

FDA Executive Summary

*Prepared for the June 25, 2008, meeting of the
Gastroenterology-Urology Devices Advisory Panel*

P010045
Medical Enterprises, Ltd.
Synergo SB-TS 101.1 Device + Mitomycin C

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Introduction

The subject of this executive summary is P010045, a premarket approval (PMA) application for a combination product, consisting of a hyperthermia system (the Synergo SB-TS 101.1 device) and a chemotherapeutic drug (mitomycin C). This combination product is intended to prevent recurrence of superficial transitional cell carcinoma of the bladder, a form of bladder cancer. Treatment involves heating the wall of the urinary bladder using radio frequency energy emitted from a specialized urinary catheter, concomitant with intravesical instillation of mitomycin C. The Synergo SB-TS 101.1 Device + Mitomycin C (collectively referred to as the Synergo system) is a novel, first-of-a-kind product.

This summary contains six sections. The first section (Clinical Study Design and Conduct) describes the challenges facing the FDA with respect to the interpretation of the pivotal clinical study data. The Panel will be asked to consider the study outcomes, taking into account the design and conduct of this study including, for example, the collective impact of multiple sources of bias resulting from the study protocol and conduct, inconsistent methods for obtaining and recording pathology information, differences in the drug exposure time between the study groups, and the limited study sample size.

The second and third sections (Indications for Use and Principle of Operation and Device/Drug Description, respectively) provide background information on the design and use of the combination product.

The fourth section (Preclinical Studies) describes the preclinical data that were collected to characterize the combination product and support its safety and effectiveness.

The fifth section (Clinical Studies) describes the pivotal clinical investigation and other clinical and statistical information that were provided to support the safety and effectiveness of the combination product. The primary evidence provided in support of safety and effectiveness is Study 101.1, a multi-center clinical trial, in which subjects were randomized between Synergo + mitomycin C treatment (Synergo group) and mitomycin C alone (Control group). This section also contains a detailed description of the clinical topics on which the Panel is being asked to comment.

The sixth and final section (Postapproval Plan) describes the postapproval study that the firm proposes to conduct if the combination product is approved. This section also contains the topics the Panel will be asked to focus on when considering the proposed postapproval study.

I. Clinical Study Design and Conduct

The pivotal clinical study consisted of a prospective, randomized study of patients with surgically resected Stage Ta or T1 and Grade G1-G3 superficial transitional cell carcinoma of the bladder (STCCB), conducted at three clinical centers. The study included 42 patients treated with hyperthermia and mitomycin C as compared to 41 patients treated with mitomycin C alone. Following 8 treatment sessions, patients in both study arms were assessed at 3-month intervals up to 24 months for disease-free interval, recurrence rate, progression of stage and grade, occurrence of carcinoma *in situ* (Cis), occurrence of urethral cell carcinoma in the upper tract or in the prostatic urethra, and occurrence of distant metastasis. Although not specifically stated in the study protocol, patient success was defined in the clinical report as freedom from disease throughout the study period (as assessed on follow-up cystoscopy).

The challenge that FDA faces when interpreting the outcomes of this pivotal study relate to specific issues regarding its design and conduct. In general, these concerns arise from the manner in which the pivotal clinical trial protocol was written and interpreted during the study period. Specifically, these include;

1) multiple sources of potential bias due to:

- key elements of the protocol not being pre-specified,
- retrospectively created case report forms,
- asymmetric drop-out rate,
- unblinded cystoscopy evaluations,
- the absence of a blinded review committee for tumor-related data,
- randomization problems, and
- absence of concomitant medication information;

2) inconsistent methods for obtaining and recording pathology information;

3) differences in mitomycin C exposure between the study groups; and

4) the small, limited size of the study population.

During their deliberations the Panel will be asked to consider the study outcomes, taking into account the design and conduct of the pivotal study and supporting clinical information as they evolved during the study period. These issues are discussed in further detail in Section V.

II. Indications for Use

[Sponsor Summary (Section 4.1)]

The proposed indications for use statement based on the pivotal clinical trial states:

“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 indicated 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.”

III. Principle of Operation and Device/Drug Description

The Synergo system is a combination product consisting of two principal components:

- Synergo Hyperthermia Device
- Synergo Kit, consisting of:
 - Disposable catheter-tubing set
 - Mitomycin C (2 vials, 20 mg each)

a. Principle of Operation

[Sponsor Summary (Sections 2 and 3)]

Treatment with this combination product involves hyperthermia of the internal urinary bladder wall concomitant with circulation of an intravesical dose of the chemotherapy drug, mitomycin C. The hyperthermia device heats the urinary bladder using radio frequency (RF) energy, delivered from a catheter-based antenna. In addition to the antenna, the specialized transurethral catheter contains five thermocouples (three inserted within the patient’s bladder and two positioned along the patient’s urethra) to provide temperature feedback to the system, and internal lumens for the continuous circulation of the drug solution between the bladder and an external heat exchanger (contained within the Synergo hyperthermia device). The treating physician adjusts both the RF power output and drug circulation flow rate to maintain the bladder temperature in the range of $42 \pm 2^{\circ}\text{C}$.

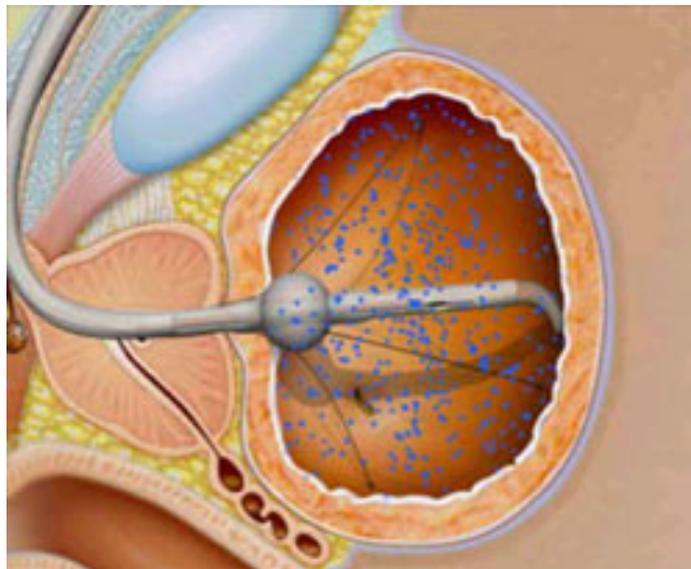
Treatment is started 20-40 days after definitive transurethral resection of all STCCB tumors. A complete course of treatment consists of 8 weekly “inductive” sessions, followed by 4 monthly “maintenance” sessions. Each treatment session lasts 60 minutes, with “time over 41°C ” targeted to be at least 40 minutes. Prior to the session, the patient’s bladder is drained, local anesthesia is given along the urethra, and the treatment catheter is inserted into the bladder. Mitomycin C is administered in two consecutive instillations of 20 mg in 50 mL distilled water, each for a dwell time of 30 minutes. After instilling the first 50 mL preparation of mitomycin C through the catheter, the bladder wall thermocouples are deployed from the catheter, the drug circulation system is turned on, and RF power is manually increased to achieve a target temperature at the bladder wall of 42°C . Treatment continues for 30 minutes, after which the session is paused to drain the first drug preparation and replace it with the second. The session continues for

another 30 minutes, after which heating is terminated, the patient's bladder is emptied, and the catheter is removed.

Picture of the Synergo hyperthermia device:



Picture of the treatment catheter within the bladder:



b. Synergo Hyperthermia Device

[Sponsor Summary (Section 3)]

The Synergo hyperthermia device (Synergo) is a computer-controlled device which delivers RF energy to the antenna, circulates the mitomycin C drug solution during treatment, controls the drug solution temperature via a heat exchanger, and monitors system operation and status. The device consists of the following main components, mounted on a transportable cart:

- an operator console;
- a RF generator;
- a drug circulating unit;
- a power supply; and
- a console arm.

The operator console contains a computer to monitor, display, and record temperatures from the catheter thermocouples and heat exchanger, forward and reflected RF energy, tubing line pressure, and patient treatment parameters. Although treatment is administered by the physician under manual control, the operation of the Synergo device is monitored by the system software. The software tasks consist of (i) performing a set of system self-checks; (ii) recording patient information and treatment data; and (iii) monitoring critical treatment parameters to verify that they are within acceptable limit. If a critical parameter (such as temperature or RF energy level) becomes out of range, the software either issues an error message or halts microwave delivery. In addition to the software controls, RF power can be manually shut off at any time by either the patient or user by pressing the emergency stop button (located on the front of the operating console).

The RF generator delivers energy at 915 MHz (in the microwave range of the RF spectrum). The generator has an output rating of 0-60 W, but is limited by the device design to 0-36 W. The typical treatment power necessary to achieve the desired 42°C target temperature at the bladder wall is 12-15 W.

The drug circulating unit consists of a peristaltic pump (0-20 mL/min), a Peltier element heat exchanger (to cool the reservoir bag circulating drug solution to 2-10°C), a reservoir bag fluid level sensor (using a proximity-action capacitive sensor), two pressure transducers (at bladder inflow and outflow), and a pinch clamp. Tubing line pressure is limited to 230 mmHg by pressure relief valves.

The Synergo device also contains a power supply and a console arm (i.e., the connection site for the catheter's thermocouples and antenna).

c. Synergo Kit

[Sponsor Summary (Section 3) and Proposed Labeling]

The Synergo Kit consists of:

- the disposable catheter-tubing set, contained in a sealed sterile pouch (within which the catheter and tubing set are packaged separately in individual sterile pouches);
- two vials of mitomycin C (20 mg each); and
- labeling inserts for both the drug and the combination product.

A separate Synergo Kit is required for each treatment session.

i. Disposable Catheter-Tubing Set

The disposable catheter-tubing set consists of (i) a catheter system and (ii) an interconnecting tubing line. These two components are sterile, for single use only.

The catheter system is the transurethral catheter used to deliver Synergo treatment to the patient. It is a silicone, triple lumen, 20 Fr. balloon catheter, which contains the RF antenna for delivery of energy to the bladder and inflow/outflow channels for drug circulation. The catheter system contains three thermocouples for monitoring bladder wall temperature (“bladder thermocouples”), and two thermocouples located on the cable to the antenna (“feeding cable thermocouples”). Once the catheter is inserted, the bladder thermocouples are deployed from the catheter tip and spread out to contact the bladder wall. In male patients, the two feeding cable thermocouples are used for measuring temperature on the feeding cable at the area of the prostatic urethra for additional safety. In female patients, the feeding cable thermocouples are disabled.

The tip of the catheter system contains the active portion of the antenna, as well as the holes through which the drug solution circulates in/out of the bladder and from which the bladder wall thermocouples deploy. Therefore, the tip of the catheter system extends farther into the bladder than does the tip of a conventional Foley catheter.

The interconnecting tubing line is used to connect the catheter to the drug circulating unit to provide a closed-loop drug circulating system. The purpose of the drug circulating system is to reduce the risk of bladder overheating by continuously cooling and reinstilling the drug solution. The tubing line consists of PVC tubing, a drug reservoir, luer-lock connectors, protection caps, 3-way valves, unidirectional hydrophobic transducer protectors, filter, and clamps.

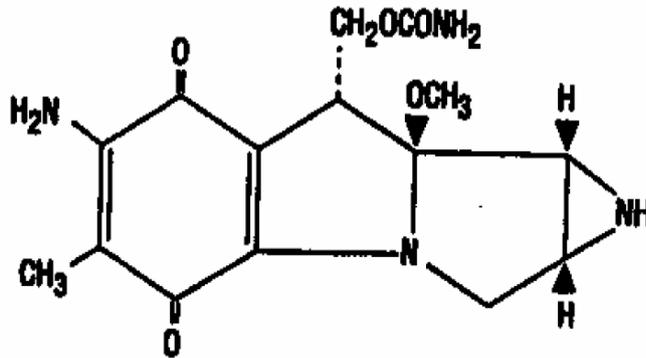
ii. Mitomycin C

The Synergo Kit contains 2 vials of mitomycin C, provided in its intended dosage (20 mg each).

Mitomycin C is legally marketed in the U.S., but not for either the indication or route of administration proposed in this PMA. Rather, this drug is approved for intravenous administration in the treatment of adenocarcinoma of the stomach and pancreas.

Although not approved in the U.S. for intravesical administration in the prophylactic treatment of STCCB recurrence, mitomycin C is approved for this use in many foreign markets and is commonly used off-label in the U.S. for this purpose. As described in the American Urological Association “Report on the management of non-muscle invasive bladder cancer” (1999), the literature reports intravesical dosages from 20 to 60 mg per instillation. A commonly used dose is 40 mg in 40 mL of saline or sterile water (1-hour dwell time), administered weekly for 8 weeks followed by monthly instillations for 1 year.

Mitomycin C is an antibiotic isolated from the broth of *Streptomyces caespitosus*, which has been shown to have antitumor activity. Mitomycin C inhibits DNA synthesis. The structural formula of mitomycin C (M.W. = 334.33) is shown below:



The specific drug product provided in the Synergo Kit is distributed by Bedford Laboratories (approved under ANDA 94-117; trade name “Mitomycin for Injection, USP”) and provided to Medical Enterprises in final packaged form (sterile, dry powder) with a 2-year expiration date. The Bedford Laboratories drug label insert is included in the Synergo Kit.

IV. Preclinical Studies

a. Preclinical Testing

[Sponsor Summary (Section 5)]

i. Mechanical and Functional Performance Testing

The firm conducted a battery of mechanical and functional performance tests on the device components of the Synergo system. These studies were performed on samples of final, finished devices to verify that the design output conforms to the design input requirements described in the product specification.

System-level testing: The firm conducted system-level testing of the Synergo hyperthermia device to verify functional performance during simulated operation, which included visual inspection tests, subsystem functionality tests, measurement system accuracy tests, and subsystems/safety features. All subsystems operated within design specifications.

ASTM testing: To verify the performance and safety of the transurethral catheter, the firm conducted testing in accordance with the ASTM F 623 standard (Standard Performance Specification for Foley Catheter).

Functional testing: The following tests were performed to verify the integrity and performance of the catheter system's antenna and thermocouples:

- thermocouple connection, electrical isolation, short circuit, resistance, and measurement stability tests;
- antenna spatial emission profile verification; and
- bladder thermocouple deployment verification.

The results of these mechanical and functional tests demonstrate that the design output conforms to the design input requirements described in the product specifications.

ii. RF Output Testing

The firm conducted temperature mapping and RF field distribution tests in simulated phantoms. The purpose of these bench tests is to characterize the spatial distribution of RF energy output. The results of this testing demonstrate that the device's heating pattern is consistent with the proposed requirements for its intended use.

iii. Electrical Safety/Electromagnetic Compatibility Testing

The firm conducted the following testing on the device components of the Synergo system:

Electrical safety testing:

The device was tested in accordance with the IEC 60601-1 standard (General Requirements for Safety). The results demonstrate conformance with this standard. In particular, the device meets the standard's acceptance criteria for electrical safety.

Electromagnetic compatibility (EMC) testing:

Results of this testing show the device conforms to the IEC 60601-1-2 standard (Electromagnetic Compatibility).

iv. Software Testing

The Synergo hyperthermia device software (i) performs system self-checks; (ii) records patient information and treatment data; (iii) monitors critical treatment parameters to verify that they are within acceptable limits; and (iv) communicates system status and error messages to the operator.

The firm provided documentation demonstrating that they followed an appropriate software development program; performed a hazard analysis from both the patient's and user's standpoint and addressed those hazards; and carried out an appropriate validation process.

v. Biocompatibility Testing

Biocompatibility studies were conducted to support the safety of the patient-contacting materials of the disposable catheter-tubing set. Under the intended use, this component has limited (< 24 hours) contact with intact mucosal tissue. Consistent with ISO 10993-1: 2003 (Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing), the patient-contacting materials of the disposable catheter-tubing set underwent the following tests:

- cytotoxicity;
- sensitization;
- intracutaneous reactivity; and
- systemic toxicity.

The test results demonstrate that the disposable catheter-tubing set did not cause cell lysis, sensitization, significant irritation, or systemic toxicity.

vi. Chemistry Testing

The firm conducted the following chemistry tests to evaluate the use of mitomycin C with the Synergo system:

Thermal stability testing:

Testing was performed to determine the effect of heat upon the chemistry of mitomycin C. In particular, solutions of mitomycin C were heated to 50°C for 1 hour, after which they were chemically analyzed for degradants. The results of this testing demonstrate that mitomycin C is thermally stable over the range of temperatures produced in the bladder during treatment with the Synergo hyperthermia device.

Leaching study:

Testing was performed to assess whether the heated, circulating mitomycin C solution leaches chemicals from the elastomeric components of the disposable catheter-tubing set with which it has contact. For this test, heated mitomycin C solution (50°C; 20 mg/50 mL) was circulated through final, sterilized samples of the disposable catheter-tubing set for 1 hour, after which the solution was chemically analyzed. The results of this testing did not detect any quantifiable leachate within the mitomycin C solution.

vii. Animal Study

The firm performed an animal study in which two sheep were exposed to one treatment session with the Synergo device concomitant with mitomycin C, followed by pathological evaluation (macroscopic and microscopic) of the bladder and adjacent organs. To evaluate a worst case scenario, the sheep bladders were treated at 46°C which exceeded the range for human use. Two additional sheep (anesthetized, but not exposed to the Synergo device or mitomycin C) were used as controls. The purpose of this study was to assess

the incidence and severity of tissue damage related to treatment. Temperature measurements obtained during treatment confirm that the heating pattern was consistent with prior bench studies. The pathology results showed that treatment did not cause irreversible damage to the bladder or adjacent tissues.

viii. Sterilization

The disposable catheter-tubing set is ethylene oxide sterilized. The sterilization process was validated to a sterility assurance level of 10^{-6} in accordance with ISO 11135 (Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization). Ethylene oxide and ethylene chlorhydrin residue levels on the device surface were found to be within acceptable limits.

ix. Packaging Description and Testing

The components of the disposable catheter-tubing set (i.e., the catheter system and interconnecting tubing line) are separately packaged in Tyvek pouches, which, in turn, are packaged together within a larger Tyvek pouch. Package integrity testing was performed per ASTM F 1980 (Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices), and successfully passed.

Mitomycin C is packaged sterile in 20 mg vials by Bedford Laboratories, and obtained in final, packaged form. No further packaging testing is necessary.

x. Shelf Life Testing

The firm conducted accelerated and real-time stability testing on the disposable catheter-tubing set and its packaging. Based on this testing, the firm proposes to label the disposable catheter-tubing set with a 1.5-year (18-month) shelf life.

b. Preclinical Issues

FDA believes that the firm conducted the appropriate preclinical tests to characterize the performance and safety of the device and drug components of the Synergo system. Except for one aspect of the shelf life testing where information remains pending, the results of these tests do not raise issues of safety or effectiveness.

V. Clinical Studies

a. Human Pharmacokinetic Study

[Sponsor Summary (Section 5.7)]

This pharmacokinetic study was performed to determine the impact of local hyperthermia within the urinary bladder upon the systemic absorption of intravesically-instilled mitomycin C, and to compare the systemic drug levels to the critical toxic level. For this study, the firm enrolled 51 patients with confirmed STCCB, 40 of whom underwent definitive transurethral resection (TUR) of their tumors 21-40 days prior, and 16 of whom were treated with their tumors left intact (i.e., not curable with TUR). These subjects were divided into the following treatment groups:

- Group 1: 20 mg mitomycin C in combination with hyperthermia (n=13)
- Group 2: 20 mg mitomycin C alone (n=12)
- Group 3: 40 mg mitomycin C in combination with hyperthermia (n=16)
- Group 4: 40 mg mitomycin C alone (n=10)

In all groups, 50 mL mitomycin C solution was instilled into the bladder. This solution was held in the bladder for 30 minutes, after which the bladder was emptied and instilled with a second dose (50 mL) for an additional 30-minute period. In addition to drug instillation, groups 1 and 3 received local hyperthermia to the urinary bladder during this 60-minute period using the Synergo system. All subjects were scheduled for a total of 8 weekly treatment sessions.

To avoid any potential confounding effects from prior treatment exposure, the pharmacokinetic data for this study were obtained during the first treatment session only. In all groups, blood samples were collected before and during treatment (i.e., 15, 30, 45 and 60 minutes after instillation), and plasma concentrations of mitomycin C were determined by HPLC using a validated method.

The study found that hyperthermia treatment significantly increases the systemic exposure to mitomycin C following intravesical administration, possibly due to an increase in bladder wall permeability. The highest individual mitomycin C concentration measured was 67.9 ng/mL (Group 3; mean level = 24.7 ng/mL). However, in all patients the increased systemic levels were below the threshold for bone marrow toxicity (400 ng/mL).

b. Pivotal Clinical Trial (Study 101.1)

[Sponsor Summary (Section 7) and Study Protocols]

The firm conducted a prospective, randomized study at three clinical centers outside the U.S.:

- San Raffaele Hospital (Milan, Italy),
- University Hospital of Palermo (Palermo, Italy), and
- Rabin Medical Center – Beilinson Campus Hospital (Petach Tikva, Israel).

The study enrollment period was February 1994 to January 1999. A total of 83 subjects were enrolled. Following standard transurethral resection (TUR) of all tumors, subjects were prospectively randomized 1:1 between hyperthermia with the Synergo system plus intravesical instillation of mitomycin C (Synergo group) versus mitomycin C alone (Control group).

Before evaluating the actual patient outcomes following treatment, the impact of the study protocol and statistical plan should be considered. The challenges in determining the impact of these parameters in the data collection and analysis methods and study conduct follow. The Panel will be asked to deliberate the impact of these challenges on the data submitted to support the safety and effectiveness of this device.

Study Overview and Protocol

Study Chronology

This study did not originate as a planned study to support a marketing application in the U.S. To understand how the data and patients were managed, a brief discussion of the progression of events is outlined. The protocol for the study originated in 1993. In 1997, the study sponsorship was transferred from San Raffaele Hospital to Medical Enterprises, Ltd (MEL). In the same year, MEL's investors contracted with SMS (a British firm), to create case report forms (CRFs) and conduct monitoring visits. During the monitoring visits conducted in 1997, the CRFs were retrospectively completed by transcribing existing data from the patients' medical records for the elapsed study period (1994 through mid-1997). From mid-1997 through the end of study follow-up in 2001, the CRFs were completed prospectively. After study completion, MEL met with FDA to discuss the regulatory process and submitted this PMA in August of 2001.

To better understand how the clinical data reported in the PMA were derived, bioresearch monitoring inspections of the firm and the three clinical sites were conducted in 2005. These inspections verified that the data contained in the CRFs and PMA data listings are accurate reflections of the investigators' source documents (patient medical records). However, limitations to the use of retrospectively created and transcribed CRFs include the potential for relevant study data not being collected in the patient records and recall bias.

Statistical Hypothesis/Sample Size

The study protocol does not explicitly pre-specify a statistical hypothesis or analysis plan. Rather, Section 11 of the study protocol ("Number of Patients and Statistical Considerations") includes the following related information from which the hypothesis may potentially be inferred retrospectively:

- the expected 2-year recurrence rate with mitomycin C alone is 40% (based on estimates from the literature);
- a sample size of 158 patients (79 per treatment group) will allow 80% power to detect a relative reduction of 50% in the recurrence rate; and

- a 2-tailed test will be conducted using a significance level of 5%.

The protocol does not provide the following information regarding the primary statistical analysis, which, when selected after study completion, may impact the statistical and clinical significance of the patient outcomes:

- the statistical method to be used to analyze the recurrence rate is not prospectively stated;
- the study population to be analyzed (e.g., intent-to-treat) is not specified; and
- rules for handling missing data in the statistical analyses are not stated.

The protocol includes an interim analysis plan, in which the treatment groups are to be compared with respect to recurrence rate once 80 subjects complete 1-year follow-up. Based on the interim analysis results, the protocol states that study will either be suspended (in the case of a statistically significantly higher recurrence rate in one group relative to the other) or continued (until 2-year follow-up or longer is completed). No other details regarding the timing or statistical methods (e.g., significance-level adjustment) of this interim analysis are provided, and no statistical basis for the revised sample size (n=80) is provided.

The Panel will be asked how the absence of these pre-specified protocol elements may impact interpretation of the treatment results, given that final decisions on these items may have occurred during or after the study.

Study Endpoints

The study protocol lists the following endpoints, which are typical for studies of bladder cancer recurrence:

- disease-free interval;
- recurrence rate;
- progression of stage and grade;
- occurrence of carcinoma *in situ* (Cis);
- occurrence of urethral cell carcinoma in the upper tract or in the prostatic urethra; and
- occurrence of distant metastasis.

The protocol does not provide the following endpoint information, which is generally defined in studies that have multiple endpoints:

- identification of the primary versus secondary endpoints; and
- method for significance-level adjustment for the evaluation of the secondary endpoints.

The Panel will be asked how the absence of pre-specified information regarding the hierarchy and analysis of the study endpoints may impact interpretation of the treatment results, given that final decisions on these items may have occurred during or after the study.

Summary of Relevant Inclusion Criteria

- Resected Stage Ta or T1 and Grade G1-G3 superficial transitional cell carcinoma of the bladder (STCCB) only
- Complete tumor eradication by TUR
- Life expectancy > 24 months

Summary of relevant Exclusion Criteria

- Ta, G1 single transitional tumors at first episode of disease
- Tumor stage >T1
- Solitary, multifocal, or associated Cis
- Clinical presence of distant or lymphatic metastases
- World Health Organization (WHO) performance status > 2
- Presence of other tumors
- Allergy to topical or systemic mitomycin C
- Previous systemic or local chemotherapy treatments within the previous 3 months
- Untreated urinary tract infection or recurrent severe bacterial cystitis
- Significant BPH
- Neurogenic bladder
- Persistent hematuria not due to known tumor
- Other abnormalities of the kidneys, ureters, bladder, or urethra

Treatment Procedure

Prior to entering the study, patients underwent resection of all bladder tumors, after which they had to be tumor-free. Eligible and consenting patients were randomized 1:1 to either the Synergo group (Synergo hyperthermia device + mitomycin C) or the Control group (mitomycin C alone).

The treatment schedule was identical for the two groups, and was initiated 20-40 days post-TUR. All subjects were to receive 8 weekly “inductive” sessions plus 4 monthly “maintenance” sessions (for a total of 12 treatments). All patients were scheduled to receive the same mitomycin C dose, given as two instillations of 20 mg in 50 mL distilled water, one after the other, with each dwell time of 30 minutes in the bladder. Thus, the intended duration of each treatment session was 60 minutes. Details regarding each treatment group are provided below:

Synergo Group: For each treatment session, the Synergo group received 60 minutes of local hyperthermia concomitant with two 30-minute intravesical instillations of mitomycin C, with removal of each mitomycin C dose performed via catheter by the investigator. The details of the Synergo treatment procedure are described earlier in the “Principle of Operation and Device/Drug Description” section of this summary.

Control Group: The control treatment followed the same procedure as described for the Synergo group, but without the use of the Synergo catheter system or the delivery of hyperthermia. The mitomycin C was delivered in

two, consecutive, 30-minute doses via a standard urinary catheter. Unlike the Synergo group, the intravesical solution was not circulated during the indwell period of the Control treatment. After 60 minutes, the patient was instructed to void his/her bladder spontaneously. However, the duration of the mitomycin C indwell period was not directly controlled by the investigator in the Control treatment (i.e., subjects may have delayed voiding the final mitomycin C instillation until they experienced urgency) and not consistently recorded on the CRFs. Therefore, actual drug exposure times may have varied in this group.

The Panel will be asked how this variation in mitomycin C exposure duration may impact our ability to interpret the treatment results.

Follow-Up Schedule

Quarterly follow-up visits began at the end of the 8 inductive treatment sessions up to 24 months or until first recurrence, whichever was sooner. The 4 maintenance treatment sessions were carried out concurrently with the initial follow-up period. Procedures performed at each follow-up visit included:

- physical exam;
- cystoscopy;
- laboratory tests;
- cytology; and
- cold-cup or TUR biopsy (if required*).

* Cold-cup or TUR biopsies were performed only in cases of suspected recurrence, as observed during cystoscopic evaluation of the bladder.

The collection and recording of pathology information are critical for subject screening and assessment of the recurrence rate. However, the protocol did not pre-specify methods for obtaining and recording complete and adequate pathology information, and in several cases either the pathology specimens did not contain the bladder muscle layer (to permit tumor staging) or the pathology reports did not contain this information (details provided under “Secondary Effectiveness Analysis”). The Panel will be asked how the absence of a structured, prospective format for capturing pathology information may impact our ability to interpret the study results.

Concomitant medications were not recorded during the study. Concomitant medication information is typically recorded during clinical studies to enhance our understanding of the subjects’ medical conditions and assess the potential influence of these medications on the safety and effectiveness of treatment. The Panel will be asked how the omission of concomitant medication information may impact our ability to interpret the study results.

Blinding

The study was not blinded. Both the subjects and the investigators conducting the follow-up cystoscopies could determine which treatment was received. (The bladders of most subjects in the Synergo group had visible

changes to the bladder wall caused by the hyperthermia process, making their treatment assignment evident upon cystoscopy.) Since the tumor recurrence endpoint is based on the judgement and perception of the cystoscopist (i.e., deciding whether or not to biopsy a given site), the lack of blinding introduces a potential bias. Although an independent, blinded review committee to adjudicate tumor-related endpoints may have reduced the bias associated with pathology-related endpoints, this was neither specified in the protocol nor implemented. During their deliberations, the Panel will be asked how the absence of investigator blinding and an independent, blinded review committee may impact our ability to interpret the study results.

In addition to the blinding issues discussed above, clinical information was available on the form used to obtain the randomization assignment, which could introduce another source of bias. The Panel will be asked how this issue may impact our ability to interpret the study results.

Results of the Study

Patient Accountability

A total of 158 subjects were planned for enrolled into this randomized trial. An interim analysis comparing the recurrence rates between the Synergo and Control groups was conducted in 1997, at which time 64 subjects had been enrolled into the study. Based on this analysis, the target sample size was revised to 84 subjects (42 per group).

The study enrolled and randomized a total of 83 subjects (42 Synergo, 41 Control), which form the All Study Patients population. The following table lists the various populations that were analyzed and provides the associated patient accountability information.

Patient Accountability

Analysis Population	Control Group	Synergo Group	Total
All Study Patients	41	42	83
Evaluable Patients: Randomized As Intended	41	36	77
Evaluable Patients: Randomized As Treated	40	37	77
Per-Protocol	40	35	75

The All Study Patients population are analyzed according to the received treatment (as opposed to the randomized treatment). This distinction impacts 10 subjects (12% of the total population) who were misrandomized due to clerical errors. The misrandomizations occurred in pairs, where subject pairs received the opposite treatment than their randomized assignment. The Panel will be asked to consider how these randomization errors impact the interpretation of the study results.

The firm defines the Evaluable Patients: Randomized As Intended population as the All Study Patients population, excluding 6 subjects (6 Synergo, 0 Control) who exited the study prior to the first follow-up visit: 3 withdrew consent (1 due to distance from site, the others not specified), 1 was withdrawn by the investigator (deteriorating health), and 2 had an allergic skin reaction to mitomycin C (an anticipated complication of this drug). These subjects are analyzed according to the treatment to which they were randomized.

The population identified by the firm as the Evaluable Patients: Randomized As Treated population is the Evaluable Patients: Randomized As Intended population, except subjects were analyzed according to the treatment they received rather than the one to which they were randomized. Since one of these misrandomized subjects was excluded from the Evaluable Patients: Randomized As Intended population, the Evaluable Patients: Randomized As treated population includes one additional Synergo subject and one fewer Control subject.

The Per-Protocol population identified by the firm is the Evaluable Patients: Randomized As Treated population, excluding two subjects (2 Synergo, 0 Control) due to major protocol deviations. Specifically, both of these subjects withdrew their consent to participate in the study after 1 or 2 Synergo treatments (one due to pain and anxiety, the other due to severe bladder spasms) and switched their treatment to mitomycin C alone.

Of the 35 Synergo subjects in the Per-Protocol population, 32 completed the study, 2 had not reached the 2-year follow-up visit at the time of database closure, and 1 was lost to follow-up. Of the 40 Control subjects, 32 completed the study, 4 had not reached the 2-year follow-up visit, and 4 were lost to follow-up.

In all, of the 83 subjects enrolled, 75 completed treatment and 64 successfully completed the study. Not only was the sample size of evaluable patients less than originally planned, but the analysis shows that failure to complete treatment was asymmetric between the study groups (7 Synergo, 1 Control). The small sample size limits the ability to draw conclusions between the study population and the general U.S. patient population, and perform a risk/benefit analysis. The asymmetric drop out rate prior to the first follow-up visit could introduce a significant source of bias. In their deliberations, the Panel will be asked to consider how the small sample size and the asymmetric drop out impacts the understanding of patient outcome in their deliberations.

Study Demographics / Baseline Characteristics

The tables below compare the study groups with respect to baseline demographics, baseline tumor characteristics, and number of treatment sessions completed. Control subjects were an average of 5 years older (65 versus 60 years old). Other baseline disease characteristics such as tumor size, number of previous tumors, number who had received previous therapy, and gender were evenly balanced. Similar numbers of subjects in each group did not complete the inductive treatment phase.

Demographics

Baseline Demographics		Control N=41		Synergo N=42		P-Value
		N	%	N	%	
Gender	Female	7	17.0%	7	16.6%	1.00
	Male	34	82.9%	35	83.3%	
Age (yrs)	≤65	16	39.0%	25	59.5%	0.08
	>65	25	60.9%	17	40.4%	

Baseline Characteristics

Baseline Tumor Characteristics		Control N=41		Synergo N=42		P-Value*
		N	%	N	%	
History of recurrence	First Episode	16	39.0%	15	35.7%	0.952
	Recurrent	11	26.8%	12	28.5%	
	High Recurrent	14	34.1%	15	35.7%	
Number of previous occurrences	0	16	39.0%	15	35.7%	0.842
	1	5	12.1%	7	16.6%	
	2	7	17.0%	5	11.9%	
	3+	13	31.7%	15	35.7%	
Previous Tumor Stage	Ta	17	41.4%	15	35.7%	0.737
	T1	24	58.5%	26	61.9%	
	CIS	0	0.0%	1	2.3%	
Previous Tumor Grade	G1	1	2.4%	4	9.5%	0.195
	G2	33	80.4%	27	64.2%	
	G3	7	17.0%	11	26.1%	
Previous Tumor Size	<2 cm	18	43.9%	22	52.3%	0.440
	≥2 cm	23	56.0%	20	47.6%	
Previous Multifocal Tumor	≤5	29	70.7%	30	71.4%	0.944
	>5	12	29.2%	12	28.5%	
Previous MMC treatment	No	30	73.1%	35	83.3%	0.261
	Yes	11	26.8%	7	16.6%	
Previous BCG treatment	No	34	82.9%	32	76.1%	0.447
	Yes	7	17.0%	10	23.8%	
Previous Epirubicin treatment	No	30	73.1%	35	83.3%	0.297
	Yes	11	26.8%	7	16.6%	
Previous Therapy	None/1 st Episode	24	58.5%	24	57.1%	0.898
	Prior Therapy	17	41.4%	18	42.8%	
EAU Risk Group	Low risk					0.225
	Intermediate risk	24	58.5%	19	45.2%	
	High risk	17	41.4%	23	54.7%	

*Chi-square or Fisher's exact test.

Treatment Completion Information

Number of Treatment Sessions [†]	Control N=41		Synergo N=39*		P-Value
	N	%	N	%	
8 inductive + 4 maintenance	25	61.0%	29	74.4%	0.426
At least 8 sessions	12	29.3%	7	17.9%	
Less than 8 sessions	4	9.8%	3	7.7%	

* Three Synergo subjects are excluded since they did not receive any treatment.

[†] The numbers of treatment sessions in this table reflect the numbers of sessions subjects received, irrespective of whether there were randomization errors.

Effectiveness Results

Primary Effectiveness Analysis

For the primary effectiveness analysis, the firm presents the results of survival analyses (defining “survival” as freedom from tumor recurrence) for study patients through 24-month follow-up using the Kaplan-Meier method. Per the protocol, tumor recurrence was defined by pathological confirmation of cancer on biopsy. The number of documented recurrences during the study follow-up period was 6 in the Synergo group and 23 in the Control group.

The results of the primary effectiveness analysis are presented for each of the study populations. For the All Study Patients analysis, subjects who withdrew prior to the first follow-up cystoscopy are imputed as a worst case scenario (failures in the Synergo group, successes in the Control group).

Kaplan-Meier Estimated 2-Year Probability of Recurrence

Analysis Population	Control Group	Synergo Group	p-value*
All Study Patients (worst case scenario)	59.9%	30.9%	0.0219
Evaluable Patients: Randomized As Intended	54.4%	25.0%	0.0097
Evaluable Patients: Randomized As Treated	61.6%	18.9%	0.0002
Per-Protocol	61.6%	17.1%	0.0002

* Log-rank test

In addition to the above analyses, the All Study Patients population was analyzed in another worst case scenario with subjects analyzed according to their intended (rather than actual) treatment. This analysis (which is not provided in the Panel materials) failed to show a statistically significant difference between study groups in the estimated 2-year probability of Recurrence (54.4% Control vs. 38.1% Synergo; p=0.2254).

As shown in the above table, the rate of tumor recurrence in the Synergo group is consistently lower than in the Control group, regardless of the analysis population used. With the exception of the All Study Patients population (randomized as intended), the observed rates are statistically

significantly lower in the Synergo group than in the Control group. The differences in recurrence between the two study arms were consistent among the 3 sites and not statistically influenced by one site.

Long-Term Effectiveness Analysis

The firm continued to follow study subjects beyond the 2-year follow-up exam outside of the protocol. Kaplan-Meier estimates of the 5- and 10-year probability of recurrence continued to demonstrate a benefit in favor of the Synergo group. The table below shows the results for the Evaluable Patients: Randomized As Treated population.

Kaplan-Meier Estimated 5- and 10-Year Probabilities of Recurrence

	Control	Synergo
5-year	78.1%	39.4%
10-year	85.0%	48.2%

Overall Survival Analysis

Overall survival, defined as the time of first study treatment to time of death (for any reason), was compared between Synergo and Control groups. During the period between 1994 and 2006, there were a total of 14 deaths (5 Synergo, 9 Control). None of these deaths were attributed to STCCB. Kaplan-Meier analysis of the Evaluable Patients: Randomized As Treated population found no statistically significant difference in the overall survival between the treatment groups.

Secondary Effectiveness Analysis

The secondary effectiveness analysis included analyses of the remaining endpoints listed in the study protocol. As noted earlier, the protocol did not specify the method for the analysis of these endpoints.

- Stage progression at recurrence: Among the 30 cases of recurrence, there were no documented cases of stage progression in either group. (*Note*: The pathology staging data were definitive in 24/30 recurrences, and unavailable/not definitive in 6/30 (20%) cases).
- Worsening of grade at recurrence: Among the 30 cases of recurrence, there was only one documented case of worsening of tumor grade. This case was in the Control group. (*Note*: The pathology grading data were definitive in 26/30 recurrences, and unavailable/not definitive in 4/30 (13%) cases.)
- Occurrence of Cis: There were no cases of Cis documented in the study subjects.
- Occurrence of urothelial cell carcinoma in the upper tract or prostatic urethra: There were no cases of urothelial cell carcinoma documented in

the study subjects.

- Occurrence of distant metastasis: There were three cases of distant metastasis documented in the study, all in the Control group (not statistically significant).

Prognostic Factors

The effect of baseline demographics, tumor characteristics, and clinical center as prognostic factors for tumor recurrence were evaluated in the Evaluable Patients: Randomized As Treated population. The only factors that showed a significant effect on the rate of recurrence were (i) history of tumor recurrence, and (ii) and European Association of Urology (EAU) risk group. After adjusting for these factors, the recurrence rate remained significantly lower in the Synergo group than in the Control group.

Safety Results

Although not pre-specified in the protocol, the primary safety analysis was incidence of adverse events. The following table presents the adverse events for the entire patient population, grouped by the treatment that they actually received:

Adverse Events

Event Category	Control Group		Synergo Group	
	N	%	N	%
Posterior Wall Tissue Reaction*	1	2.4	27	64.3
Tissue Reaction	20	48.8	21	50.0
Pain*	-	-	17	40.5
Dysuria	4	9.8	10	23.8
Skin Allergy (i.e., allergic skin reaction)	2	4.9	5	11.9
Hematuria	2	4.9	3	7.1
Urethral Stenosis	2	4.9	3	7.1
Urinary Tract Infection	-	-	3	7.1
Bladder Wall Necrosis	2	4.9	2	4.8
Reduced Bladder Capacity	-	-	2	4.8
Anxiety	-	-	1	2.4
Amnesia	-	-	1	2.4
Bronchial Bleeding	-	-	1	2.4
Nephrolithiasis	-	-	1	2.4
Hydronephrosis	1	2.4	-	-
Hypotonic Bladder	-	-	1	2.4
Suspicious MI	-	-	1	2.4
CVA	1	2.4	-	-
Leukemia	1	2.4	-	-
False Passage	-	-	1	2.4
Fever	1	2.4	-	-
General Weakness	1	2.4	-	-

* p<0.05

Overall, the incidence of adverse events was higher (but not statistically significant) in the Synergo group, with 88% of Synergo subjects reporting at least one adverse event as compared to 63% of Control subjects.

Among specific events, posterior wall tissue reaction and pain were statistically significantly more frequent in the Synergo group. This finding suggests that these events are likely related to the addition of the hyperthermia treatment.

Posterior wall tissue reaction was an asymptomatic finding on follow-up cystoscopy, which included eschar (n=23), hyperemia/inflammation (n=3), or ulceration (n=1) of the posterior bladder wall. The one case of ulceration did not include muscle involvement. These events were attributed to the location of the RF antenna in the bladder. In terms of severity, 67% (18/27) of the cases of posterior wall necrosis rated as “mild,” 18% (5/27) were rated as “moderate,” and 15% (4/27) were rated as “severe.” Regardless of severity, all events of posterior wall necrosis resolved without residual effect and without medical intervention.

Pain was reported as either pain/intolerability to treatment (n=10) or bladder spasms caused by catheter placement (n=7). Of these 17 events, 41% were rated as “mild,” 41% were rated as “moderate,” and 18% were rated as “severe.” The severe events included two cases of general pain and one case of bladder spasms. The subject reporting severe bladder spasms was discontinued from the Synergo group (withdrew consent) and was treated with mitomycin C alone. The other cases of pain were generally managed by shortening the treatment session by 10-30 minutes. Out of 426 treatment sessions in the Synergo group, 10 were shortened due to pain. Occurrences of pain were localized and transient.

Although not statistically significant, dysuria and skin allergy were reported approximately twice as often in the Synergo group as compared to the Control group. Dysuria was transient and spontaneously resolved. Skin allergy, an anticipated side effect of mitomycin C, typically occurred during the treatment phase of the study, particularly during the inductive treatment period.

The following events were categorized by investigators as not treatment related: amnesia, hypotonic bladder, bronchial bleeding, nephrolithiasis, hydronephrosis, suspected myocardial infarction (MI), cerebrovascular accident (CVA), leukemia. CVA and leukemia resulted in patient deaths, both in the Control group. These were the only deaths to occur during the 2-year study period.

Sixty-six percent (67%) of the complications were reported as resolved with no residual effect. The remaining events (33%) were reported as ongoing during the study, but were not considered by the investigators as posing an additional risk to the subjects.

Device Failures and Malfunctions

The following device failures and malfunctions occurred in the Synergo group:

- Thermocouple problems (n=33 cases): In these treatments one of the three bladder thermocouples failed to work properly (noisy signal). Since the two remaining thermocouples functioned correctly, treatment was not interrupted.
- Catheter obstruction (n=2 cases): The catheter lumen became blocked due to either prostatic pressure or urinary debris. Treatment was interrupted and the catheter was replaced.
- RF transmission failure (n=1 case): Treatment was interrupted.
- Balloon rupture (1 case): Treatment was interrupted and the catheter was replaced.

Since there were a total of 426 Synergo treatments sessions, the incidence rate of device failure/malfunction is relatively low. None of these device failures/malfunctions impacted safety or effectiveness.

c. Supportive Clinical Studies

The firm submitted the results of the following additional clinical studies as additional supporting evidence of the safety and effectiveness of the Synergo system.

i. Study 102.1

[Sponsor Summary (Section 8) and Study Protocols]

Overview

Study 102.1 is an ongoing randomized, controlled, multi-center study being conducted at 10 sites in Europe and Israel. The objective of this study is to compare Synergo delivered local hyperthermia combined with intravesical instillation of mitomycin C (Synergo treatment), versus intravesical instillation of Bacillus Calmette Guérin (BCG) immunotherapy (Control treatment) for prophylactic treatment in patients with intermediate-high risk of recurrence following TUR of STCCB.

Study 102.1 is designed to enroll a total of 300 subjects (150 per group). However, the firm presents the results of an unscheduled interim analysis of this ongoing study to provide additional data to support the consistency of the Study 101.1 safety and effectiveness results. Between July 2002 and April 2007, a total 104 subjects with papillary tumors (51 Synergo, 53 Control) were enrolled into Study 102.1. An additional 19 Cis subjects are excluded from this analysis at the request of FDA. To address the statistical problems associated with conducting an unscheduled interim analysis, the results are only descriptively analyzed using means and standard deviations (i.e., no tests of statistical significance).

The Synergo system used in this study is the same as investigated in Study 101.1, and the drug dosage/administration (two 30-minute instillations of 20 mg mitomycin C in 50 mL distilled water) and session duration (60 minutes) are unchanged. However, a different treatment schedule was used – the Synergo group underwent 6 weekly induction sessions, followed by 6 maintenance sessions at 6-week intervals.

The Control group received BCG (from one of four different commercial sources) administered in 6 weekly induction sessions, followed by 3 mini-series, each with 3 weekly treatment sessions. This treatment regimen is different from typical U.S. BCG regimen.

In both study groups, follow-up begins 7 weeks following completion of the 6 induction sessions. Subsequent follow-up visits are conducted every 3 months until 24 months or recurrence (whichever is sooner). As in Study 101.1, follow-up visits include physical examination, cytology, cystoscopy (with cold-cup biopsy, if necessary), and laboratory tests. The study is not blinded, and the study protocol does not specify a structured method for the collection of pathology data.

Except for the inclusion of Cis, the inclusion and exclusion criteria were similar to those of Study 101.1. The non-Cis population described in this interim analysis is similar to that of Study 101.1 with respect to baseline and demographic characteristics.

As with Study 101.1, this study does not include either pre-specified methods for pathology evaluation/documentation or a blinded pathology endpoint verification.

Effectiveness Results

As of the April 2007 cut-off for this interim analysis, a total of 90 subjects (42 Synergo, 48 Control) had completed the induction treatment sessions and had one or more follow-up cystoscopy visits. Therefore, this population is analyzed for effectiveness. The remaining 14 subjects (9 Synergo, 5 Control) either dropped out of the study prior to first follow-up or had not yet completed the induction sessions.

The primary and secondary effectiveness endpoints are recurrence-free survival and progression rate (defined as progression to stage > T1 or metastases), respectively.

Primary Effectiveness Endpoint

Recurrence-free survival was analyzed using Kaplan-Meier methods. The results of this analysis show that recurrence in the Control group is sooner and more frequent than in the Synergo group. Specifically, the estimated probability of recurrence at 2 years is 16.9% in the Synergo group and 31.7% in the Control group. The estimated 2-year recurrence rate in Study 102.1 for the Synergo group is similar to that observed in the Study 101.1 Evaluable

Patients: Randomized As Treated population (i.e., 16.9% and 18.9%, respectively). However, valid statistical conclusions regarding the effectiveness results of the Study 102.1 Synergo group cannot be made to either the Study 102.1 Control group or the Study 101.1 Synergo group since these comparisons are unplanned.

Secondary Effectiveness Endpoints

Progression to invasive bladder tumor was not observed in the Synergo group. However, one Control subject had progression in both stage and grade. No subjects in either arm had progression to Cis or metastases. These results were similar to those presented for the Study 101.1.

Safety Results

Safety data, in the form of adverse events rates, were available for 98 of the 104 enrolled subjects (50 Synergo, 48 Control).

The adverse events reported in the Synergo group of Study 102.1 were similar to those reported in Study 101.1. The most common adverse events continued to be posterior wall tissue reaction (occurring in 40% of Synergo subjects), bladder spasms (occurring in 19% of Synergo treatment sessions), and pain (occurring in 18% of Synergo treatment sessions). These events were anticipated, resolved spontaneously, and were rated as either “mild” or “moderate” in severity in 90-95% of cases. As in Study 101.1, all posterior wall tissue reactions were asymptomatic.

In addition, Synergo subjects experienced higher incidences of bladder tissue reaction (48% vs. 25%), urethral stricture/stenosis (22% vs. 8%), and allergic reaction/hypersensitivity (16% vs. 6%). The higher incidence of urethral stricture/stenosis among Synergo subjects was associated with use of the larger diameter Synergo catheter. These events were anticipated, and were typically rated as “mild.”

Lastly, seven (7) treatment-related serious adverse events occurred (5 Synergo, 2 Control). The five events in the Synergo group were: (i) urethral stricture, (ii) contracted bladder with severe irritative symptoms, (iii) urethral bleeding, (iv) urosepsis, and (v) dysuria, urgency, and fever. All serious adverse events occurred in male subjects, and all required medical and/or surgical intervention.

Since this clinical report is an unplanned interim analysis of an ongoing (uncompleted) study, these results are considered to be supportive only (in contrast to definitive evidence of safety and effectiveness).

ii. Combined Analysis of Studies 101.1 and 102.1

[Sponsor Summary (Section 9)]

The firm combines the results of the Study 101.1 and Study 102.1 Synergo groups to assess the effectiveness of the Synergo + mitomycin C treatment within a larger population. The firm states that this analysis is justified since both studies are randomized, enrolled similar patient populations, treated and followed Synergo subjects using identical methods, and evaluated the same primary endpoint (2-year recurrence rate). However, since this analysis was not pre-specified and involves populations from two separate studies, the firm analyzed the results using only descriptive statistics (i.e., no tests of statistical significance).

Prior to combining the Synergo groups from these two studies, the demographic, baseline tumor characteristics, and treatment effects were compared to evaluate the poolability of these two populations. Based on this analysis, the two Synergo groups appeared similar and were combined to obtain a pooled 2-year recurrence rate (Kaplan-Meier estimate). This pooled Synergo 2-year recurrence rate is based on 79 subjects, consisting of 37 subjects from the Evaluable Patients: Randomized As Treated population of Study 101.1 and 42 subjects from Study 102.1, and was descriptively compared to the Control groups of these respective studies.

- Combined Study 101.1/102.1 Synergo 2-year recurrence rate: 17.1%
- Study 101.1 Control (mitomycin C) 2-year recurrence rate: 61.6%
- Study 102.1 Control (BCG) 2-year recurrence rate: 31.7%

From this comparison, the Synergo + mitomycin C treatment appears more effective than either mitomycin C alone or BCG.

Since these comparisons between Studies 101.1 and 102.1 are not pre-specified, the combined results are considered to be supportive only (in contrast to definitive evidence of effectiveness).

iii. Study 101.4

[Sponsor Summary (Section 14)]

Overview

Study 101.4 is a single-arm study, conducted at two sites (Milan, Italy and Petach Tikva, Israel) between 1994 and 1999. The purpose of the study is to explore the effect of the combination of intravesical hyperthermia (using the Synergo system) plus mitomycin C in patients with STCCB for whom TUR is not possible or recommended. The principal endpoint was disease status at 12-month follow-up.

This study investigated the combination product for a different indication for use than pivotal Study 101.1 (i.e., ablation of STCCB, rather than prophylactic

use to prevent STCCB recurrence). Due to this difference in indications for use and study population, Study 101.4 is summarized as supporting safety data for the purposes of this PMA. Based on the single-arm study design, the study results are only descriptively analyzed (i.e., no tests of statistical significance).

Summary of Relevant Inclusion Criteria

- Stage Ta-T1, Grade G1-G3 STCCB
- TUR not possible or recommended due to: size or number of tumors; or positive cytology following complete tumor eradication; or a combination of factors such as recurrent, multifocal, or large tumors; or unable to have anesthesia
- Life expectancy > 2 years

Summary of Relevant Exclusion Criteria

- Tumor stage >T1
- Other than transitional cell tumors
- Second primary tumor other than skin basal cell carcinoma
- Presence of distant or lymphatic metastasis
- Solitary or multifocal Cis not associated with Ta and/or T1 at study entry
- WHO performance status > 3
- Known allergy to topical or systemic mitomycin C
- Untreated urinary tract infection or recurrent severe cystitis
- Urethral stricture
- Neurogenic or spastic bladder

Treatment Procedure

The Synergo system used in this study is the same as investigated in Study 101.1, and the treatment regimen (8 weekly inductive sessions followed by 4 monthly maintenance sessions; 60 minutes per session) was unchanged. However, this was an exploratory study that used two different drug dosages:

- The Milan, Italy site administered two 30-minute instillations of 40 mg mitomycin C in 50 mL distilled water; and
- The Petach Tikva, Israel site administered two 30-minute instillations of 20 mg mitomycin C in 50 mL distilled water.

Follow-Up Schedule

Follow-up was performed at intervals of 3 months, up to 12 months, and included physical examination, cystoscopy (with cytology or cold-cup biopsy), and laboratory tests.

Patient Accountability

A total of 42 subjects (11 females and 31 males) were enrolled into this study and followed for 12 months. The median age of this population was 69 years. All 42 subjects are included in the safety analysis.

Safety Results

In this study, safety was assessed by analysis of the rates of adverse events. The primary adverse events that occurred were: posterior wall tissue reaction (n=27), pain (n=13), tissue reaction to treatment (n=11), dysuria (n=10), bladder wall necrosis (n=6), skin allergy (n=4), hematuria (n=4), and urethral stenosis (n=1). These events are similar to those observed in Studies 101.1 and 102.1.

Due to differences between the use of the combination product in this study and in the proposed indications for use (i.e., ablative vs. prophylactic treatment of STCCB), these results are considered supportive safety data only.

d. Supportive Clinical Information

The firm submitted the following information as additional supporting evidence of the safety and effectiveness of the Synergo system.

i. Literature Reports of Mitomycin C/BCG Effectiveness

[Sponsor Summary (Section 10)]

Intravesical instillation of mitomycin C is commonly used off-label to prevent STCCB recurrence, and BCG is approved in the U.S. for this use. To further evaluate the effectiveness of Synergo + mitomycin C treatment, the firm conducted a systematic review of the literature on the effectiveness of mitomycin C and BCG adjuvant treatment of STCCB recurrence. Based on the results of this literature search, the firm calculated the recurrence-free survival probabilities for each of these drug therapies, and compared these rates to those obtained from the Synergo groups in Studies 101.1 (Evaluable Patients: Randomized As Treated) and 102.1. Acknowledging the statistical issues that arise with comparisons to historical data from the literature (such as publication bias and differences in patient characteristics), the firm does not present statistical conclusions regarding these comparisons.

The results of this comparison are as follows:

- Meta-analysis of mitomycin C literature:
 - 2-year recurrence rate = 41.5% (95% C.I. = 36.8-46.3%)
 - This rate is less than reported in the Study 101.1 mitomycin C recurrence rate (61.6%), which is likely due to the inclusion of low risk subjects in the literature studies.
- Meta-analysis of BCG literature:
 - 2-year recurrence rate = 35.5% (95% C.I. = 32.4-38.7%)
 - This is similar to the Study 102.1 BCG recurrence rate (31.7%), which is expected since both the Study 102.1 and clinical practice restrict BCG use to intermediate and high risk subjects.

- Synergo 2-year recurrence rates:
 - Study 101.1 = 18.9%
 - Study 102.1 = 16.9%
 - Combined Study 101.1/102.1 = 17.1%

From this descriptive comparison, the Synergo + mitomycin C treatment continues to appear more effective than either mitomycin C alone or BCG.

ii. European Prophylactic Study

[Sponsor Summary (Section 11)]

The European prophylactic patient study is an ongoing, single-arm registry, being conducted to document the clinical experience with the Synergo + mitomycin C treatment at clinical centers in Europe and Israel. As of 2006, 186 patients with intermediate or high risk STCCB had been treated. Approximately 30% of these patients either did not complete sufficient follow-up or did not meet the eligibility criteria of Study 101.1, and are excluded. Based on the available data collected on the remaining 122 patients, the estimated 2-year risk of recurrence is 32.2%. As in Study 101.1, the reported adverse events primarily consisted of posterior wall tissue reaction and pain. No statistical conclusions are supported by this report of clinical experience.

iii. Bladder Salvage Patients

[Sponsor Summary (Section 12)]

Synergo + mitomycin C was used to treat 82 patients at several clinical centers in Europe and Israel, of which 59 are available for analysis. All subjects were highly recurrent, had failed multiple prior therapies, and were high risk for recurrence according to EAU guidelines. Since this extreme high-risk group does not represent the overall patient population proposed in the indications for use, only safety results are presented here. The reported adverse events primarily consisted of posterior wall tissue reaction and pain, and are similar to those observed in Study 101.1. No statistical conclusions are supported by this report of clinical experience.

iv. European Ablation Patients

[Sponsor Summary (Section 13)]

Synergo + mitomycin C was used to treat 104 patients at several clinical centers in Europe and Israel. Similar to the subjects treated in Study 101.4, European Ablation Patients were indicated for ablative treatment (i.e., treatment without prior TUR). Since this group does not represent the overall patient population proposed in the indications for use, only safety results are presented here. The reported adverse events primarily consisted of posterior wall tissue reaction and pain, and are similar to those observed in Study 101.1. No statistical conclusions are supported by this report of clinical experience.

e. Clinical Data Summary

The Synergo system is a combination product involving a device and a drug for an indication of prevention of bladder cancer recurrence.

Study 101.1

The primary study provided in support of the safety and effectiveness of the Synergo system, Study 101.1, was a prospective, randomized controlled pivotal trial of Synergo + mitomycin C versus mitomycin C alone. While the control therapy (i.e., intravesical instillation of mitomycin C) is not FDA-approved for this indication or route of administration in the U.S., it is commonly used for this off-label use in the clinical community, and is approved for this use in foreign markets. The dose of mitomycin C used was symmetric in both study groups, and the rate of recurrence observed in the Control group seems plausible. This study was conducted outside of the U.S., and the investigational plan was not prospectively reviewed by FDA.

The effectiveness results are statistically significant (in favor of Synergo system treatment) for all of the study populations except for the worst case analysis performed on All Study Subjects (randomized as intended). Adverse events are numerically increased in the Synergo group, with posterior wall tissue reaction and pain being statistically significantly higher. However, these adverse events were generally mild, localized and transient, and resolved without residual effects.

The main challenges that limit our ability to fully interpret the patient outcomes described by the firm's presentation in the PMA are summarized below:

1. There are several different sources of potential bias, and the collective impact on the interpretation of the product's safety and effectiveness are unclear:
 - a. Important study elements (e.g., hypothesis, statistical analysis plan, interim analysis plan, identification of primary vs. secondary endpoints, procedures for handling missing data) do not appear to have been pre-specified in the protocol, and final decisions on these items may have occurred both during the study and after its conclusion.
 - b. A proportion of the case report forms (CRFs) were not completed prospectively (i.e., forms for study events from 1994 through mid-1997). While the transcription to the CRFs was performed diligently (confirmed in FDA inspections), limitations to the use of retrospectively created and transcribed CRFs include the potential for relevant study data not being collected in the patient records and recall bias. The data reported in these CRFs include screening and follow-up data, and adverse events.
 - c. There was a disproportionate rate of patient drop out prior to the first follow-up visit (7 (16.7%) Synergo group, 1 (2.4%) Control group), which could introduce a significant source of bias.

- d. Systematic bias may have occurred in clinical impression interpretations and follow-up biopsy decisions (investigator bias) during the follow-up cystoscopies since the investigators knew which treatments were given.
 - e. An independent, blinded review committee to adjudicate tumor-related endpoints was not implemented in this study.
 - f. From the clinical report, at least 10 subjects of the total enrolled population (12.0%) were discovered to have been misrandomized.
 - g. Clinical information was available on the form used to obtain the randomization assignment, allowing for potential bias that cannot be quantified.
 - h. Concomitant medications were not recorded during the study, potentially limiting the ability to fully assess their influence on the safety and effectiveness of treatment.
2. The methodology for obtaining and reviewing biopsy samples lacks important details which may impact the ability to draw conclusions:
 - a. Pathology information regarding baseline and follow-up biopsy results does not appear to have been captured in a structured, prospective format to assure accuracy and completeness of the reported information. For example, description of muscular layer involvement was inconsistent in the reports that were provided for review.
 - b. The study documents provided do not include prospective guidance to investigators requiring them to verify that the bladder wall muscle layer was included in the tissue sample (necessary for accurate staging evaluation).
 3. The methods of treatment and supporting documentation introduce uncertainty in the overall comparability of the chemotherapy exposure between the two groups:
 - a. The procedure to remove mitomycin C from the bladder varied by treatment group. In the Synergo group, the bladder was to be emptied by catheter at the end of the session, whereas the protocol states that the Control subjects were to void to end the treatment session. It is possible that Control subjects who did not feel the need to urinate at the end of the 60-minute treatment session could have delayed voiding for an additional period of time, resulting in increased mitomycin C exposure.
 - b. The mitomycin C instillation starting and stopping times have not been provided for several patients.
 4. It is unclear whether the information obtained from this small, limited study (i.e., 42 subjects enrolled into the Synergo group, 35 completing treatment; 41 enrolled into the Control group, 40 completing treatment) is adequate:
 - a. It is unclear how closely the limited study population represents the general U.S. population.
 - b. The limited sample size creates uncertainty in the risk/benefit analysis.

FDA will be asking the Panel to consider how these issues, when taken together, impact the ability to draw clinically meaningful conclusions regarding

the Study 101.1 results to sufficiently support the safety and effectiveness of the Synergo system for the intended population.

Other Clinical Studies/Information

The clinical information submitted for review from sources other than Study 101.1 provides additional supportive data on the Synergo system, primarily safety data. Of note, the results of the pharmacokinetic study demonstrate that although systemic levels of mitomycin C are increased during hyperthermia, these levels are lower than the known threshold for bone marrow toxicity. While the clinical outcomes observed in these other supporting studies were generally consistent with the Study 101.1 results, these supporting studies have substantial scientific limitations that prohibit their use as independent sources of pivotal data for the proposed indication:

1. The Synergo system vs. BCG study (Study 102.1) is an ongoing randomized study where approximately a third of subjects have been enrolled. BCG is a currently FDA-approved drug for the proposed indication. Potential limitations of this study include a different BCG regimen from U.S. practice; lack of blinded endpoint verification; lack of a prospective, structured pathology evaluation; and the results presented in the PMA are from an unscheduled interim analysis.
2. The combining of Study 101.1 and 102.1 Synergo group data was not a prospectively planned analysis.
3. The Study 101.4 is an uncontrolled, exploratory study for a different indication for use than the indication proposed in the PMA (i.e., ablation vs. prophylaxis).
4. The comparison of Study 101.1 and 102.1 data to historical mitomycin C and BCG data from the literature is of limited value due to unknown differences in patient populations and treatment regimen, as well as publication bias.
5. Data on existing European Prophylactic Patients are uncontrolled data from clinical practices in Europe and Israel.
6. Data on existing Bladder Salvage Patients are uncontrolled data from clinical practices and involve very high risk patients who are otherwise candidates for cystectomy (i.e., a different patient population than the proposed indication for use).
7. Data on existing European Ablation Patients are uncontrolled data from clinical practices in Europe and Israel and involve patients who are not candidates for TUR (i.e., a different patient population than the proposed indication for use).

VI. Postapproval Plan

NOTE TO PANELISTS: *FDA's inclusion of a section/discussion on a Post-Approval study in this memo should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a postapproval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether to approve a device or not must be based on the premarket data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any postapproval study could be considered. The issues noted below are FDA's comments regarding a potential postapproval study should the panel find the device approvable following its discussions and deliberations of the premarket data.*

a. Proposed Postapproval Plan

[Post Approval Study Synopsis]

Objectives

The proposed postmarketing surveillance study will evaluate the safety of the Synergo system in the U.S., when used to deliver adjuvant intravesical hyperthermia in conjunction with mitomycin C instillation.

Study Design, Hypotheses, and Sample Size

The firm proposes a prospective, single-arm study to evaluate the safety of the device by comparing the frequencies of significant side effects and adverse events occurring in this study to the frequencies of similar events reported in the pivotal PMA study (Study 101.1). The study will also evaluate the safety of the device by detecting any rare side effects or adverse events not previously reported. The study is not designed to evaluate the effectiveness of Synergo + mitomycin treatment.

The Null or alternative hypothesis is formulated as follows:

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

Alternative Hypothesis: $P < P_i - \Delta$

where P_i represents the (per person) occurrence rate of the i^{th} adverse event as established in the Study 101.1 and Δ is the largest acceptable difference between the study rate and the established rate. The sponsor choose Δ to be 10% for proportions over 50% and 5% when the adverse event occurrence rate is small, i.e. a rare event. The clinical rationale for these difference levels is not provided. Additionally, the firm does not explain why the data are being compared to the Study 101.1 Synergo data, as opposed to the current standard of care.

The firm states that a sample size of 211 subjects would enable testing of all hypotheses with 80% power. The study plan does not state the number of study sites that will be enrolled.

Patient Population and Sample Size

The study population will consist of patients with intermediate and high-risk STCCB, undergoing transurethral resection of their tumors as part of the routine medical treatment.

Inclusion Criteria:

- Status post complete TUR bladder tumor(s) no more than 2 months prior to first treatment.
- Last TUR specimen should include muscle layer: pathological Stage Ta-T1, papillary or solid, STCCB (not single Ta-G1 first episode), pathological Grade G1-G3.
- Intermediate-high risk patients, according to the European Association of Urology guidelines.

Exclusion Criteria:

- Transitional cell carcinoma outside the urinary bladder (urethra, ureters, kidneys, distant organs).
- Urinary bladder diverticulum larger than 1 cm in diameter
- Bladder volume < 150 cc
- Patients after partial cystectomy
- Urethral stricture – special consideration is required during the cystoscopy to verify any possibility of existing or forming stricture in the urethra before first session is administered
- Any situation impeding a 20 Fr. catheterization.

Study Endpoints

The primary endpoint of the study includes evaluating the occurrence rate of the following eight (8) 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. The secondary study endpoint includes the evaluation of any unanticipated adverse events not previously reported with the Synergo device.

Follow-Up Visits and Length of Follow-Up

Follow-up examinations will be performed at 1 month after the end of the 8 weekly treatment sessions, and then every 3 months. All patients will be followed until their 12 month follow-up visit. Follow-up examinations will consist of video-cystoscopy examinations of the bladder, urine cytology, and biopsy of any suspected areas.

Patients will be removed from the study in the case of any of the following occurrences, whichever comes first: study completion, tumor recurrence, tumor metastasis, adverse event (if warrants patient's discontinuation), or other cause (such as patient death, another primary malignancy, or other co-morbidities).

Enrollment Plan and Follow-Up Measures

Subjects who satisfy the inclusion criteria will be enrolled into the study. These patients will be asked to sign an informed consent form, following a physician's explanation of the treatment, treatment alternatives and the benefits and risks, including potential side effects of the treatment. No details are provided regarding how study sites will be selected and enrolled, or how subjects will be selected.

Data collection

The investigators will collect the following patient data:

- A. Pre treatment data:
 - ◆ Demographic information
 - ◆ Bladder cancer history
 - ◆ General medical history
 - ◆ Outcome of pre-treatment work-up
- B. Treatment session data
- C. Safety data
 - ◆ Adverse events observed during treatment sessions
 - ◆ Adverse events that occurred between sessions
 - ◆ Adverse events recorded at cystoscopies (e.g., tissue reactions, urethral stenosis, etc.)
- D. Follow-up data
 - ◆ Adverse events since last visit
 - ◆ Results of cystoscopies, cytological and histological exams, imaging exams, etc.

Statistical Analysis

Upon study completion, the study hypotheses will be tested. The occurrence rate of each adverse event will be reported as a percentage and reported with a 90% exact binomial confidence interval. The non-inferiority hypothesis for each adverse event type will be tested via the confidence interval where the null hypothesis will be rejected and non-inferiority will be claimed if the upper limit is less than $P_i + \Delta$. Unanticipated adverse events will be presented as a percentage and reported with 95% exact binomial confidence interval.

Study Timeline

Based on the sample size and the predicted recruitment rate, the estimated duration of the postapproval study surveillance program is 30 months: 18 months for recruitment and another 12 months for completion of follow-up. There is no information on the expected recruitment rate; however, based on the total sample size and 18 months for recruitment, it is about 12 patients per month.

Reporting of safety issues will be done via two channels:

- A summary of all adverse events, including statistical analysis and clinical summary will be submitted in an Interim Post-Approval Surveillance Status Report at 6 months follow-up. The Final Post-Approval Surveillance Report will be submitted no later than 3 months after study completion.
- Serious adverse events will be reported to the FDA within 10 days of the firm's becoming aware of their occurrence. The initial report will include all data available at that moment. Further analysis will be performed and reported, as appropriate.

b. Postapproval Plan Issues

The firm proposes a single-arm postapproval study, in which 211 subjects are treated with the Synergo system and followed for 12 months. The objectives of this study are (i) to assess whether the incidences of anticipated adverse events are equivalent to those observed during the pivotal clinical trial (Study 101.1), and (ii) to document the rates of any unanticipated adverse events. If this PMA is approved, the Panel will be asked to comment on the following issues.

1. The proposed study does not include a plan to assess long-term postmarket effectiveness of the Synergo system in a larger population.
2. The postapproval study proposes to evaluate the postmarket safety of the Synergo system by comparing the frequencies of significant side effects and adverse events occurring in this study to the frequencies of similar events reported in the pivotal PMA study (Study 101.1). The Panel will be asked to comment on the use of the premarket device experience as a control in light of the fact that premarket studies include highly selected physicians and study subjects that may not be comparable to the general physician and patient population that will be using the Synergo system postmarket. FDA will ask the Panel to discuss alternative comparators to assess the postmarket device safety such as assessment of the frequency of side effects and adverse events between the Synergo system and the current standard of care for the indicated population.
3. The postapproval study proposes to follow subjects for 1 year. The Panel will be asked to discuss the appropriate time frame to adequately assess long-term effectiveness endpoints.