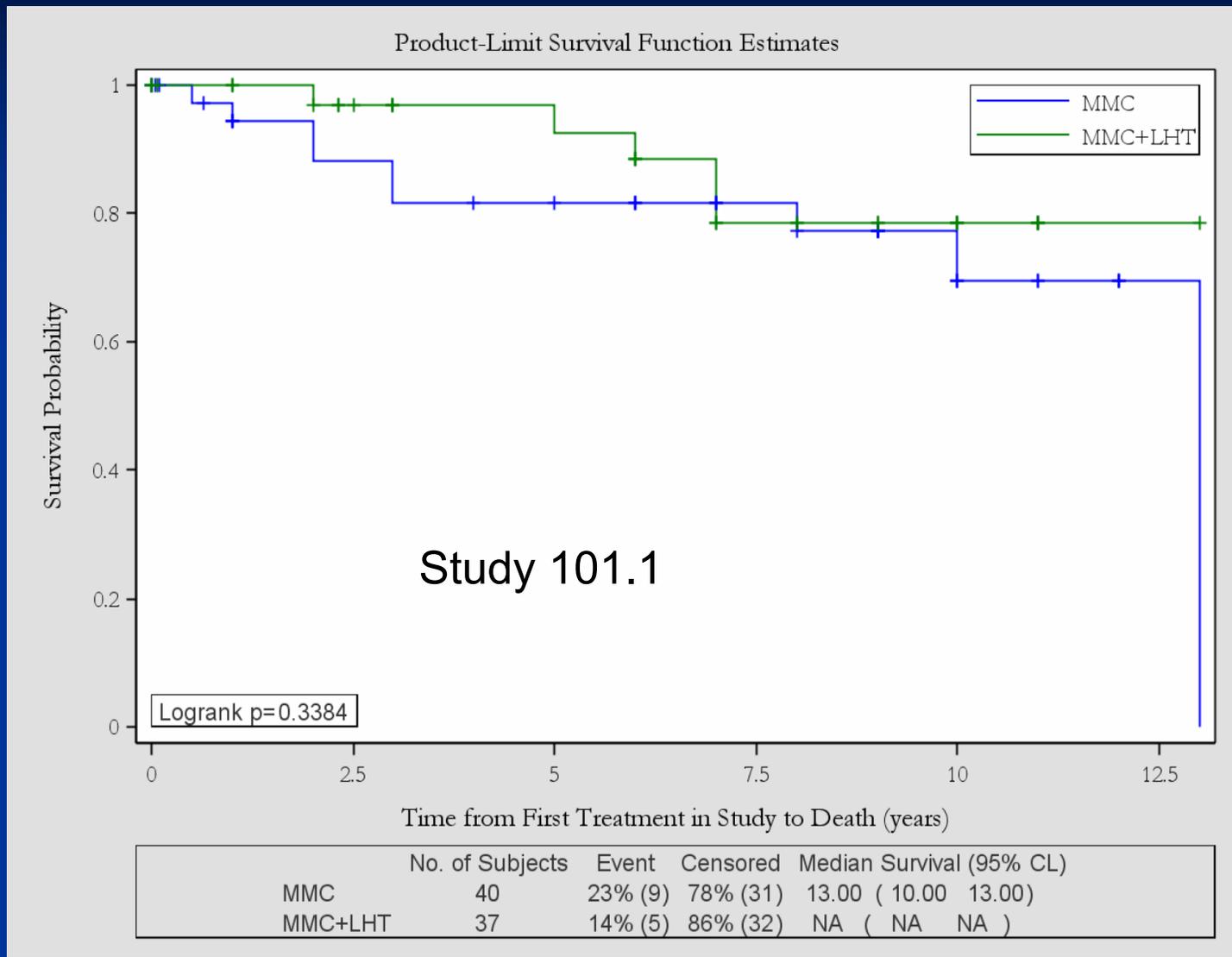


All patients (ITT), analyzed based on the intended therapy
 Assumes 1 missing control patient was recurrence-free and
 5 missing Synergo patients had disease-recurrence at follow-up

Secondary endpoints 101.1

- Stage progression – none reported
- No Cis observed
- Late followup performed 2006
 - No overall survival differences
 - Total of 14 deaths – no bladder cancer deaths
 - “5 due to tumors in other organs” (no pathology)
 - 3 patients reported to have metastases on MMC arm by scans – no pathology reported

Applicant's analysis of overall survival (2008)*



* Not Intention-to-treat population (N = 77 of 83)



Adverse Events (AEs) – 101.1

	N	MMC + Synergo	MMC
Number of patients	83	42	41
Any AE	53	88 %	63 %
Tissue reaction	41	50 %	49 %
Pain	17	40 %	0
Dysuria	14	24 %	10 %
Hematuria	5	7 %	5 %
Urethral stenosis	5	7 %	5 %
Bladder wall thermal necrosis RF-antenna	28	64 % 10% severe	2 %
Skin allergy (MMC)	7	12 %	5 %

Synergo Adverse Events (AEs)

- Pain with Synergo therapy 17/42 (40%)
- “Pain or intolerance” to treatment 10/42 (24%)
- Bladder spasms - catheter placement 7/42 (16%)
Of these 17 events:
 - 7 were rated as “mild,”
 - 7 were rated as “moderate,”
 - 3 were rated as “severe”
- One Synergo patient – false urinary passage attributed to the larger size catheter needed

Synergo Adverse Events (AEs)

- Posterior wall thermal tissue reaction related to RF antenna, visible by cystoscopy
 - Tissue necrosis in 23/42 (55%)
 - Mild 15
 - Moderate 4
 - Severe 4
 - Posterior wall ulcer in 1/42 (2%)
- Not transmural; no interventions described for this condition

Other Synergo Studies - EPP

- European Prophylactic Patients study – ongoing of commercial use of Synergo + MMC
- single-arm study
- 186 enrolled
- 122 evaluated for efficacy
- EPP estimated 2 year recurrence rate = 32%
- Study 102.1, 2 year recurrence with BCG=32%

Synergo studies

- Study 102.1 addresses a different question than 101.1, but the safety on the Synergo-MMC arm appears similar
 - About 1/3 accrued, await full study report
- 101.1 is a prospective study of 83 patients (42 on Synergo) for the proposed approval indication
- 101.1 general treatment plan, endpoints, and 2 year followup are reasonable choices for the disease
- Adverse events are greater on the Synergo arm including: all AEs, pain, dysuria, and posterior bladder wall tissue reaction

Clinical limitations regarding 101.1

- At the time of randomization, patient baseline characteristics were disclosed on the form submitted to obtain the randomization
- ‘Mis-randomization’ occurred - at one site, 4 of 8 BIMO audited patients were “mis-randomized”
 - A total of 5 pairs of patients’ Rx assignments switched (10/83, 12%)

Clinical limitations regarding 101.1

- The original study protocol lacked pre-specified definition for the primary endpoint, or for interim efficacy analyses performed after 64 patients, or the decision to stop the study at 83 patients, or a plan for analysis of missing data

Clinical limitations regarding 101.1

- Data collection: Case report forms to document study events were not introduced until 3-4 years after the study started. While the source records appear to be transcribed accurately to these forms, there is no assurance that additional vital study information was not lost by the failure to document prospectively for all patients.

Clinical limitations regarding 101.1

- Pathology information regarding baseline and followup biopsy results was not prospectively and consistently captured in a structured format to assure accuracy and completeness of the information.
- For example, baseline description regarding presence of or involvement of the muscular layer was inconsistent.

Clinical limitations regarding 101.1

- No central pathology review performed
- No pathology report available for 4/29 reported recurrences

Clinical limitations regarding 101.1

- Blinding: Patients and investigators knew their treatment plan
- While blinding of treatment was not practical, no independent adjudication of the endpoint of tumor recurrence was performed

Clinical limitations regarding 101.1

- Dwell time in the bladder for the intravesical MMC was not consistently recorded on either study arm and treatment differences may have resulted from that variable.
- For Synergo patients, MMC was removed via catheter; MMC control patients were advised to void per schedule
- Follow-up cysto exams were not performed consistently at the study sites

Clinical limitations regarding 101.1

- Concomitant medications were not prospectively recorded; therefore, concurrent use of other medicines (which may inform further regarding efficacy or safety) is uncertain.

Clinical limitations regarding 101.1

- Potential for bias was not minimized
- A substantial asymmetry in early drop-outs on the Synergo arm (7 versus 1) suggests additional adverse features of this therapy
- Strength of efficacy conclusions vary with analysis population
- Study 102.1 shares some concerns

Colombo, Da Pozzo, Rigatti, Leib et al. J Clin Oncol 2003; 21: 4270-76

- Study 101.1 was reported in 2003 by the investigators
- “Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma”

Colombo, Da Pozzo, Rigatti, Leib et al.

- San Raffaele, Milan, Italy
- Beilinson Hospital, TelAviv, Israel
- Palermo, Italy
- 83 patients randomized between MMC alone versus MMC delivered by Synergo RF hyperthermia

Colombo, Rigatti, Leib et al. J Clin Oncol 2003; 21:4270-76

- “These results are preliminary and need to be confirmed by larger, prospective, multicenter studies. The combined treatment was more cumbersome and requires a larger catheter. However, the reduction in the proportion of recurrences at 24 months in favor of the thermo-chemotherapy encourages further clinical investigations.”

FDA Statistical Review

Synergo SB-TS 101.1 Device + Mitomycin C

Xuefeng Li, PhD

Division of Biostatistics
Office of Surveillance and Biometrics / CDRH
June 25, 2008

Outline

1. Pivotal Study Design
2. Effectiveness Results
3. Limitations of the study
4. Other data and studies
5. Summary

Study Design

- **Pivotal Trial: A randomized, multi-center, unblinded study**
 - Synergo+MMC (n=42) vs. MMC (n=41)
 - 3 Centers (Milan, Italy 36, Palermo, Italy 14, Israel 33)
 - Randomized 1 : 1 at each center
 - Originally planned to enroll 150 patients
 - An interim look when 64 patients enrolled and study stopped when 83 patients have 24 month data

Patient Accounting

Analysis Population	Treatment Group		Total
	Control	Synergo	
All Study Patients	41	42	83
Patient consent withdrawn	0	3	3
Physician withdrawn	0	1	1
Skin allergy - terminated	0	2	2
Evaluable as Intended	41	36	77
Misrandomized	5	4	9
Evaluable As-Treated	40	37	77
Protocol deviations	0	2	2
Per-Protocol	40	35	75

Sponsor's Effectiveness Results

	Estimated 2-Year Probability of recurrence		
Analysis Population	Control Group	Synergo Group	p-value*
All Study Patients (worst case scenario)	54.42%	38.10%	0.2254
Evaluable As-Intended	54.42%	25.00%	0.0097
Evaluable As-Treated	61.57%	18.92%	0.0002
Per-Protocol	61.57%	17.14%	0.0002

*: Not adjusted for the interim look or the early stopping.

Secondary Endpoints

Endpoints	Synergo	Control
Stage progression at recurrence	0	0
Worsening of grade at recurrence	0	1
Occurrence of Cis	0	0
Occurrence of urothelial cell carcinoma in the upper tract or prostatic urethra	0	0
Occurrence of distant metastasis	0	3

Limitations of Study 101.1

1. Lack of blinding
2. No pre-specified primary endpoint and secondary endpoints
3. No pre-specified hypotheses and statistical analyses
4. No pre-specified rules for handling the missing data
5. Lack of details in interim analysis

Other Data and Studies

- Long-term data of Study 101.1
- Interim look of ongoing Study 102.1
- Combining analysis of Study 101.1 and Study 102.1
- Literature review of control treatments

Long-Term Data of Study 101.1

■ Recurrence rates (evaluatable as-treated)

	Control N=40	Synergo N=37
5 year	78.05%	39.44%
10 year	84.95%	48.18%

- Overall survival (secondary endpoint)
 - 1994~2006: 14 deaths (9 control, 5 Synergo)

Limitations of Long-Term Data

- **Analyses not pre-specified**
- **Missing data not considered (Use as-treated)**

Interim Look of Study 102.1

	Synergo	BCG
# Subjects planned	150	150
# Subjects enrolled	51	53
# Subjects had effectiveness data	42	48
2-year recurrence rate*	16.9%	31.7%
Progression rate	0	0

*: Use as-treated population

Limitations of Study 102.1

- Unplanned interim look of an ongoing study
- Different treatment regimen
- Patient comparability

Combined Analysis: 101.1 + 102.1

Treatment	2-year recurrence rate*
Combined Synergo	17.1%
MMC (Study 101.1)	61.6%
BCG (Study 102.1)	31.7%

*: Use per protocol population

Limitation of Combined Analysis

- Unplanned analysis
- Patient poolability cannot be fully verified

Literature Review of Controls

	2-year recurrence rate 95% CI
MMC*	41.53% (36.8%, 46.3%)
BCG**	35.55% (32.4%, 38.7%)

*: Meta-analysis of 8 studies

** : Meta-analysis of 13 studies

Limitation of Literature Review

- **Unplanned analysis**
- **Study poolability cannot be verified**
- **Subject to publication bias**

Summary

- Pivotal study appears to show that Synergo has smaller recurrence rate than the control
- Limitations of pivotal study
 - Lack of blinding
 - No pre-specified hypothesis
 - No pre-specified primary endpoint
 - No pre-specified imputation of missing data
 - No pre-specified interim analysis
- Other analyses appears to show supportive evidence but have limitations

Post-Approval Considerations

Synergo SB-TS 101.1 Device + Mitomycin C

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Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

Outline

- General Principles and Objectives for Post-Approval Studies
- Overview and Assessment of Sponsor's Post-Approval Study Proposal
- Post-Approval Study Issues for Panel Discussion

General Principles for Post-Approval Studies

- To evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of reasonable assurance of device safety and effectiveness.

Objectives for Post-Approval Studies

- Gather postmarket information
 - Longer-term performance
 - Community performance
 - Effectiveness of training programs
 - Sub-group performance
 - Rare adverse events and real world experience
- Account for Panel recommendations

Outline

- General Principles and Objectives for Post-Approval Studies
- Overview and Assessment of Sponsor's Post-Approval Study Proposal
- Post-Approval Study Issues for Panel Discussion

Overview of Sponsor's PAS

Study Design	A prospective, single-arm study to evaluate the safety of the device compared to premarket study 101.1
Study Endpoint	Primary: the frequency of anticipated adverse events Secondary: Unanticipated adverse events
Hypothesis	Null Hypothesis: $P \geq P_i + \Delta$ Alternative Hypothesis: $P < P_i + \Delta$
Population	Patients with intermediate and high-risk STCCB, undergoing transurethral resection of their tumors.
Sample size	211 patients will be enrolled, power=80%
Follow-up	Every 3 months until 12 months

Overview of Sponsor's PAS

Study Safety Endpoints

- Primary endpoint is frequency of anticipated adverse events:
 - Posterior wall thermal reaction, urethral stenosis, hematuria, false route, hypotonic bladder, reduced bladder capacity, urinary tract infection and necrosis in other areas of the bladder.

Overview of Sponsor's PAS

Hypothesis

- The Null and alternative hypotheses are formulated as follows:

Null Hypothesis: $P \geq P_i + \Delta$

Alternative Hypothesis: $P < P_i + \Delta$

- Δ to be 10% for proportions over 50%
- Δ to be 5% when the adverse event occurrence rate is small, i.e. a rare event.

Assessment of PAS Proposal

Study Design: Comparison Group

- Proposal to evaluate the safety of the Synergo system by comparing the frequencies of AEs occurring in this study to that reported in the Study 101.1
- All premarket data came from outside US.
- Premarket studies are performed in selected patient populations and conducted in highly specialized centers which limit their use as postmarket comparators.

Adverse Events (AEs) % Distribution Premarket

Adverse event	Study	
	101.1 (n=42)	102.1 (n=50)
Posterior wall reaction	27 (64.3 %)	20 (40.0 %)
Urethral stenosis	3 (7.1 %)	11 (22 %)
Hematuria	3 (7.1 %)	29 (58 %)
Urinary tract infection	3 (7.1 %)	7 (14 %)
Reduced bladder capacity	2 (4.8 %)	-
Bladder wall necrosis	2 (4.8 %)	-
False route	1 (2.4 %)	1 (2.0 %)
Hypotonic bladder	1 (2.4 %)	1 (2.0 %)

Assessment of PAS Proposal

Study Design: Endpoint

- The proposed study only considers the evaluation of safety but **does not** include a plan to assess postmarket effectiveness.
- The long-term effectiveness (cancer recurrence and survival) in large and diverse patient population is still not clear.

Assessment of PAS Proposal

- Although both 101 and 102 studies show Synergo has a reduced 2-year recurrence rate, the deficiencies in these studies make the recurrence data difficult to interpret.
- There was no significant difference in the overall survival rate between the two treatment groups (9 in Control and 5 in Synergo). None of the deaths were known to be due to STCCB.

Assessment of PAS Proposal

Study Design: Length of Follow-up

- Current proposal considers only a 1 year of follow-up.
- Given the slow progression of this type of tumor, the proposed duration of follow-up might be not sufficient to assess the long-term performance of this device.

Assessment of PAS Proposal

Statistical Analysis Plan

- Proposal to conduct a non-inferiority hypothesis test for each anticipated adverse event (8). The sponsor proposes to use 10% Δ for AE with $\geq 50\%$ and 5% Δ for rare AE.
- The definitions of a common versus a rare event are not explicit.
- The rationale for selection of delta is not presented.

Adverse Events (AEs) % Distribution Premarket

Adverse event	Study 101.1
Posterior wall reaction	64.3 +10
Urethral stenosis	7.1 + 5
Hematuria	7.1 + 5
Urinary tract infection	7.1 + 5
Reduced bladder capacity	4.8 + 5
Bladder wall necrosis	4.8 + 5
False route	2.4 + 5
Hypotonic bladder	2.4 + 5

Outline

- General Principles and Objectives for Post-Approval Studies
- Overview and Assessment of Sponsor's Post-Approval Study Proposal
- Post-Approval Study Issues for Panel Discussion

Issues for Panel Discussion

Study Design: Comparison Group

- Proposal to evaluate the safety of the Synergo system by comparing the frequencies of AEs occurring in this study to that reported in the Study 101.1.
- *What would panel suggest as the most appropriate comparator?*

Issues for Panel Discussion

Study Design: Endpoint

- The proposed study **does not** include a plan to assess postmarket effectiveness (recurrence and/or survival).
- *Should effectiveness be studied postmarket? If so, what endpoint should be studied?*

Issues for Panel Discussion

Study Design: Length of Follow-up

- Current proposal considers only a 1 year follow-up. Please discuss:
- *Is 1-year of follow-up long enough to assess the long-term performance of the device?*

Issues for Panel Discussion

Statistical Plan

- Proposal to conduct a non-inferiority hypothesis test for each anticipated adverse event. The sponsor proposes to use 10% Δ for AE with $\geq 50\%$ and 5% Δ for rare AE.
- *Please discuss and make recommendations on the definition for rare versus common adverse events and the rationale for the chosen deltas.*

Questions?

Back-up slides

Device Malfunctions

- 37 malfunctions in 426 treatment sessions
 - 33 thermocouple problems (noisy signal)
 - 2 catheter obstructions
 - 1 RF transmission failure
 - 1 balloon rupture
- Treatments either continued uninterrupted or paused/resumed using a new catheter
- No associated adverse events

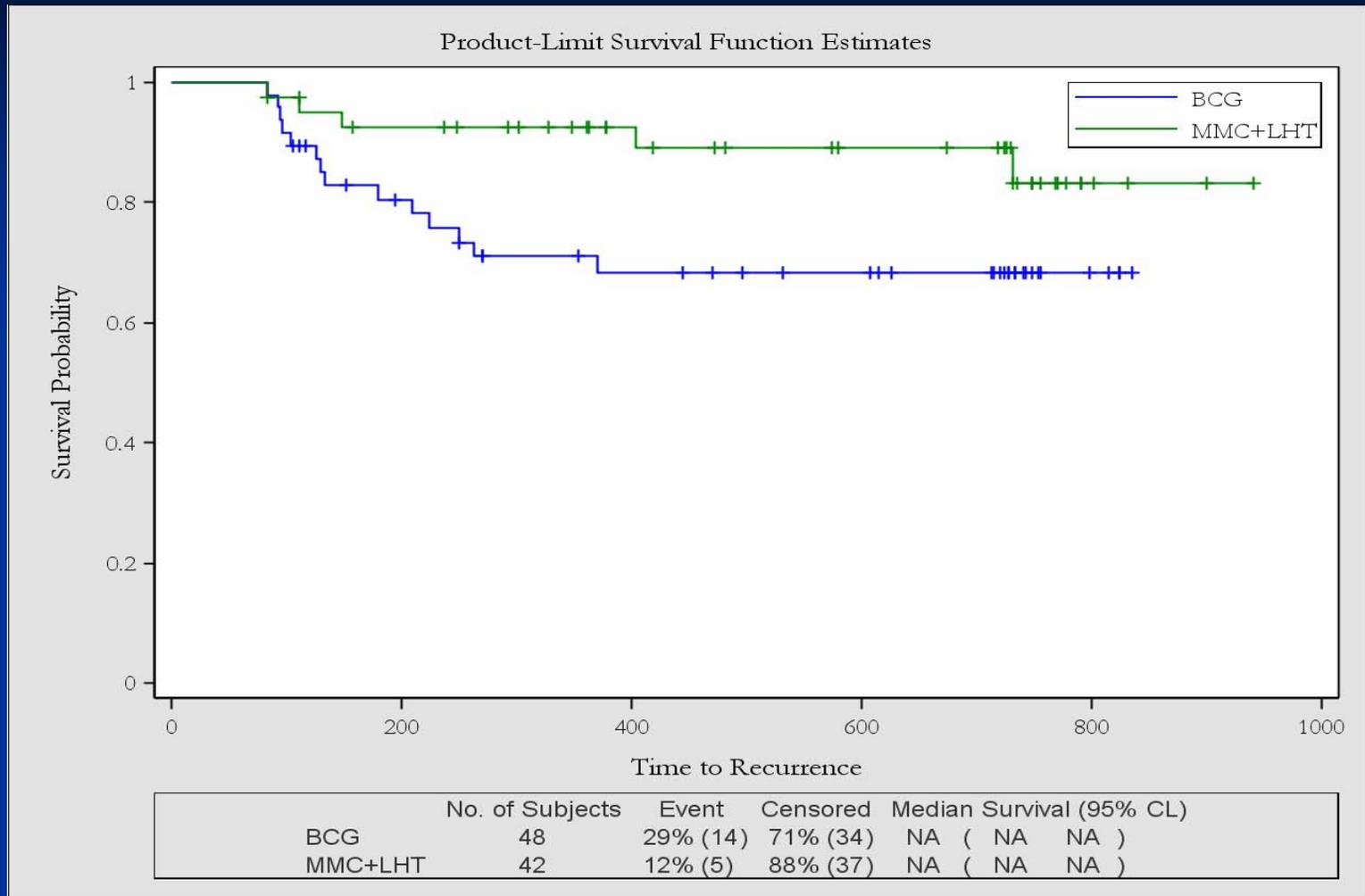
Applicant table (PMA amdt 16)

study 101.1	Treatment Group*		Total
	Control	Synergo	
Analysis Population			
ITT	41	42	83
Patient consent withdrawn	0	3	3
Physician withdrawn	0	1	1
Skin allergy – study term.	0	2†	2
ITT Completers	41	36	77
Incorrectly randomized	5	5†	5
As-Treated	40	37	77
Protocol deviations	0	2	2
Per-Protocol	40	35	75

*Treatment assigned for the ITT population; Treatment received for the As-Treated pop.

†Patient B8705-001-022 was counted in both categories. This patient was incorrectly randomized to the Control group and was excluded from the ITT completers, as-treated and per-protocol analysis populations.

Applicant analysis 102.1 (Jan 2008)



N = 104; 90 evaluated for efficacy

Estimated probability of recurrence at 2 years is 16.9% (95% CI: 2.1%-31.7%) in the Synergo group and 31.7% (95% CI: 17.8%-45.6%) in the BCG group

Adjustment of Interim Look Threshold for p-value

	Look when 64 out of 150 pts	Look when 83 out of 150 pts
O'Brian-Fleming	0.0013	0.005
Pocock Boundary	0.0277	0.033

FDA Panel Questions

Question 1

- **Effectiveness**

Under 21 CFR 860.7(e)(1), effectiveness is defined as reasonable assurance, based upon valid scientific evidence, that, in a significant portion of the population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Question 1

- The PMA for the Synergo system presents clinical data from a single pivotal trial (Study 101.1) and several additional supporting clinical data sources, the review of which present the following challenges in assessing the effectiveness of this combination product:

Question 1

- Significant limitations exist in the design and conduct of Study 101.1, which when considered collectively, potentially impair the ability to interpret the results and increase the uncertainty of the stated conclusions, including:
 - multiple sources of bias;
 - the absence of structured methods for obtaining pathology samples and recording pathology information;
 - potential variation in mitomycin C exposure between the study groups; and
 - reliance on a small, limited study population to perform the risk/benefit analysis and generalize the study results to the general U.S. population.

Question 1

- The supporting clinical data sources were not designed to provide stand-alone evidence of the safety and effectiveness of the Synergo system for the proposed indication.

Question 1

- Considering the design and conduct of Study 101.1 and the supporting clinical data sources, please discuss whether the clinical data in the PMA provide reasonable assurance that the Synergo system is effective. If not, what additional data or analyses are needed?

Question 2

- **Safety**

Under 21 CFR 860.7(d)(1), safety is defined as reasonable assurance, based upon valid scientific evidence, that the probable benefits to health under conditions of the intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks.

Question 2

- As observed in pivotal Study 101.1 and the supporting clinical data sources, treatment with the Synergo system results in an increased rate of adverse rates over mitomycin C alone, particularly posterior bladder wall tissue reaction, pain, and bladder spasms. These events were generally mild, localized, and transient. However, limitations in the design and conduct of the pivotal study potentially impair the ability to interpret the safety analysis, including:

Question 2

- the absence of concomitant medication information;
- the retrospective completion of a portion of case report forms; and
- reliance on a small, limited study population to perform the risk/benefit analysis and generalize the study results to the general U.S. population.

Question 2

- Considering the design and conduct of Study 101.1 and the supporting clinical data sources, please discuss whether the clinical data in the PMA provide reasonable assurance that the product is safe. If not, what additional data or analyses are needed?

Question 3

- **Postapproval Study**

The firm proposes to conduct a single-arm postapproval study, in which 211 subjects will be followed for 12 months to further evaluate the safety of this combination product. If the Synergo system is recommended for approval (with or without conditions), please discuss whether the proposed design of this postapproval study is adequate to address all relevant remaining safety and effectiveness issues. In your deliberations, please discuss the following:

Question 3

- The firm proposes to evaluate safety by comparing the frequencies of adverse events to those reported in Study 101.1. What would you suggest as the most appropriate comparator, and why?
- The proposed study does not include a plan to assess longer term postmarket effectiveness in a larger, more diverse population. Should longer term effectiveness be studied postmarket? If so, what endpoint(s) should be evaluated?

Question 3

- The current proposal includes 1-year follow-up. Is 1-year follow-up sufficient to assess the long-term performance of this combination product?
- The firm proposes non-inferiority tests for the 8 specified adverse events, using delta values of 10% and 5% for “common” (i.e., $\geq 50\%$) and “rare” events, respectively. Please discuss the need for clarification of definitions of common versus rare events, and the rationale for delta values and what might be appropriate in each case.

Question 4

■ Labeling and Training

The firm provides physician and patient labeling for the Synergo system, as well as the approved package insert for mitomycin C. A physician training program is not proposed. If the Synergo system is recommended for approval (with or without conditions), please discuss whether the information provided is adequate to assure the safe and effective use of this combination product. If not, what additional information should be included in these labeling documents?

Safety

There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness

There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence

Evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

Panel recommendation options for the vote:

APPROVAL – If there are no conditions attached.

APPROVABLE with conditions – The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel.

NOT APPROVABLE – The panel may recommend that the PMA is not approvable if the data **DO NOT** provide a reasonable assurance that the device is safe, or the data **DO NOT** provide a reasonable assurance that the device is effective, under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

VOTING OPTIONS

