GASTROENTEROLOGY & UROLOGY DEVICES PANEL

Gaithersburg, Maryland

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MEL-Medical Enterprises Ltd. Synergo SB-TS 101.1 Hyperthermia Device

PMA P010045

SPONSOR SUMMARY

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SPONSOR SUMMARY

1 ABBREVIATIONS

AUA – American Urological Association
BCG – Bacillus Calmette-Guérin
BS – Bladder Salvage (Patients)
CIS – Carcinoma In-Situ
CRF - Case Report Forms

EAP - European Ablation Patients
EAU – European Association of Urology
EPP - European Prophylactic Patients
GCP - Good Clinical Practice
K-M - Kaplan-Meier

MMC – Mitomycin C
TUR – Transurethral Resection
STCCB - Superficial Transitional Cell Carcinoma of the Bladder
Synergo - Synergo SB-TS 101.1 Hyperthermia Device

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2 EXECUTIVE SUMMARY

The Synergo SB-TS 101.1 device delivers heat transurethrally by means of radio frequency (RF) energy to the urinary bladder walls. Synergo hyperthermia is delivered concomitantly with cooled intravesical instillation of Mitomycin C. Synergo treatment is intended for prophylactic treatment of recurrence in patients following endoscopic removal of Ta-T1 and G1-G3, superficial transitional cell carcinoma of the bladder (STCCB). Synergo treatment is clinically indicated for STCCB patients of intermediate and high risk.

The Synergo device is a combination device/drug product and includes the Synergo Kit containing the device accessories and the co-packaged MMC drug.

The device design and the preclinical studies (animal model and pharmaco-kinetics) are comprehensively discussed in this document.

The Synergo device has been used and studied in several clinical pre- and post-marketing studies since 1992. The device is legally marketed and is in routine commercial use in Europe and Israel since 2000. The following information summarizes each of the clinical studies submitted to the FDA in support of the PMA No. P010045. Together these studies show the efficacy of Synergo treatments in 260 patients, and the safety profile of 4502 treatment sessions in 507 patients.

2.1 Study 101.1

Study 101.1 is the pivotal study submitted in support of PMA No. P010045. It is a randomized, controlled trial designed to compare the efficacy and safety of the combined Synergo hyperthermia and Mitomycin-C treatment (hereinafter referred to as “Synergo treatment” or “Synergo Group”) to that of Mitomycin-C alone (hereinafter referred to as “MMC treatment” or “MMC Group”) in the treatment of STCCB, for the prevention of tumor recurrence after complete tumor eradication by transurethral resection (TUR). A total of 83 intermediate and high risk patients were recruited to the study; 42 randomized to Synergo treatment and 41 randomized to MMC treatment. Each Synergo treatment session included two 30 minutes cycles of intra-vesical hyperthermia in conjunction with intravesical instillation of 20 mg of MMC dissolved in 50 ml of distilled water. The MMC treatment included intravesical chemotherapy only, with the same doses of MMC. Both study group patients received 8 weekly inductive treatment sessions, followed by 4 monthly maintenance treatment sessions. Follow-up exams (cystoscopy and cytology) were performed every 3 months, up to 2 years follow-up. Primary efficacy endpoint was disease free survival at 2 years (comparison of recurrence rates) between the study groups.

The primary efficacy analysis results demonstrated that the Synergo treatment was significantly superior to MMC treatment. Kaplan-Meier estimated 2-year recurrence rates are presented in **Table 1** for the different patient cohorts.

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Table 1 – Kaplan-Meier estimated 2 year recurrence rate, Study 101.1

Patient Population	**MMC**	**Synergo**	**Log-Rank P**
Evaluable: Randomized As Intended	54.4% (n=41)	25.0% (n=36)	0.0097
Evaluable: Randomized As Treated	61.6% (n=40)	18.9% (n=37)	0.0002
Per-Protocol	61.6% (n=40)	17.1% (n=35)	0.0002

The primary efficacy analysis was based on 77 evaluable patients who had at least one follow-up evaluation of recurrence status. Evaluable Patients: Randomized As intended, refers to the patient cohort in which the patients are grouped according to the treatment to which they should have been randomized according to the randomization scheme prepared by the study statistician. Evaluable Patients: Randomized As Treated, refers to the patient cohort in which the patients are grouped according to the treatment that they actually received during the study. As is explained later in **Section 7.3.2.3**, the difference in patient cohorts were due to administrative errors, which occurred at the central randomization office resulting in 5 pairs of switched treatments. As can be seen from the results, the error had no effect on treatment outcome. The Per Protocol Patients refers to the patient cohort who did not have a major protocol deviation. As shown in **Table 1**, the rate of tumor recurrence is consistently lower and statistically significant in the Synergo group than in the MMC group regardless of the analysis populations used.

No tumor progression, no occurrence of CIS or urothelial call carcinoma, and no occurrence of distant metastasis were observed in the Synergo group. Furthermore, the cystectomy rate was lower in the Synergo group.

The safety analysis demonstrates that most of the expected adverse events were common amongst both treatment groups (**Table 2**). The only adverse events that presented significant difference between the treatment groups were pain and posterior wall tissue reaction, which were higher in patients treated with Synergo treatment than in patients treated with MMC treatment. These findings are anticipated due to the nature of the hyperthermia device. All these events were localized, transient and resolved without any significant residual effects and were asymptomatic.

No serious adverse events were classified by the investigators as treatment related.

Table 2 – Expected Adverse Events (All Study Patients)*

Adverse Events	MMC N=41		Synergo N=42	
	N	**%**	**N**	**%**
Dysuria	4	9.8	10	23.8
Hematuria	2	4.9	3	7.1
Tissue Reaction	20	48.8	21	50
Urethral Stenosis	2	4.9	3	7.1
Skin Allergy	2	4.9	5	11.9
Pain	-	-	17	40.5
Posterior Wall Tissue Reaction	1	2.4	27	64.3
Urinary Tract Infection	-	-	3	7.1
Bladder Wall Necrosis	2	4.9	2	4.8

*Based on Evaluable Patients: Randomized As Treated cohort

2.2 Study 102.1

Study 102.1 is an ongoing multi-center, multinational, randomized, controlled trial, designed to compare the efficacy and safety of the Synergo treatment to that of Bacillus Calmette-Guérin (BCG), in the treatment of STCCB for the prevention of tumor recurrence after complete tumor eradication by TUR. Although the study is planned for 300 patients, interim results are presented to FDA to support the results of the PMA pivotal study 101.1. The purpose of submitting the results of this study is not to conclusively evaluate the endpoints of this study. Rather, the purpose of submitting the results of this study is to demonstrate the consistency of the safety and efficacy results for the Synergo treatment in another randomized, controlled, clinical study. At data lock 104 intermediate and high-risk patients were recruited, 51 were randomized to Synergo treatment and 53 to BCG treatment.

The general design of Study 102.1 and the pivotal Study 101.1 were similar except for the control arm, including similar treatment regimens, follow-up exams (cystoscopy and cytology) performed every 3 months, up to 2 year follow-up, and study endpoints. The primary efficacy endpoint was recurrence free survival at 2 years (comparison of recurrence rates) between the study groups.

The interim efficacy results are presented in **Table 3**. The recurrence rate in the Synergo group is substantially lower compared to the BCG group and is consistent with the findings in Study 101.1.

Table 3 – Study 102.1 interim results – Kaplan-Meier estimated 2 year recurrence rates (Per Protocol patient population)

Per Protocol Patient Population	**BCG (n=48)**	**Synergo (n=42)**
K-M Estimated 2-year Recurrence Rates	31.7%	16.9%

The adverse events reported for the Synergo patient population in Study 102.1 are mostly the same as those reported in the pivotal Study 101.1, including dysuria, hematuria, tissue reaction, urinary tract infection, pain, posterior wall tissue reaction and bladder wall necrosis. The most common adverse events are pain and posterior wall tissue reaction in both Study 101.1 and Study 102.2. When compared to the BCG group, systemic symptoms (arthralgia, fever, and fatigue) and urinary incontinence were significantly more frequent in the BCG group than in the Synergo group.

The interim results of Study 102.1 provide additional supportive evidence that Synergo is a safe and effective treatment for intermediate to high risk STCCB patients. Efficacy and safety data from this study are similar to those of the pivotal Study 101.1.

2.3 Synergo Arm Results (Studies 101.1 and 102.1)

Efficacy results from Synergo arms of Studies 101.1 and 102.1 were combined to provide additional supportive data. Study results demonstrated that the two Synergo arms were similar and therefore, may be pooled and analyzed as a single group. The pooled Synergo arms were compared to: (1) the MMC arm from Study 101.1, and (2) the BCG arm from Study 102.1.

The recurrence rates in the MMC arm and the BCG arm are significantly higher than that in the combined Synergo arms. The estimated 2-year recurrence rates are 17.1% for Synergo (combined studies 101.1 and 102.1), 31.7% for BCG, and 61.6% for MMC. The hazard ratio for MMC versus Synergo is 5.1 (95% confidence interval (CI)=2.5-10.3) and the hazard ratio for BCG versus Synergo is 2.3 (95% CI=1.1-5.0).

The combined analysis of Synergo arms of Studies 101.1 and 102.1 provides additional supportive evidence that the Synergo treatment is significantly more efficacious than MMC treatment and BCG treatment.

2.4 Comparison of Synergo Treatment with Historical MMC & BCG Controls

A systematic review of the efficacy of MMC and BCG treatment of STCCB was performed based on reports available in the literature to provide additional comparative data for the efficacy of Synergo treatment. The weighted estimates of 2-year recurrence rates for MMC and BCG treatments were calculated based on a meta-analysis of recurrence data extracted from the literature.

The 2-year recurrence rates for the Synergo group from Study 101.1 (18.9%), Study 102.1 (16.9%), and the combined Synergo arms (Studies 101.1 and 102.1) (17.1%) are significantly lower than the 2-year recurrence rates for either the MMC or BCG group observed in Study 101.1 (61.6%), Study 102.1 (31.7%), or reported in the literature (MMC 41.5%; BCG 35.6%).

2.5 European Prophylactic Patients (EPP)

Safety and efficacy data were collected from patients treated commercially in Europe and Israel with Synergo for prophylactic treatment of STCCB. Patients receiving Synergo treatment in these countries were selected for treatment, underwent treatment sessions and follow-up examinations in a similar manner to the Study 101.1 and Study 102.1 procedures.

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A total of 186 intermediate and high-risk patients were commercially treated with Synergo treatment. As this experience is ongoing, many patients have not yet reached the first cystoscopy evaluation. The efficacy results of 122 evaluable patients presented a Kaplan-Meier estimated recurrence rate at 2 years of 32.2%. This result, which appears to be slightly less favorable than the results presented for Study 101.1 and Study 102.1, was influenced by several factors, including a higher risk patient population (higher median age, higher proportion of patients who failed on previous treatments, and a higher average number of previous tumor episodes) and treatments that were many times compromised by reimbursement issues causing inherent bias. That is, tumor free patients tend to have their follow-up in the primary care clinic (where the data is unavailable to the sponsor), as opposed to recurrent patients who are sent back to the hospital for treatment.

Despite the higher risk nature of these patients and the inherent bias described above, the EPP results are comparable to or better than or at least as good as the conventional, alternative treatments, including BCG and MMC. That is, the EPP estimated 2-year recurrence rate of 32.2% is far better than conventional MMC treatment reported for the Study 101.1 control arm for intermediate/high risk patients (61.6%) or reported in the literature for the general STCCB patient population (41.5%). Furthermore, the EPP results are at least as good as the conventional BCG treatment reported for the Study 102.1 control arm (31.7%) or reported in the literature (35.6%).

More important than the efficacy results, the EPP provides additional safety data for another 186 patients treated with Synergo. The adverse events in the EPP were very similar to those presented for Study 101.1 and Study 102.1.

2.6 Additional Safety Data

Additional safety data in support of the Synergo treatment are provided for another 228 patients from the following studies or patient populations: (1) Bladder Salvage (BS) patients (n=82) treated with Synergo as a last resort treatment, after failed BCG treatments; (2) Study 101.4 patients (n=42) treated with Synergo for ablative (neo-adjuvant) treatment of bladder tumors in a controlled study originally submitted and then withdrawn from the PMA; and (3) European Ablation Patients (EAP) (n=104) also treated with Synergo for ablative (neo-adjuvant) treatment of bladder tumors in routine, commercial use of the device in Europe and Israel.

The safety results of these patients demonstrated that the adverse events were consistent with those presented for Study 101.1 and Study 102.1.

2.7 Conclusions

2.7.1 Efficacy

The Synergo PMA No. P010045 presents the efficacy results of 201 patients, including 79 patients from controlled, randomized studies and another 122 patients from real-life, commercial use of the device. The efficacy results are consistent throughout the studies and patient populations. The Synergo results are better than the conventional MMC and at least as good as if not better than BCG treatment results reported in the control arms of these studies or

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reported in the published literature or presented to FDA in the BCG NDA approval studies for the same intermediate/high risk patient populations, as shown in the **Table 3**.

Table 4 – Summary of Efficacy Results – Kaplan-Meier estimated 2-year recurrence rates

	Synergo	**MMC**	**BCG**
Study 101.1*	18.9%	61.6%	
Study 102.1	16.9%	--	31.7%
Combined Studies 101.1 + 102.1	17.1%	--	--
EPP	32.2%	--	--
Meta-Analysis of Literature Reports	--	41.5%	35.6%
BCG NDA (92-0306)	--	55%	43%

*Based on Evaluable Patients: Randomized As Treated cohort.

2.7.2 Safety

The safety profile of the Synergo treatment is very similar to that of routine intravesical use of chemotherapeutic agents, such as MMC and immunotherapy, such as BCG. The only anticipated adverse events that reported more frequently in the Synergo group were pain and posterior wall tissue reaction. In all occurrences of pain, the event was localized and transient during delivery of therapeutic heat during treatment and resolved without any residual effects. The higher incidence of posterior wall tissue reaction in the patients treated with the Synergo device was also anticipated due to the nature of the hyperthermia treatment. This event occurred due to the location of the RF antenna in the bladder, and in some cases there is an accumulative effect of the dissipated heat in the area around the antenna causing a small, localized area of superficial tissue reaction (hyperemia, inflammation, ulceration or necrosis) in the posterior wall of the bladder. In fact, as MMC has been reported to also cause some necrotic reaction as a result of treatment, the combination of hyperthermia and MMC may have caused this reaction. In all Synergo patients, these events were noted during follow-up cystoscopies, superficial (no muscle involvement), asymptomatic and resolved without medical intervention or significant residual effects other than residual signs of hyperemia in a few patients.

Complications observed in the Synergo studies have been well reported with chemotherapy and/or immunotherapy intravesical instillations in the published literature. The most frequently observed immediate symptoms are irritative lower urinary tract problems, including dysuria, frequency/nocturia, urgency, pain and cramping and passing of debris in the urine, including blood or clots. Patients also experience bacterial cystitis, urinary incontinence and bladder perforation. Intravesical instillation of MMC in patients who have undergone resection of superficial bladder tumors had led to the development of indolent asymptomatic ulcers at the resection site which may persist for months before healing. Severe eczematous symptoms in patients receiving intravesical MMC appear to be due to delayed hypersensitivity reaction, which also appears to be responsible for the bladder irritation and cystitis which follow intravesical MMC. Furthermore, intravesical chemotherapy administration has led to severe bladder contracture.

In summary, the safety profile of the Synergo treatment is not substantially different from that of the conventionally available MMC or BCG treatments. The same types of side effects and adverse events have been reported and with similar frequencies. This has been seen in the

Study 101.1 MMC Control group and the Study 102.1 BCG Control group, as well as in the published literature. Furthermore, systemic (and potentially life threatening) treatment related events seen with BCG have not been reported with the Synergo treatment.

The benefits offered by the Synergo treatment, as demonstrated by the clinical efficacy results, outweigh the risks of potential complications. This safety profile should be considered acceptable for a cancer treatment that has shown to be highly efficacious as demonstrated in the pivotal Study 101.1 and the additional supportive data.

The Synergo study data described in this PMA demonstrate that Synergo is a safe and effective prophylactic treatment for superficial transitional carcinoma of the bladder.

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3 DEVICE DESCRIPTION

3.1 The Synergo Device

The Synergo SB-TS 101.1 device delivers heat transurethrally by means of radio frequency (RF) energy to the urinary bladder walls. Synergo hyperthermia is delivered concomitantly with cooled intravesical instillation of Mitomycin C.

Synergo is intended for prophylactic treatment of recurrence in patients following endoscopic removal of Ta-T_1 and G_{1-3}, superficial transitional cell carcinoma of the bladder (STCCB). Synergo treatment is clinically indicated for STCCB patients of intermediate and high risk.

The Synergo SB-TS 101.1 device consists of the following two main components: (1) the hyperthermia device; and (2) the disposable catheter-tubing set.

The hyperthermia device consists of an operator console containing computer controls to obtain, display and record data from the thermocouple devices, RF directed and reflected energy, pressures in the tubing line, temperature of the heat exchanger and a means to display and record relevant patient treatment parameters. The computer controls enable the operator to control the treatment settings (i.e., RF energy and pump flow). The operator console contains the keyboard computer interface, computer monitor, computer and application specific software. The device software monitors treatment parameters and provides a monitor based visual display that alerts the user of "out-of-range" parameters. The console also contains the drug circulating unit (heat exchanger, peristaltic p--- - ---- -- --- -- - -- ------- -- ----- -- -- -- - -- --- -- - ---- -- -- --- - typical power output o- [redacted] The device is presented - - ----- -

The disposable catheter-tubing set consists of the following: a catheter system; and an interconnecting tubing line.

The catheter system consists of the transurethral silicon catheter, thermocouple device and radiofrequency antenna device. The catheter is loaded with both the thermocouple and the radiofrequency antenna devices. The transurethral catheter is a silicone triple lumen, Foley type, 20Fr, balloon catheter. It contains a radiofrequency antenna device for delivery of energy to the bladder. The catheter system also contains three thermocouples for monitoring bladder wall temperature, a balloon for positioning and anchoring the catheter against the bladder neck and provisions for drug delivery to the bladder. On the feeding cable of the antenna device, there are two additional thermocouples (FC1 and FC2). In male patients, the two additional thermocouples are used for measuring temperature on the feeding cable at the area of the prostatic urethra, for additional safety. In female patients, these thermocouples are disabled when patient gender is entered into the computer. The Catheter System is presented in **Figure 2**. The Catheter System applied in the bladder is presented in **Figure 3**.

The interconnecting tubing line is used to connect the catheter to the drug circulating unit to provide a closed-loop drug circulating system. The drug circulating system includes external cooling of the chemotherapeutic solution and return circulation to the bladder. The tubing line consists of a drug reservoir, luer-lock connectors, protection caps, three-way valves, unidirectional hydrophobic transducer protectors, filter and clamps. One section of the tubing line extends from the bladder, through the catheter lumen loaded with the bladder

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thermocouples to the heat exchanger. The other section of the tubing line brings the cooled solution from the heat exchanger to the bladder through the catheter lumen loaded with the antenna device and feeding cable thermocouples. In order to prevent the risk of overheating, the chemotherapeutic solution is continuously pumped out of the bladder and re-instilled after being cooled. This circulatory system is closed, thus allowing control of the temperature along the urethra and in the bladder. The heat-exchanger is based on a Peltier element.

The disposable catheter-tubing line set is supplied in a sterile, ready to use bag. The catheter-tubing line set is a single-use, EtO sterilized accessory component. The catheter-tubing line set has been tested for biocompatibility according to the ISO 10993 standard.

Figure 1 – Synergo Device

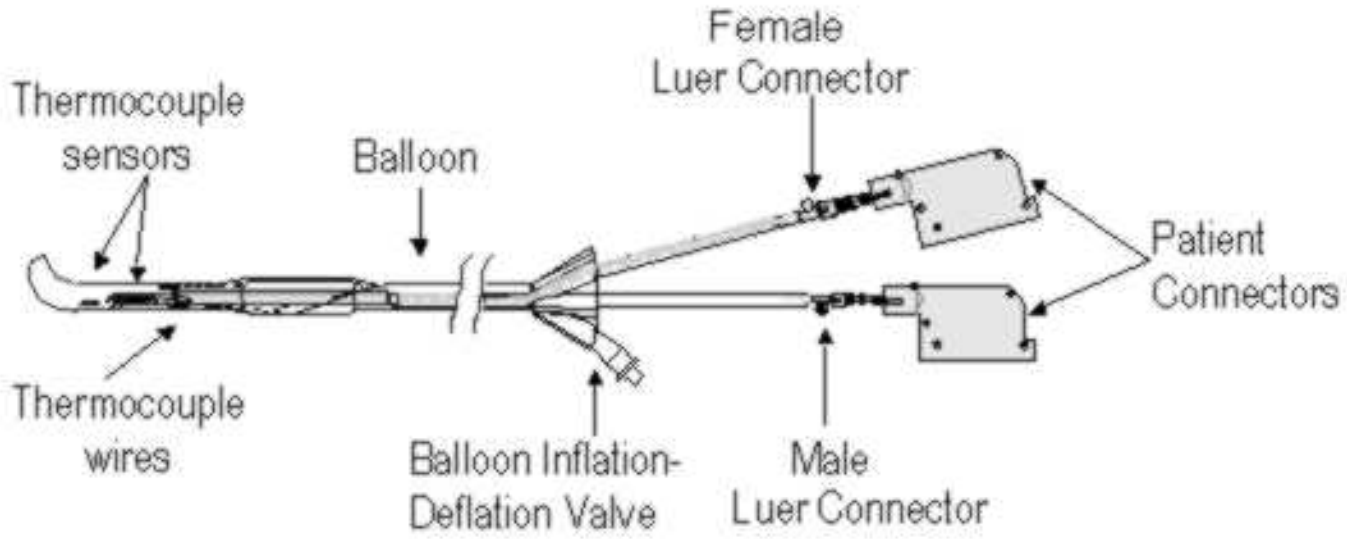

Figure 2 - Catheter System

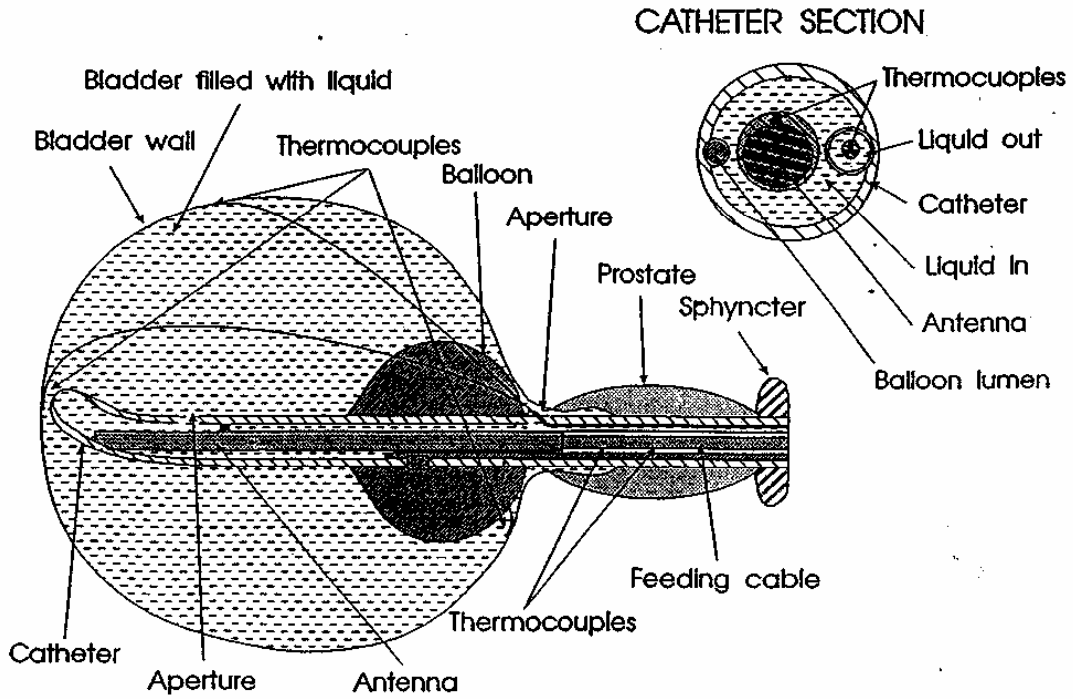

Figure 3 – Catheter System Applied in Patient

4 INDICATIONS FOR USE / CONTRAINDICATIONS FOR USE

4.1 Indications for Use

The Synergo 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-T_1 and G_{1-3}, superficial transitional cell carcinoma of the bladder (STCCB). Synergo and Mitomycin C treatment is clinically indicated for STCCB patients of intermediate and high risk.

4.2 Contraindications For Use

Use of Synergo is contraindicated in the following patients and conditions:

- Synergo treatment is contraindicated in patients whose pain response has been significantly decreased by any means (previous surgery or ionizing radiation therapy, general anesthetic, or other condition), as the patient's ability to detect pain is an essential safety mechanism.
- Synergo treatment is contraindicated in patients with cardiac pacemakers, as electromagnetic radiation from the Synergo antenna may interfere with the operation of an electronic device.
- Patients with Ta, G_1 single transitional tumors at first episode of disease and patients with tumor stage greater than T_1 are not appropriate candidates for this treatment.
- Mitomycin is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

In addition:

- The Synergo should not be used under clinical conditions that preclude treatment administration (e.g., urinary tract infection, urethral stricture, fistula, partial cystectomy, previous pelvic irradiation therapy, bladder volume <150 ml).
- Febrile patients whose' temperature is not in the range of 35.5 – 37.5°C should not receive Synergo therapy.
- Mitomycin should be used with caution in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes.

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5 SUMMARY OF PRECLINICAL TESTING

5.1 Animal Studies with the Synergo System

The purpose of the animal study was to administer a Synergo device treatment in an animal bladder, simulating actual clinical conditions and methods utilized in treating patients with the device. The aim was to demonstrate that during normal treatment conditions there are no risks of damage to the bladder or adjacent organs. This was achieved by temperature mapping of the bladder walls and adjacent organs during treatment with Synergo device and subsequent pathological evaluation of the organs after the treatment, in comparison with control animals. Four adult sheep were used for this study; two were treated with the Synergo device for temperature mapping and pathological evaluation and two served as control models for the pathological evaluation.

Thermocouple junctions were sewn to the internal and external bladder surfaces as well as on adjacent organs. The study animals underwent a full session of Synergo treatment. During the treatment session, thermocouple temperatures were monitored using a stand-alone, multi-channel temperature measuring system and thermocouple verification was performed. Temperature measurements were taken over the 60-minute treatment session, every 20 seconds. Temperatures above 46°C were intentionally employed to investigate the worst-case influences outside the bladder.

The temperatures measured were correlated with the three Synergo device catheter thermocouples' readings. The temperatures measured by different junctions evolved nearly parallel profiles, especially for internal and ex ---- --- unctions. On average, the temperature of the external bladder walls were [redacted] cooler than the internal bladder walls, and the temperature of adjacent organs were [redacted] cooler than the internal bladder wall, over the whole treatment session. That is, at -- ----- ---- der temperatures of 46°C -------- heating temperature is 40±2°C), the maximum ex ---- - ladder wall temperature was [redacted] and the maximum adjacent organ temperature was [redacted] both well below the -- ------d to produce tissue damage.

The sheep were sacrificed following the procedure and evisceration of their urinary bladder and adjacent organs was performed. The harvested organs were macroscopically and histologically examined for possible damage, using the control sheep samples for comparison purposes. Macroscopically, all organs of the four sheep were found to be intact. The main histological observation was ulceration of the epithelium, mild edema and inflammation of the lamina propria, as well as foci of fresh hemorrhage in the serosa. There was one microscopic focus of necrotic epithelium. These observations were noted at the suturing sites of the thermocouples to the organs and therefore, attributed to the surgical procedure and not to the Synergo treatment.

Temperature mapping of the urinary bladder and adjacent organs, and their pathological evaluation, clearly show that treatment with the Synergo System can be administered safely. There were no examples of histopathological findings associated with irreversible damage to the urinary bladder or adjacent tissues even under "worse-case" conditions, such as high temperatures and anesthesia.

5.2 Mechanical and Electrical Safety and EMC Safety Testing of the Synergo System

The Synergo device was tested and conforms to the IEC 60601-1 standard for mechanical and electrical safety. The Synergo device was tested and conforms to the IEC 60601-1-2 standard for electromagnetic emissions and immunity compatibility. Software validation testing was also performed according to IEC 60601-1-4.

5.3 Catheter Testing according to ASTM F623-89

The Synergo catheter was tested and complies with the requirements of the ASTM F 623-89 standard for Foley Catheters.

5.4 Biocompatibility Testing of Patient Contacting Components

The Synergo catheter components were tested for biocompatibility and were found in compliance with the ISO 10993 biocompatibility standard.

5.5 Bench Testing with the Synergo System

Bench testing included phantom tests to evaluate two aspects of the device, the electromagnetic field generated by the antenna and its interaction with simulated biological tissues. A correct estimate of the electromagnetic field shape permits the calculation of the energy generated around the antenna. Therefore, a direct electric field measuring system working in a liquid environment surrounding the antenna was developed. Secondly, a realistic phantom of the bladder was developed to estimate the tissue temperature rise during a simulated treatment. The specific absorption rate (SAR) was measured in a simple non-perfused phantom simulating the electromagnetic characteristics of the bladder. The SAR values were demonstrated to reach more than 100W/Kg in order to obtain effective hyperthermia over the desired treatment regions and decrease rapidly across the bladder wall.

5.6 Pharmacology/Toxicology, Bioavailability and Pharmacokinetic Studies of Mitomycin C

The Synergo kit contains two 20mg vials of Mitomycin for Injection, USP as finished products manufactured by Bedford Laboratories. The drug product produced by Bedford Laboratories™, (Mitomycin for Injection, USP) has been approved for marketing based on Bedford Laboratories™ (Ben Venue Laboratories) ANDA.

Pharmacokinetic, bioavailability and pharmacokinetic studies were presented for Mitomycin C (MMC) in the original AADA/ANDA submissions for MMC by Bristol Myers Squibb and Bedford. We have been granted authorization by Bedford Laboratories™ to refer to their ANDA No. 94-117. We have been also granted authorization from Bristol Myers Squibb to refer to the pharmacology/toxicology studies in their AADA application No. 62-336. Letters of authorization from both companies were submitted in the original PMA submission.

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5.7 Bioavailability and Pharmacokinetic Studies of Synergo with Mitomycin C

Paroni et al. (1) performed a study to assess the effect of Synergo on the systemic absorption of MMC during intravesical chemotherapy. The population was divided into four groups receiving different MMC doses (20 and 40 mg) both with and without hyperthermia. The instillation time was 60 minutes with replenishment of solution after the first 30 minutes. After the first 30-minute instillation, Synergo hyperthermia with MMC at 20 mg dose significantly enhanced the passage of MMC thr---- - -- -- ------- -- - -- -- ------ - - ---- - --- ---- pared with MMC alone at the sa--- ----- - [redacted] - This effect -- ------- -- -- --- -- --- -- - [redacted] - and 60 minutes - [redacted] - - -- -- ----- - -- -- -------- - a statistically significant increase in the tissue permeability to MMC du- - -- - --- - - ermia. The study demonstrated that the highest MMC plasma concentration - [redacted] - occurred after 45 minutes of a Synergo treatment employing 40 mg MMC (--- -- -- -- ndicated dosage). Despite the significantly higher systemic concentrations of MMC during intravesical instillation associated with hyperthermia, the systemic MMC levels are still far below the systemic threshold toxic concentrations for myelosuppression of 400 ng ml^{-1} MMC, both during conventional intravesical instillation and during Synergo treatment.

These findings support the safety of the chemotherapy and hyperthermia treatment. The marked effect on bladder wall permeability results in enhanced MMC penetration through the urothelium and the tissue layers, a possible explanation of treatment efficacy.

The test results also show that the dose administered in the Synergo treatment, consisting of two 30-minute dwell periods of 20 mg MMC each (2x20 mg), actually represents a total dose of more than 20 mg for the 60 minute treatment. The serum levels at the indicated dose (2x20 mg) of MMC with Synergo heat treatment are similar to the serum levels of one 40 mg MMC dose without hyperthermia. The “re-fueling” of the bladder with a fresh instillation of 20 mg MMC solution (following 30 minutes of treatment) after the bladder is drained of residual urine, eliminates the dilution of the drug with urine and thereby maintains a more optimal and homogenous drug dose throughout the entire treatment duration. This technique also minimizes the inter-patient variability.

5.8 Degradation Studies of Synergo with Mitomycin C

A test was performed to determine the degradation of the Mitomycin C dissolved in intravenous (I.V.) fluids, at 50°C (temperature higher than that used during Synergo treatment). In each of the sample preparations, the chemotherapy agent did not degrade below the approved Gensia Sicor Pharmaceutical bulk drug specification limits.

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6 OVERVIEW OF CLINICAL STUDIES

The following table summarizes the different clinical studies conducted in support of the Synergo device PMA.

Table 5 – Synergo Clinical Studies

Protocol#	Study Status (Start Date)	Location of Clinical Centers	Study Design	Treatment Group	No. of Patients	Treatment Administration
Study 101.1 (PMA Pivotal Study)	Complete (Jan 1999)	Italy Israel	Randomized, Controlled	Synergo: Hyperthermia + MMC 2 x 20 mg vs. Control: MMC 2 x 20 mg	42 41	12 treatment sessions, consisting of 8 weekly Inductive treatments and 4 monthly maintenance treatments.
Study 102.1	On going (Jul 2002)	Netherlands France Italy Israel Belgium Germany	Randomized, Controlled	Synergo: Hyperthermia + MMC 2 x 20 mg vs. Control: BCG $5X10^8$ bacilli	51 53	12 treatment sessions, consisting of 6 weekly inductive treatments, followed by 6 maintenance treatments every 6-7 weeks over a treatment period of one year. vs. BCG treatments consisting of 6 weekly induction treatments, followed by 3 maintenance treatment sets (3 weekly consecutive instillations in each set) every 2-4 months over a treatment period of one year.
European Prophylactic Patients (EPP)	Ongoing (Aug 2000)	Netherlands France Italy Israel Austria Germany	Single arm, uncontrolled	Synergo: Hyperthermia + MMC 2 x 20 mg	186	12 treatment sessions, consisting of 6-8 weekly Inductive treatments, and 6-4 monthly Maintenance treatments.

7 CLINICAL INVESTIGATIONS – PMA PIVOTAL STUDY 101.1

7.1 Background

Bladder cancer is a malignant neoplasm originating from the surface lining (urothelium) of the bladder, the most common form of which is transitional cell carcinoma (TCC). TCC accounts for more than 90% of all bladder cancers; the remainder are squamous cell carcinoma (7% to 8%), adenocarcinoma (1% to 2%), and rarely neuroendocrine or small cell carcinoma (1%). When the cancer is confined to the mucosa or submucosa of the bladder, it is referred to as "superficial," so defined because it is accessible to local surgical cystoscopic removal. However, even superficial bladder cancer can display highly aggressive behavior. Three fourths of all patients with bladder cancer initially present clinically with superficial disease.

The National Cancer Institute reports that in 2008 that there will be 68,810 new cases of bladder cancer in the United States with 14,100 deaths from the disease. As such, bladder cancer represents the fourth most common cancer in men and the eighth most common in women for a net 3:1 male predominance. The highest incidence occurs in men over 60 and women over 70 years of age. There is also a strong ethnic disparity, with disease much more common in Caucasians than in people of African, Latino, or Asian decent. Because the median age at presentation is about 70 years and the overall death rate is under 25%, the actual prevalence of patients living with a bladder cancer is approximately 10 times its incidence. Moreover, since bladder cancer, especially the superficial variety, is marked by frequent recurrences, this translates into an economic burden to the health care system of about $4 billion per year in the United States.

Accurate pathological staging and grading of cystoscopically obtained bladder tumor tissue is essential in determining clinical prognosis and directing therapy. In the Tumor-Node-Metastasis (TNM) classification system, superficial bladder cancer can be one of three types: stage Ta (confined to the mucosa), stage T1 (invasive into the submucosa or lamina propria), and CIS (flat high-grade lesion in the mucosa). Among newly diagnosed patients, approximately 70% have stage Ta, 25% T1, and <5% CIS. However, CIS more commonly co-exists with stage T1 disease. The intrinsic aggressive potential of this malignancy, on the other hand, is strongly associated with tumor grade. Traditionally, a three-tier grading system encompassing low, medium, or high grade (also known as grades G1, G2, or G3, respectively) has been used by pathologists.

For tumorous lesions of the bladder, the standard of care endorsed by both the AUA and EAU is endoscopic removal through the cystoscope in a procedure commonly referred to as TURB or TURBT (transurethral resection of bladder tumor). The goals of such a procedure are to obtain adequate tissue for pathologic examination and complete obliteration of all tumor either by resection or fulguration. CIS is not amenable to surgery because of its diffuse surface-spreading property and sometimes nearly invisible appearance. Unfortunately, even for papillary tumors, the aggregate chance of disease recurrence approximates 60% by 5 years and 80% by 10 years after surgery alone.

Adjuvant medical treatment in the form of intravesical drug therapy is commonly used to combat this otherwise high recurrence rate of superficial bladder cancers. Even for low-risk group patients with low-grade, solitary, papillary TCCs, a single dose of early post-

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operative therapy is now recommended by both the AUA and EAU Guidelines. The EAU further advocates this practice for all risk groups as an initial step. For intermediate and high-risk groups, either specified formally as such by the EAU or recognizable as “index patients” by the AUA, additional longer courses of intravesical therapy are recommended.

After more than three decades of empirical clinical testing, only a few cytotoxic chemotherapeutic agents have emerged with an acceptable efficacy and toxicity profile to be used as solo agents for routine intravesical use: the alkylating agent thiotepa (and a related drug in Europe, ethoglucid), the topoisomerase inhibitor doxorubicin (and its derivatives epirubicin, pirarubicin, and valrubicin), and the bifunctional alkylating agent mitomycin. Although, MMC is recommended for prophylactic treatment of STCCB in the American Urology Association (AUA) guidelines for the treatment of bladder cancer and thus, widely used in this manner in the US, it and other chemotherapy agents (except for valrubicin) are not specifically approved by FDA for this indication in the US. BCG immunotherapy is an alternative treatment which is approved in the US.

There are a number of agents under development and already in early clinical trials. These include an agent to facilitate passive chemotherapy drug penetration, several gene therapy vectors, a pseudomonas exotoxin armed monoclonal antibody, new cytotoxic chemotherapeutics, a mycobacterial cell wall-DNA complex, and even several natural products. Most are interventional treatment-oriented but several are also exploring chemoprevention. There remain many unmet needs in superficial bladder cancer, most notably more efficacious durable therapies for primary disease, reduced toxicity alternatives and effective salvage treatment after initial intravesical failure. In it’s recently published 2008 guidelines, the EAU states that device-assisted chemotherapy instillations can yield responses in selected cases.

Additional background information concerning the epidemiology, staging, and treatment for superficial bladder cancer can be found under the References and Guidelines tab in the Panel Pack.

7.2 Summary of Study Protocol

7.2.1 General Information

The study described in this section is the pivotal, randomized, controlled, PMA Study 101.1 (Comparative Study of Intravesical Mitomycin C Instillation Or Mitomycin C and Local Hyperthermia for Prophylaxis of Recurrences of Superficial Transitional Bladder Tumors) provided in the original PMA submission. The purpose of the study was to evaluate the safety and efficacy of the Synergo hyperthermia treatment in conjunction with Mitomycin C (“Synergo treatment” or “Synergo group”) compared to intravesical instillation of Mitomycin C alone (“MMC treatment” or “Control group”), for prophylactic treatment of superficial transitional cell carcinoma of the bladder (STCCB) in intermediate and high-risk patients following complete surgical removal of the tumor.

The study began in 1994 and patients were enrolled through January of 1999. A total of eighty-three (83) patients were enrolled in the study at three clinical centers: San Rafaelle Hospital (Milan, Italy), University Hospital of Palermo (Palermo, Italy) and Rabin

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Medical Center – Beilinson Campus Hospital (Petach Tikva, Israel). All of the patients were defined as intermediate or high-risk STCCB patients according to the European Association of Urology (EAU) guideline. The American Urological Association (AUA) guidelines do not define risk categories, therefore, the EAU definitions for risk categories were adopted.

7.2.2 Study Design

The aim of the study was to evaluate the safety and efficacy of Synergo treatment compared to MMC treatment in a randomized, controlled study.

Prior to entering the study, the patients underwent staging of all evident bladder tumors. Patients were evaluated by the investigator according to the inclusion and exclusion criteria for possible participation in the study. Patients eligible for study recruitment were requested to sign the informed consent form and were randomized to either the Synergo treatment group or the MMC treatment group.

The Synergo treatment group received hyperthermia treatment in conjunction with MMC, delivered in 2 doses of 20 mg in 50 ml sterile distilled water. The first dose was administered at the start of treatment and the second dose was administered after 30 minutes of treatment and after emptying the bladder of the first instillation dose. The control group received only MMC, also delivered in the same manner consisting of two intravesical instillations of 30 minutes each.

The total number of treatments in each treatment group was identical, consisting of eight (8) weekly inductive sessions, followed by four (4) monthly maintenance sessions. Each treatment session lasted for 60 minutes. The treatment began within 20-40 days after eradication of tumors. All treatment sessions for all the study patients are recorded on videotape.

MMC is an FDA approved drug (NDA 62-336) and has been shown to be useful in the therapy of adenocarcinoma of the stomach or pancreas or in combination with other approved chemotherapeutic agents and as a palliative treatment when other modalities have failed. However, it is not approved for the treatment of STCCB by intravesical instillation. Nevertheless, MMC has been recommended for prophylactic treatment following endoscopic removal of STCCB by the American Urological Association (AUA)[1]. Furthermore, MMC was used in the control arm in both studies accepted by FDA in support and approval of the BCG NDA (92-0306).

Follow-up began at the end of the eight inductive treatment sessions. Follow-up visits were performed at intervals of three months, up to 24 months or until first recurrence, whichever was sooner. Follow-up exam included a physical examination, cystoscopy, laboratory tests, cytology or cold-cup biopsy, if required. Cold-cup biopsies were performed only in the case of recurrence or suspicion of recurrence. As long as the patient remained tumor-free, no further adjuvant treatment, either local or systemic was administered.

[1] Guideline for the Management of Nonmuscle Invasive Bladder Cancer (Stages Ta, T1, and Tis): 2007 Update2 (J of Urology, Vol. 178, 2314-2330, December 2007)

7.2.2.1 Study Population

7.2.2.1.1 Inclusion Criteria

Patients with the following Inclusion Criteria were recruited to the study:

- Subjects with resected Stage Ta or T1 and Grade G1-G3, STCCB
- Complete tumor eradication must be possible
- Subjects with a life expectancy > 24 months
- Subjects able to understand the characteristics, the purpose and the procedures of the study
- Subjects willing to sign informed consent

7.2.2.1.2 Exclusion Criteria

Patients with any of the following Exclusion Criteria were excluded from the study:

- Subjects with Ta, G1 single transitional tumors at first episode of disease
- Subjects with tumor stage > T1
- Subjects with positive cytology after complete eradication of tumors
- Subjects with residual tumor after complete eradication of tumors
- Other than transitional (STCCB) tumors
- Transitional tumors of the bladder involving the prostatic urethra
- Primary transitional tumors of the prostatic urethra
- Solitary, multifocal or associated carcinoma in situ (CIS) at entry on-study
- Clinical presence of distant or lymphatic metastases
- Performance status WHO > 2
- Presence of another tumor
- Well known allergy to topical or systemic chemotherapy agent (specifically, MMC)
- Subjects who have been treated with chemotherapy instillations during the last three months
- Subjects treated for systemic cancer treatment with immunotherapy, cytotoxic agents or radiotherapy during the last three months
- Subjects with untreated urinary tract infection or recurrent severe bacterial cystitis
- Patients suffering from large BPH
- Neurogenic bladder
- Persistent hematuria not due to known tumor
- Urethrorragia
- Urethral strictures or other urethral pathology
- Subjects mentally unable to collaborate
- Subjects not willing to sign informed consent

Note: the first exclusion criteria excludes patients who have a low stage and grade tumor at first episode of the disease. These patients are categorized as low-risk patients and were not included in the study. As mentioned in the indications for use of the device, the Synergo treatment is intended for use only for intermediate and high-risk STCCB patients.

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7.2.2.2 Description of Study Procedures

7.2.2.2.1 Randomization Procedure

Eligible patients were randomized in 1:1 ratio to either the Synergo group or the MMC group. The randomization schedule was administered at a central randomization center, independent of the clinical sites, using pre-prepared randomization envelopes containing the treatment assignment.

7.2.2.2.2 Synergo Treatment

The Synergo treatment consisted of eight (8) weekly inductive sessions, followed by four (4) monthly maintenance sessions. Each treatment session lasted for 60 minutes. The treatment began within 20-40 days after eradication of tumors. The Synergo group was treated according to the following parameters:

- Intravesical chemotherapy: 40 mg of MMC dissolved in 100 ml of sterile distilled water (delivered in two portions of 20 mg in 50 ml, at the start of treatment and after 30 minutes of treatment); and
- Hyperthermia: Temperature 42 ± 2°C

7.2.2.2.3 MMC Treatment

The total number of treatments in the MMC group was identical to the Synergo group, consisted of eight (8) weekly inductive sessions, followed by four (4) monthly maintenance sessions. Each treatment session lasted for 60 minutes. The treatment began within 20-40 days after eradication of tumors. The MMC group was treated according to the following parameters:

- Intravesical chemotherapy: 40 mg of MMC dissolved in 100 ml of sterile distilled water (delivered in two portions of 20 mg in 50 ml, at the start of treatment and after 30 minutes of treatment).

7.2.2.2.4 Follow-up Evaluations

Follow-up evaluations began at the end of the eight inductive treatment sessions. Follow-up visits were performed at intervals of three months, up to 24 months or until first recurrence, whichever was sooner. The follow-up exam included a physical examination, cystoscopy, laboratory tests, cytology or biopsy, if required. Cold-cup or TUR biopsies were performed only in the case of recurrence or suspicion of recurrence. Tumor recurrence was determined based on a positive histology report from biopsy. As long as the patient remained tumor-free, no further adjuvant treatment, either local or systemic were administered.

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7.2.2.3 Study Objectives and Endpoints

7.2.2.3.1 Study Objective

The objective of the study was to evaluate the safety and efficacy of Synergo treatment compared to MMC treatment in terms of the recurrence-free interval and reported adverse events.

7.2.2.3.2 Primary Efficacy Endpoints

Recurrence at 2 years based on the survival analysis was evaluated as the primary efficacy endpoint of Study 101.1[2]. The primary efficacy endpoint assessment of tumor recurrence was determined based on a positive histology report from a cold-cup or TUR biopsy.

7.2.2.3.3 Secondary Efficacy Endpoints

Tumor progression, occurrence of CIS or carcinoma in the upper tract or prostatic urethra and occurrence of distant metastasis were secondary efficacy endpoints of the study.

The secondary endpoint assessment of tumor progression was determined based on the tumor grade and stage reported in the histology report from a cold-cup or TUR biopsy. Occurrence of CIS or carcinoma in the upper tract or prostatic urethra and occurrence of distant metastasis were also based on a positive histology report from an appropriate biopsy sample.

7.2.2.4 Statistical Methods Planned in Protocol

7.2.2.4.1 Determination of Sample Size

The sample size was calculated based on the following study hypotheses for the primary efficacy endpoint, using a log-rank test:

H_0: The recurrence rate is the same in the Synergo group and the Control group (i.e., hazard ratio=1)

H_A: The recurrence rate is not the same in the Synergo group and the Control group (i.e., hazard ratio≠1)

The original sample size required by the study protocol was 158 patients (79 patients per treatment group), based on an expected reduction of the recurrence rate in the Synergo group of 50% compared to the Control group, with a power of 80% and a 5% 2-sided type I error. Since a two-year recurrence rate of 40% was assumed for the MMC group,

[2] Although the primary efficacy endpoint was not explicitly stated in the protocol, recurrence rates are universally reported in literature for evaluation of efficacy of STCCB treatments. Therefore, Study 101.1 was in accordance with common reporting measures. Furthermore, the study sample size was also calculated based on recurrence rates. All of the required elements of a study protocol (endpoints, sample size, statistical analysis) were stated in Study 101.1 protocol, although possibly in poor English and not in the standard format to which FDA may be accustomed.

the anticipated reduction in recurrence rate for the Synergo group was 20%. All patients were followed at least 24 months or until first recurrence, whichever was sooner.

7.2.2.4.2 Interim Analysis

The study protocol also called for an interim analysis to define the future development of the study, including possible suspension of the study in case of a statistically significant higher recurrence rate in the Synergo group compared to the Control group or vice versa or possible prolongation of the study to more than two year follow-up. The interim analysis was conducted in 1997, following enrollment of 64 patients into the study. At that time, 83% of the patients had completed 1-year follow-up and 39 (61%) patients had completed 2-year follow-up (21 Control and 18 Synergo). The interim analysis, which was performed on data from subjects with 2-year follow-up, demonstrated a statistically significantly lower recurrence rate in the Synergo group (11%) compared to the Control group (62%) (p=0.002).

Thus, according to the study protocol, the results of the interim analysis justified suspension of the study at this point with 64 patients. Nevertheless, since the results of the study appeared over-optimistic for both treatment groups it was decided to increase the sample size using a conservative approach to sample size estimation and prolong the study until 2-year follow-up was obtained on all the enrolled patients. The only adjustment that was made to the study protocol at this point was the sample size re-estimation. The revised sample size was 42 patients in each treatment group, for a total of 84 patients. Two years later, enrollment into the study was terminated with a total number of eighty-three (83) patients. The study was terminated in 2001 when all study patients had completed 2 year follow-up or had reported a tumor recurrence.

7.2.2.4.3 Statistical Analysis Planned in Protocol

The primary efficacy endpoint, the recurrence rate, were compared between the Synergo group and the MMC group, using the Kaplan-Meier survival analysis. The analysis of the secondary efficacy endpoints included a comparison of tumor progression rates, local incidences of CIS and occurrences of distant metastasis in the Synergo group compared to the MMC group. The safety analysis consisted of analysis of all adverse events or complications reported during the course of the study and their relationship to the Synergo treatment.

7.2.2.4.4 Blinding

Due to the nature of the Synergo treatment, it was not possible in practice to conduct a blinded study. Firstly, it was obvious to the patients undergoing the treatment which treatment was being administered due to the heating effect of the hyperthermia or the lack thereof. Secondly, the urologist performing the cystoscopy procedures to assess the bladder condition of the patient was easily able to determine which treatment the patient received due to the appearance of the bladder following Synergo or MMC treatments. The patients undergoing Synergo treatment in many cases have more pronounced hyperemia and a large percentage of the patients have signs of a thermal reaction in the posterior wall of the bladder, presented as a yellow medallion or superficial necrosis.

Therefore, in addition to patient awareness, due to the bladder wall appearance, blinding of study patients or the treating physicians is not possible.

However, the likelihood of bias in patient evaluation in favor of the Synergo group due to the lack of blinding was minimized by the consistent long-term follow-up results confirming lower recurrence rate in the Synergo group compared to the MMC group.

7.2.2.4.5 Patient Handling

The study protocol contained pre-specified rules for handling the data from subjects who were lost to follow-up, died, or discontinued due to adverse events or for other reasons. The study protocol also provided criteria for patient study termination (e.g., in case of tumor recurrence or adverse events), requiring documentation of all adverse events.

7.3 Study Results

7.3.1 Enrollment and Accountability

Between March 1994 and January 1999, a total of eighty-three (83) patients were enrolled in the study at three clinical centers: San Rafaelle Hospital (Milan, Italy), University Hospital of Palermo (Palermo, Italy) and Rabin Medical Center (then called "Belinson", Petah Tikva, Israel). **Table 6** displays the participating clinical centers, the principal investigator at each center, and the number of patients enrolled at each center.

Table 6 – Patient Enrollment

Clinical Center	**Principal Investigator**	**No. of Patients**
San Rafaelle Hospital Milan, Italy	Prof. Rigatti	36
University Hospital of Palermo Palermo, Italy	Prof. Pavone	14
Rabin Medical Center – Beilinson Hospital Petach Tikva, Israel	Prof. Servadio	33

Patient accountability is shown in **Table 7**. All Study Patients included 83 (41 MMC and 42 Synergo) randomized patients. The Evaluable Patients cohort includes 77 patients. As reflected in **Table 7**, 6 patients assigned to the Synergo group who did not reach the first cystoscopy follow-up visit required for the evaluation of recurrence were excluded from the Evaluable Patients population. These patients and reasons for their early withdrawal are shown in **Table 8**.

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Table 7 – Patient Accountability

	Treatment Group		
Analysis Population	**MMC**	**Synergo**	**Total**
All Study Patients: Randomized As Treated*	**41**	**42**	**83**
Patient consent withdrawn	0	3	3
Physician withdrawn	0	1	1
Skin allergy – study terminated	0	2[†]	2
Evaluable: Randomized As Intended	**41**	**36**	**77**
Evaluable: Randomized As Treated	**40**	**37**	**77**
Protocol deviations	0	2	2
Per-Protocol (PP)	**40**	**35**	**75**

*All St--- - - - - - - - - - - - - - - to all patients grouped according to "Randomized As Treated."

[†]Patient ---------- --as excluded from th- ------ --- -- --in allergy, but this patient was also one of the randomization switches. Therefore, patient ---------- was excluded twice in each of the Evaluable Patient Cohorts; (1) from the Evaluable Patients: Randomized As Intended, where he was considered a Synergo patient (currently shown in the "All Study Patients"); and (2) from the Evaluable Patients: Randomized As Treated, where he was considered a MMC patient according to the 2 treatment sessions he actually received (not shown in the "All Study Patients").

The Evaluable Patients are further defined as Evaluable Patients: Randomized As Intended and Evaluable Patients: Randomized As Treated. The difference between these patient cohorts is that in the former the patients are grouped according to the treatment to which they should have been randomized according to the original randomization scheme. In the latter group, the patients are included according to how patients were actually randomized at the clinical center and according to the treatment that they actually received. Five pairs of patients did not receive the treatment designated by the original central randomization scheme. Each of these pairs of patients were consecutively randomized, mostly on the same day and had their treatment assignments accidentally switched due to clerical errors at the central randomization office.

The Per-Protocol (PP) population is formed by excluding two Synergo patients with major protocol deviations (see **Table 9)** from the Evaluable Patients: Randomized As Treated population (see **Section 7.3.2.2)**. The PP population includes 75 patients, including 64 patients who have completed the 24-month follow-up or have documented recurrence at an earlier time point, as well as 5 patients who are lost to follow-up and 6 patients who have not yet reached the 24-month follow-up. Patients who are lost to follow-up or still ongoing at the time of the analysis are treated as censored observations in the Kaplan-Meier analysis.

Table 8 - Patients Who Withdrew Before Reaching First Cystoscopy

Patient ID	Reason	Treatment Assigned	Treatment Received	No. of Treatments Received	Last Follow-up Visit
---------- -----	Skin allergy to chemotherapeutic agent	Synergo	MMC	2	None
---------- -----	Consent withdrawn (patient resided far away from hospital and declined further treatment)	Synergo	Synergo	3	None

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Patient ID	Reason	Treatment Assigned	Treatment Received	No. of Treatments Received	Last Follow-up Visit
---------- -----	Skin allergy to chemotherapeutic agent	Synergo	Synergo	1	None
---------- -----	Deteriorating health	Synergo	Synergo	0	None
---------- -----	Consent withdrawn	Synergo	Synergo	0	None
---------- -----	Consent withdrawn	Synergo	Synergo	0	None

7.3.2 Study Administration Issues

7.3.2.1 Deviations from Eligibility Criteria

There were no deviations from the eligibility criteria noted during the study.

7.3.2.2 Other Protocol Deviations

Two Synergo patients are excluded from the Evaluable Patients population due to major protocol deviations. After 1 or 2 treatments, these patients withdrew their consent to participate in the study. The physician ---- ----- --- ng them with MMC alone. These patients are shown in **Table 9**. Pa --- ---------- ----- received 1 Synergo treatment and then 10 MMC treatments. Patient ------- ----- ---- received 2 Synergo treatments and then 14 MMC treatments.

Table 9 - Protocol Deviations

Patient ID	Protocol Deviation	Treatment Assigned	No. of Treatments Received	Last Follow-up Visit
---------- -----	Consent withdrawn (patient experienced pain and anxiety)	Synergo	1 Synergo 10 MMC alone	15 month
---------- -----	Consent withdrawn (patient experienced severe bladder spasms)	ergoSyn	2 Synergo 14 MMC alone	9 month (ongoing)

Patient ---------- ---- e-- - --- -- -- - -nd anxiety and therefore, withdrew his/her informed consent. Patient ---------- ---- experienced severe bladder spasms and therefore, decided not to continue the treatment. These patients were randomized to the Synergo group. After withdrawing consent, these patients continued receiving the MMC treatments, as this is considered the standard, conventional treatment offered to these patients. Had the patients been recorded as “terminated the study” due to consent withdrawal, and then continued the conventional MMC treatments, this would not have been considered a protocol deviation. But since the physician mistakenly recorded the MMC treatments on the CRFs, this was recorded as a protocol deviation.

These two patients are included in the efficacy analysis in the All Study Patients cohort and the Evaluable Patient cohorts, but not in the PP cohort analysis. Their recorded side effects and adverse events (pain, anxiety, and bladder spasms) were included in the safety analysis.

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7.3.2.3 Randomization Errors

There were 5 pairs of randomization errors, in which the treatment assignments were inadvertently switched between two consecutive pairs of study patients. This occurred mostly in patients enrolled and randomized on the same day. The errors were due to administrative/clerical errors, which occurred at the central randomization office, independent of the clinical sites. The clinical sites were totally unaware of the treatment switches and assigned the patients to the treatment recorded on the randomization form as they received it from the central randomization office. In fact, the randomization errors were only discovered several years after the completion of the study, and only when the randomization scheme was retrieved at the request of FDA. That is, the clinical sites, as well as the Sponsor were not aware of the randomization switches until after study completion and therefore, these randomization errors could not have introduced any bias on the study results.

Nevertheless, in order to evaluate whether the randomization errors had an effect on study outcome, the primary efficacy data were analyzed according to assigned treatment both as intended (i.e., Randomized As Intended) and as actually implemented (i.e., Randomized As Treated). The results of these analyses demonstrated that the randomization errors had no effect on the study outcome (see **Section 7.3.6.1, Table 15)**.

7.3.2.4 Patients Withdrawn

Six patients withdrawn from the study were reported above in **Table 8**. As explained above, these patients were not included in the Evaluable Patient cohort or the PP cohort as no follow-up evaluation of recurrence were available for these patients. However, they were included in the All Study Patients population.

7.3.2.5 Patients Lost to Follow-up

Five patients, who did not experience a tumor recurrence, did not complete the study through 24 months follow-up. The treatment group, the number of treatments received and last follow-up session for these patients are shown in **Table 10**. These patients are included in the PP cohort as they do not have major protocol deviations. These patients are included as censored observations in the Kaplan-Meier analysis.

Table 10 - Patients Lost to Follow-up

Patient ID	Treatment Group	No. of Treatments Received	Last Follow-up Session
---------- ----	MMC	12	3 months
---------- ----	MMC	12	6 months
---------- ----	Synergo	12	21 months
---------- ----	MMC	11	2 months
---------- ----	MMC	7	21 months

7.3.2.6 Patient Deaths

Table 11 lists the two patients who died during the course of the study. Neither of these deaths were determined to be related to the study treatment.

Table 11 – Patient Deaths

Patient ID	Reason	Treatment Group	No. of Treatments Received	Last Follow-up Session
---------- ----	Patient died of other cancer (leukemia) – not related to study treatment	MMC	12	3 months
---------- ----	Patient died of a stroke – not related to study treatment	MMC	12	6 months

7.3.3 Analysis Population

The primary efficacy analyses are presented for the All Study Patients cohort (n=83), the Evaluable Patients: Randomized As Intended cohort (n=77), the Evaluable Patients: Randomized As Treated cohort (n=77) and the PP cohort (n=75). The analysis populations are described in **Section 7.3.1**.

The secondary efficacy analyses and the additional statistical analyses (subgroup analyses) are provided for the Evaluable Patients: Randomized As Treated cohort.

Baseline characteristics, including demographic, and tumor characteristics, as well as procedural (treatment) characteristics, are based on clinical data from the All Study Patients cohort. The safety analyses are also based on data from the All Study Patients cohort. Patients are grouped according to “Randomized As Treated” for evaluation of baseline characteristics and safety endpoints.

7.3.4 Poolability of Clinical Sites

The clinical sites are comparable with regard to patient demographic characteristics (age and gender) and baseline tumor characteristics, including history of recurrence, previous tumor size (>2 cm) and previous multifocal tumors (>5). However, a significant difference between clinical centers was found for previous tumor stage and previous tumor grade. No significant differences were found between the clinical centers regarding the total number of treatment sessions and the treatment groups. Poolability of patient data across clinical sites was assessed by including a center by treatment group interaction term in the Cox regression model for the analysis of time to recurrence. The Cox regression analysis found no statistically significant interaction between treatment group and center, indicating that there was no statistically significant difference between clinical sites with regard to treatment effect comparing the Synergo group to the MMC group, thus justifying the poolability of patient data across clinical sites.

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7.3.5 Baseline Characteristics

The descriptive statistical evaluations presented in this section include all available data from All Study Patients. Patients were grouped according to "Randomized As Treated" for the analysis.

7.3.5.1 Demographics

Table 12 presents baseline demographic data including patients' gender and age according to treatment groups. As can be seen in the table, about 83% of the patients were men in either treatment group. The MMC patients were slightly older than the Synergo patients (mean ages are 65.6 and 60.5, respectively). The difference in age between the treatment groups is marginally significant, but clinically not meaningful. Moreover, as shown in **Section 7.3.8.4**, there was no significant effect of age on the rate of recurrence.

Table 12 – Baseline demographics (All Study Patients)

Baseline Demographics		**MMC 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%	

*Fisher's exact test.

Table 12a		**MMC**	**Synergo**
Age (yrs)	Mean	65.6	60.5
	Median	69.0	62.0
	SD	10.8	11.0
	Min	36	35
	Max	81	77

7.3.5.2 Tumor Characteristics by Group

The following baseline tumor characteristics were evaluated, as they are indicative of the severity of STCCB:

- History of tumor recurrence (first episode, recurrent or high recurrent)
- Number of previous occurrences
- Previous tumor stage (T)
- Previous tumor grade (G)
- Previous tumor size (≥ 2 cm)
- Previous multifocal tumors (> 5)
- Current number of tumor sites (single vs. multiple tumors)
- Previous prophylactic treatments (other chemotherapeutic agent, previous MMC use, or none)
- Previous BCG therapy

- EAU Risk Group

Table 13 presents the distribution of the baseline tumor characteristics according to treatment group. The results demonstrate that no significant differences exist between the treatment groups regarding any of the baseline tumor characteristics.

Table 13 – Baseline Tumor Characteristics (All Study Patients)

Baseline Tumor Characteristics		**MMC 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%	
Current Number of Tumor Sites	Single	15	36.5%	18	43.9%	0.559
	Multiple	26	63.4%	24	57.1%	
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	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%	

*Fisher's exact test.

Following is an explanation of each of the above tumor characteristics:

<u>History of tumor recurrence</u> (first episode, recurrent or high recurrent) refers to the number of previous occurrences in which the patient presented with STCCB. First episode patients were patients who presented with STCCB for the first time at study enrollment. Recurrent patients were defined as patients with one previous episode of STCCB. High recurrent patients were defined as patients with two or more previous

episodes of STCCB within the previous 24 months. High recurrent patients are considered to be of higher risk than recurrent patients, and first episode patients are usually considered to be of lower risk. History of recurrence is not the only prognostic factor in determining the overall risk of the patient with STCCB. Additional prognostic factors include tumor stage, grade and multifocality, as described below.

Patient's previous tumor stage and previous tumor grade included the recorded stage and grade of the resected tumor/s (upon study entry) according to a histopathology report, as well as the stage and grade recorded for tumors in previous episodes (patients history). Patients with a high stage and grade (T1, G3) are considered high-risk and patients with a combined stage/grade such as Ta, G2-G3 or T1G1 are considered intermediate risk patients.

Tumor size refers to tumors that were 2 cm or greater, as recorded for the tumor(s) upon study entry.

Previous multifocal tumors refer to more than 5 tumors, as recorded for the resected tumor/s upon study entry, as well as recorded for tumors in previous episodes (patient history). Patients with multifocal tumors are considered at higher risk than patients with fewer tumors.

Current number of tumor sites refers to single tumor vs. multiple tumors, as recorded for the resected tumor(s) upon study entry. Patients with more than one tumor are considered at higher risk than patients with a single tumor.

Previous prophylactic treatments refer to prophylactic treatments that the patient underwent following eradication of bladder tumors in previous episodes of tumor occurrences. Other prophylactic treatments agents may include BCG, Mitoxantrone, etc. Previous MMC indicates a previous prophylactic treatment utilizing MMC as the chemotherapeutic agent. First episode patients did not have any previous prophylactic treatments. Patients who failed previous prophylactic treatments are considered at higher risk than first episode patients.

EAU risk groups are presented in the following table. The European Association of Urology (EAU) Risk Group categories are defined in the EAU guidelines according to tumor characteristics, as follows:

Risk Group	**Tumor Characteristics**
Low Risk	Single tumor, Ta, G1, < 3 cm diameter
Intermediate Risk	All other tumors, Ta-T1, G1-G2, Multifocal, > 3cm diameter
High Risk	T1, G3, Multifocal or highly recurrent, CIS

The American Urological Association (AUA) Guidelines do not define risk categories, and therefore, the EAU Guidelines' risk categories were used as the general guideline. Similar baseline tumor characteristic categories are applied in urology clinical practice and for reporting purposes in the urology medical scientific literature.

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Note that no low risk patients were treated with the Synergo. As clinically indicated by the Synergo treatment, only intermediate and high-risk superficial transitional cell carcinoma of the bladder patients were treated.

7.3.6 Procedural Characteristics

7.3.6.1 Number of Treatment Sessions

Table 14 presents the total number of treatments patients received according to treatment groups. Patients who completed the 8 weekly induction sessions and 4 monthly maintenance sessions had the full course of treatment. Patients who completed at least the 8 sessions, completed the full course of 8 inductive treatments but may not have completed the full course of 4 monthly maintenance sessions. Patients with less than 8 sessions did not complete the full course of 8 weekly induction treatments. The results demonstrate that no significant difference exists between the treatment groups regarding the total number of treatments that the patients received.

Table 14 – Total number of treatments patients received (All Study Patients)

Number of treatments	MMC N=41		Synergo N=42		P-Value
	N	%	N	%	
8 inductive + 4 maintenance	25	61.0%	29	69.1%	0.426
At least 8 sessions	12	29.3%	7	16.7%	
Less than 8 sessions	4	9.8%	3	7.1%	
No treatment sessions	0	0%	3*	7.1%	

*Three patients in the Synergo group did not receive any treatment: 2 patients withdrew consent prior to commencement of treatment and 1 patient was withdrawn by the physician due to deteriorating health (see **Table 7** patient accountability).

7.3.7 Primary Efficacy Analysis

7.3.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study was recurrence at 2 years. **Table 15** presents the survival analysis results for the study patients up to 24 months follow-up using the Kaplan-Meier (KM) method and log rank test for comparison for the following analysis populations: (1) Evaluable Patients: Randomized As Treated population; (2) Evaluable Patients: Randomized As Intended population; (3) PP population; and (4) All Study Patients population (worst case scenario).

In the Evaluable Patients: Randomized As Treated analysis, the study patients were grouped into the Synergo or MMC group according to the treatment that they were actually assigned by the central randomization office and actually received. In the Evaluable Patients: Randomized As Intended analysis, the study subjects were grouped into Synergo or MMC group according to the treatment that they should have received according to the original randomization scheme. The PP analysis excludes the two patients with a major protocol deviation.

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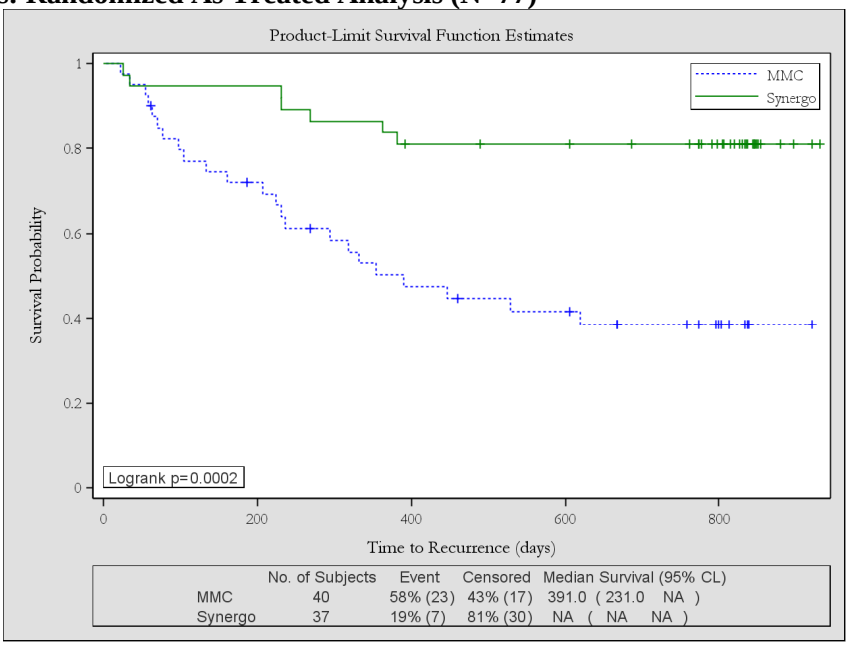
In the All Study Patients population (n=83) analysis, the study subjects were grouped in the same manner as the Evaluable Patients: Randomized As Treated, i.e., according to the treatment that they actually received. Patients who withdrew before reaching the first cystoscopy evaluation visit (n=6) (i.e., no follow-up data exists) are included in the analysis using the "worst case scenario" imputation method. This analysis assumes that the 1 MMC patient without cystoscopy evaluations were recurrence-free up to 24 months follow-up and the 5 Synergo patients without cystoscopy evaluations had recurrent disease at the start of follow-up.

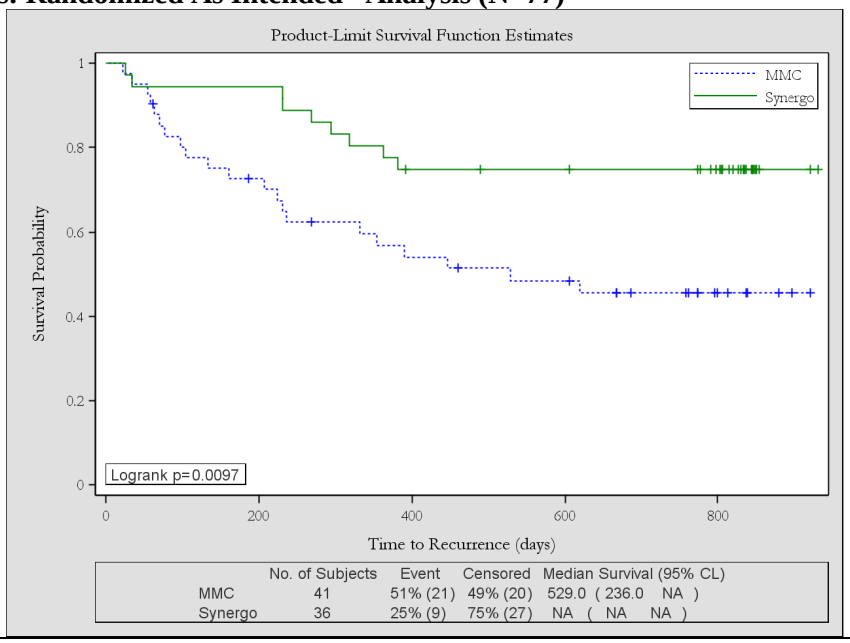
Table 15 - Primary Efficacy Analysis

1. Evaluable Patients: Randomized As Treated Analysis (N=77)



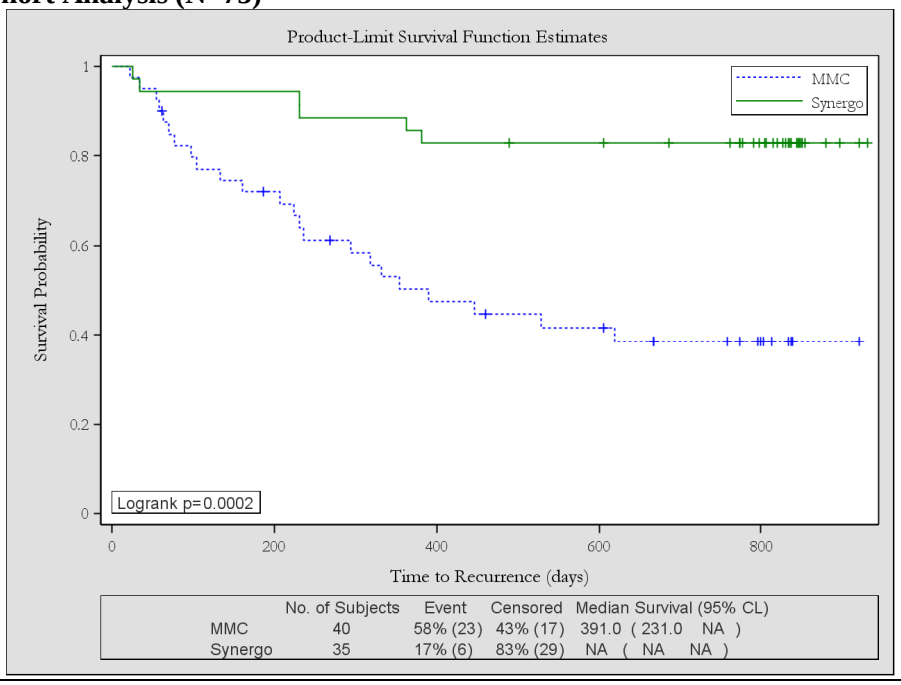
Estimated 2-year probability of recurrence: MMC – 61.6% Synergo – 18.9%
Log-rank p=0.0002; Hazard Ratio=0.231 95% CI [0.099-0.541]

2. Evaluable Patients: Randomized As Intended" Analysis (N=77)



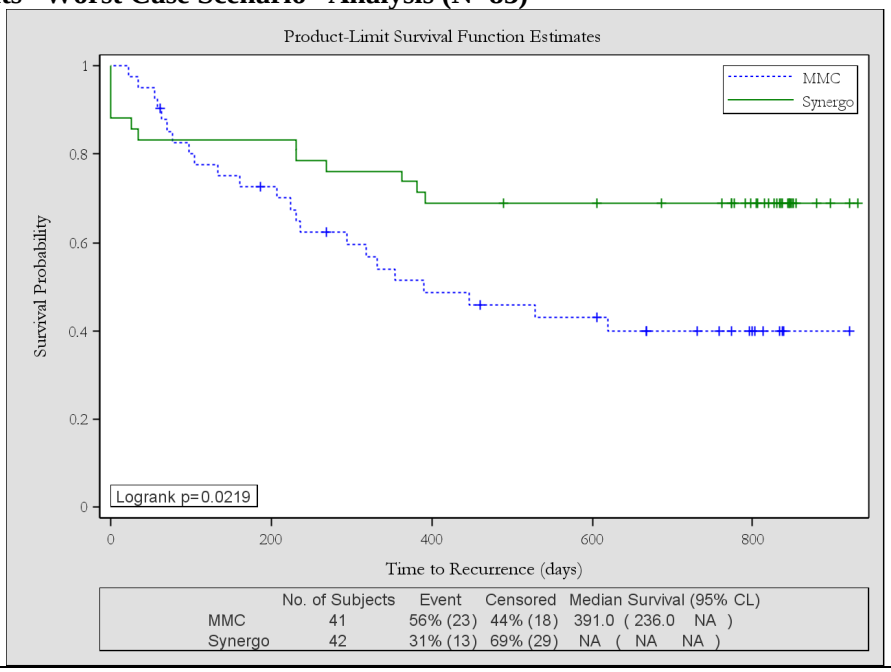
Estimated 2-year probability of recurrence: MMC – 54.4% Synergo – 25%
Log-rank p=0.0097; Hazard Ratio=0.371 95% CI [0.169-0.811]

3. Per Protocol Cohort Analysis (N=75)



Estimated 2-year probability of recurrence: MMC – 61.6% Synergo – 17.1%
Log-rank p=0.0002; Hazard Ratio=0.207 95% CI [0.084-0.512]

4. All Study Patients "Worst Case Scenario" Analysis (N=83)



Estimated 2-year probability of recurrence: MMC – 59.9% Synergo – 30.9%
Log-rank p= 0.0219; Hazard Ratio=0.459 95% CI [0.232-0.911]

As shown in **Table 15**, the rate of tumor recurrence is consistently lower and statistically significant in the Synergo group than in the MMC group regardless of the analysis populations used. The PP analysis shows the largest reduction, approximately an 80% reduction in the rate of recurrence in the Synergo group compared to the MMC group (HR=0.21; 95% CI=0.08 to 0.51; estimated 2-year recurrence rate: MMC – 61.6%, Synergo – 17.1%, p=0.0002). A similar result is seen in the Evaluable Patients: Randomized As Treated analysis; here too, the Synergo group shows nearly 80% reduction in the rate of recurrence compared to the Control group (HR=0.23; 95% CI=0.1 to 0.54; estimated 2-year recurrence rate: MMC – 61.6%, Synergo – 18.9%, p=0.0002).

Even in the worst case scenario shown in the fourth panel of the above table, the Synergo group shows nearly 50% reduction in the rate of recurrence compared to the MMC group (HR=0.46; 95% CI=0.23 to 0.91; estimated 2-year recurrence rate: MMC – 59.9%, Synergo – 30.9%, p=0.0219). This worse case scenario analysis was performed based on All Study Patients population. In this analysis, the study subjects were grouped in the same manner as the Evaluable Patients: Randomized As Treated population (*i.e.*, according to the treatment that they actually received). Even if we consider a worst case scenario in which the study subjects are grouped in the same manner as the Evaluable Patients: Randomized as Intended (*i.e.*, according to the treatment initially intended), the Synergo group still shows one third reduction in the rate of recurrence compared to the MMC group (HR=0.67; 95% CI=0.35 to 1.29; estimated 2-year recurrence rate: MMC – 54.4%, Synergo – 38.1%, p=0.2254). It is important to note that the latter worst case scenario analysis represents an unrealistic scenario that does not in any way reflect the actual clinical results of the Synergo device. [As previously discussed, the randomization errors occurred at the central randomization center and were purely administrative. It has no bearing on patient selection, treatment, or follow-up, therefore, is not expected to

introduce any bias on the efficacy results based on the Randomized as Treated patient cohort.]

7.3.7.2 Long-Term Efficacy Analysis

Table 16 presents the survival analysis results for the study patients up to 10 years follow-up using the KM method based on the Evaluable Patients: Randomized As Treated population. **Table 17** presents the KM estimates of the 5-year and 10-year probability of recurrence.

Table 16 - Kaplan-Meier Curves of Long-term Follow-up

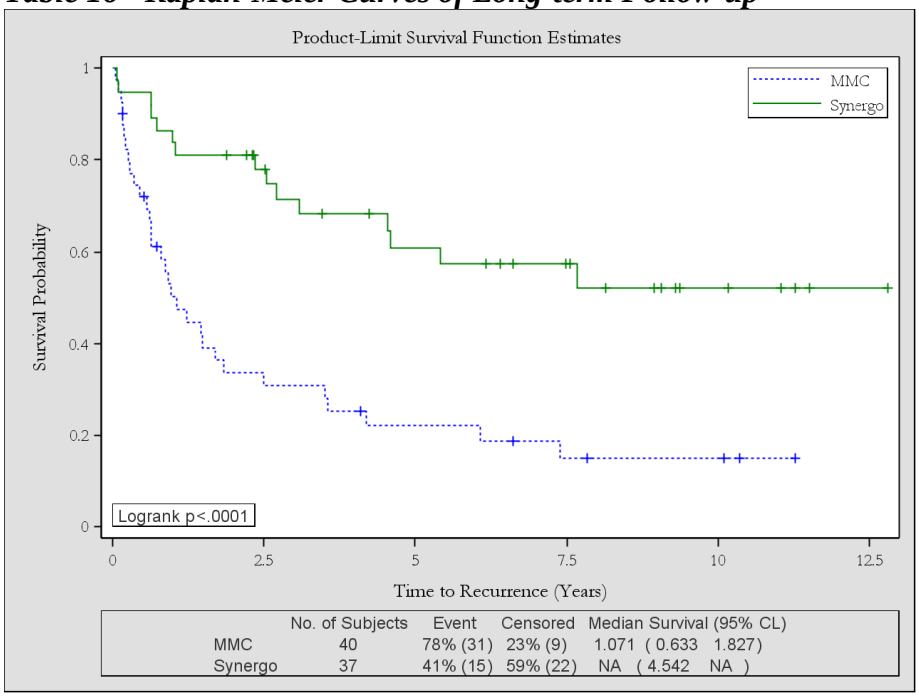


Table 17 - Kaplan-Meier Estimates of Probability of Recurrence

	MMC		**Synergo**	
Time	**Probability**	**s.e.**	**Probability**	**s.e.**
5-year	78.1%	6.9%	39.4%	8.7%
10-year	85.0%	6.3%	48.2%	9.5%
Mean Survival Time	2.45 years	0.455	5.39 years	0.512

As shown in **Table 16** and **Table 17**, even after over 10 years of follow-up, the treatment difference is still notable and highly statistically significant ($p<0.0001$).

The long-term data also included data on patients undergoing radical cystectomy. Four patients, 1 in the Synergo group and 3 in the MMC group, required radical cystectomy due to tumor progression (T>T1) at the time of recurrence. Another three patients, 1 in the Synergo group and 2 in the MMC group, underwent radical cystectomy due to recurrent high-risk, non-muscle-invasive disease. Thus, the bladder preservation rate after 10 years was 95% (40/42) for the Synergo group and 88% (36/41) for the MMC group.

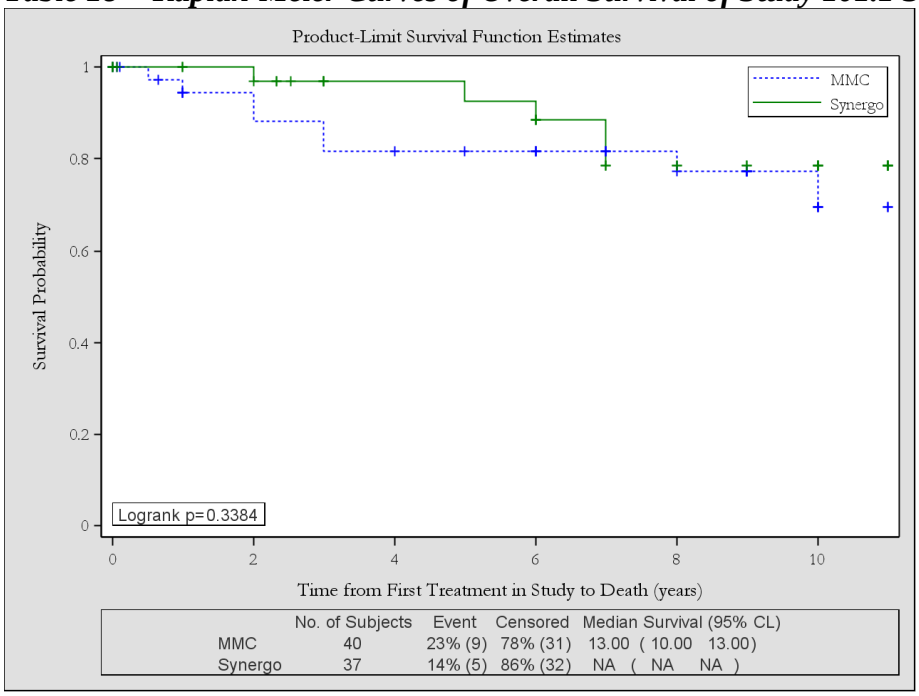
There was a trend for a higher probability of undergoing cystectomy in the MMC group than in the Synergo group, although the difference did not reach statistical significance.

These long-term results further support and confirm the positive Synergo 2-year results.

7.3.7.3 Overall Survival Analysis

Table 18 presents the overall survival analysis for Study 101.1 using the Evaluable Patients: Randomized As Treated population. The overall survival analysis is calculated from time of first study treatment to time of death.

Table 18 - Kaplan-Meier Curves of Overall Survival of Study 101.1 Subjects



The KM estimated death rate at 2 years is 3.23% (s.e.=3.17%) in the Synergo arm and 11.93% (s.e.=5.62%) in the MMC arm.

As shown in **Table 18**, there is no significant difference in the overall survival between the treatment groups, although out of a total of 14 deaths, there were more deaths in the MMC group (n=9) than in the Synergo group (n=5). Deaths were reported since the start of the clinical study in 1994 until late 2006, when the clinical investigators of the pivotal Study 101.1 initiated the collection of clinical follow-up information of the original Study 101.1 subjects. Five deaths were due to tumors in other body organs (not STCCB), 1 was due to cerebral stroke, 1 was due to a heart attack, 2 were due to old age, and 5 were due to unknown causes. No disease specific mortality can be established since cause of death was missing in 5 patients. Although the difference in long-term patient deaths is not statistically significant, it is very clear from the K-M curve that almost all deaths in the Synergo group occurred after 5 years, whereas in the MMC group most of the deaths occurred before three years.

7.3.8 Secondary Efficacy Analysis

Secondary efficacy analyses included: (1) progression of stage and worsening of grade at tumor recurrence; (2) occurrence of CIS and occurrence of urothelial cell carcinoma in the upper tract or in the prostatic urethra; and (3) occurrence of distant metastasis, all within 24 months of follow-up. These analyses were performed based on the Evaluable Patients: Randomized As Treated population.

7.3.8.1 Progression of Stage and Worsening of Grade at Tumor Recurrence

Table 19 and **Table 20** compare previous stage with stage at time of recurrence in the 30 patients who were reported as having tumor recurrence within 24 months follow-up. Previous stage was defined as the most advanced, recorded stage of the resected tumor(s) (upon study entry) according to a histopathology report, and the stage of the tumors recorded as part of the patients history (previous episodes). As can be seen in the following tables, there are no patients with progression in T stage (Ta to T1, or T1 to T>T1) of recurrent tumors from previous stage.

Table 19 - Frequency of Previous Stage in Patients with Recurrent Tumor

	MMC n=23		**Synergo N=7**	
Previous Stage	**N**	**%**	**N**	**%**
Ta	8	34.8%	2	28.6%
T1	15	65.2%	5	71.4%

Table 20 - Test Stage (at Recurrence) Compared to Previous Stage in Patients with Recurrent Tumor

	Test Stage							
Previous Stage	**MMC N=23**				**Synergo N=7**			
Frequency Row Pct	**Ta**	**T1**	**Missing**	**Total**	**Ta**	**T1**	**Missing**	**Total**
Ta	7 87.5%	0 0.0%	1 12.5%	8 100%	2 100.0	0 0.00	0 0.00	2 100%
T1	9 60.0%	3 20.0%	3 20.0%	15 100%	2 40.0%	1 20.0%	2 40.0%	5 100%

Test stage data were available for 24 of the 30 patients with tumor recurrence. Of the 6 patients whose test stage data were not available, 4 patients did not have either tumor stage or grade information as there were no pathology reports available for these patients. For the other 2 patients, a cold cup biopsy was sent to the laboratory for histopathology examination but the pathology examiner could not determine the tumor stage based on the specimen material taken, but the tumor grade was determined and recorded. In the 4 patients without pathology reports, 2 patients were diagnosed with tumor recurrence based on cystoscopy examinations alone. These patients did not return to the clinical center for tumor resection and pathology examination of the findings. One of these patients was a Synergo patient and the other was an MMC patient. The other two patients were diagnosed with tumor recurrence based not only on the cystoscopy examination;

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one underwent cold cup biopsy (Synergo patient) and the other underwent TUR (MMC patient). The pathology results for these patients were not recorded on the CRFs and the pathology reports were not available. It should be noted that one of these MMC patients with missing pathology results also reported with distant metastasis.

Table 21 and **Table 22** compare previous grade with grade at time of recurrence in the 30 patients who were reported with a tumor recurrence within 24 months of follow-up. Previous grade was defined as the most advanced, recorded grade of the resected tumor(s) (upon study entry) according to a histopathology report, and the grade of the tumors recorded as part of the patients' history (previous episodes). As described previously, test grade data were available for 26 of the 30 patients with tumor recurrence. As can be seen in **Table 22**, there is only one (1) MMC pati--- -- - - ---- --- ing in grade (G2 to G3) of recurrent tumors from previous grade. Patien --------- ----- - ---, in the Control group, was reported with a worsening in grade at recurrence from G2 to G3 at 3-month follow-up. The patient presented at pre-treatment as a first episode patient and had 13 tumor sites. The patient completed the study protocol at 3 months follow-up due to recurrence. He reported with progression in stage (Ta to T2) 4 months later and then developed metastasis in the lungs and pelvis 3 months later and soon after that, the patient died.

Table 21 - Frequency of Previous Grade in Patients with Recurrent Tumor

	MMC N=23		**Synergo N=7**	
Previous Stage	**N**	**%**	**N**	**%**
G1	1	4.3%	0	0%
G2	18	78.2%	3	42.9%
G3	4	17.4%	4	57.1%

Table 22 - Test Grade (at Recurrence) Compared to Previous Grade in Patients with Recurrent Tumor

	Test Grade									
Previous Grade	**MMC N=23**					**Synergo N=7**				
Frequency Row Pct	**G1**	**G2**	**G3**	**Missing**	**Total**	**G1**	**G2**	**G3**	**Missing**	**Total**
G1	1 100.0%	0 0.0%	0 0.0%	0 0.0%	1 100%	0	0 .	0 .	0 .	0 100%
G2	9 50.0%	7 38.9%	1 5.6%	1 5.6%	18 100%	0 0.0	2 100.0	0 0.0	1 33.33	3 100%
G3	0 0.0%	1 25.0%	2 50.0%	1 25.0%	4 100%	0 0.0	2 50.0%	1 25.0%	1 25.0%	4 100%

7.3.8.2 Occurrence of CIS and Urothelial Cell Carcinoma

There was no occurrence of CIS or urothelial cell carcinoma in the upper tract or in the prostatic urethra reported in the study.

7.3.8.3 Occurrence of Distant Metastasis

The incidence of distant metastasis was evaluated by additional tests (e.g., x-ray, CT). As shown in **Table 23**, there is no significant difference between the treatment groups regarding the incidence of distant metastasis. Although not statistically significant, it is noteworthy that all 3 cases of metastasis occurred in the MMC group. The three patients in the MMC group reported with distant metastasis, included one patient with a positive finding of distant metastasis on CT examination at tumor recurrence. The other two patients had positive findings of distant metastasis on pelvic-abdominal ultrasound examination.

Table 23 - Incidence of Distant Metastasis

Distant Metastasis	**MMC N=40**		**Synergo N=37**		**P-Value***
	N	**%**	**N**	**%**	
No	37	92.5%	37	100%	0.241
Yes	3	7.5%	0	0%	

*Fisher's exact test

7.3.8.4 Effect of Prognostic Factors on Efficacy Analysis

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 (n=77). All analyses were stratified by treatment group using the stratified log rank test. For prognostic factors that were found to be significantly associated with tumor recurrence, further analyses were performed to determine whether the treatment difference persists after adjustment for each individual prognostic factor. The effects of the following factors were analyzed and are presented in **Table 24**:

- Age
- Gender
- History of recurrence (first episode, recurrent or high recurrent)
- Number of previous occurrences
- Previous tumor stage (T)
- Previous tumor grade (G)
- Previous tumor size (≥2 vs. <2 cm)
- Previous multifocal tumor (>5 vs. ≤5)
- Current number of tumor sites (single tumor vs. multiple tumors)
- Previous prophylactic treatments (with different chemotherapeutic agents; MMC or other drugs), and first episode patients
- EAU risk category
- Clinical center

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Table 24 - Prognostic Factors Analysis for Recurrence

Prognostic Factors		MMC N=40			Synergo N=37			P-Value*
		#Events	N	%	#Events	N	%	
Baseline Demographics								
Gender	Male	20	34	58.8%	5	31	16.1%	0.770
	Female	3	6	50.0%	2	6	33.3%	
Age	≤65	9	15	60.0%	5	20	25.0%	0.232
	>65	14	25	56.0%	2	17	11.8%	
Tumor Characteristics								
History of Recurrence	First Episode	11	15	73.3%	2	12	16.7%	0.0002
	Recurrent	1	11	9.1%	1	11	9.1%	
	High Recurrent	11	14	78.6%	4	14	28.6%	
Number of Previous Occurrences	0	11	15	73.3%	2	12	16.7%	0.108
	1	1	5	20.0%	0	7	0.0%	
	2	3	7	42.9%	2	4	50.0%	
	3+	8	13	61.5%	3	14	21.4%	
Previous Tumor Stage	Ta	8	16	50.0%	2	12	16.7%	0.594
	T1	15	24	62.5%	5	24	20.8%	
	CIS	0	0	0	0	1	0.0%	
Previous Tumor Grade	G1	1	1	100.0%	0	3	0.0%	0.415
	G2	18	32	56.3%	3	23	13.0%	
	G3	4	7	57.1%	4	11	36.4%	
Previous Tumor Size	<2 cm	10	17	58.8%	6	20	30.0%	0.357
	≥2 cm	13	23	56.5%	1	17	5.9%	
Previous Multifocal Tumor	≤5	13	28	46.4%	6	26	23.1%	0.075
	>5	10	12	83.3%	1	11	9.1%	
Current Number of Tumor Sites	Single	7	15	50%	2	16	12.5%	0.269
	Multiple	16	26	62%	5	20	25%	
Previous MMC Treatment	No	17	29	58.6%	6	31	19.4%	0.642
	Yes	6	11	54.5%	1	6	16.7%	
Previous BCG Treatment	No	19	33	57.6%	5	27	18.5%	0.840
	Yes	4	7	57.1%	2	10	20.0%	
Previous Therapy	None/First Episode	15	23	65.2%	3	20	15.0%	0.834
	Prior Therapy	8	17	47.1%	4	17	23.5%	
EAU Risk Group								0.0003
	Intermediate	13	23	56.5%	0	15	0.0%	
	High	10	17	58.8%	7	22	31.8%	
Clinical Center								
Clinical Center	Milan	12	17	70.6%	1	16	6.3%	0.094
	Palermo	4	7	57.1%	2	5	40.0%	
	Beilinson	7	16	43.8%	4	16	25.0%	
Clinical Center	Milan	12	17	70.6%	1	16	6.3%	0.666
	Palermo+Belinson	11	23	47.8%	6	21	28.6%	

*Fisher's exact test.

As shown in **Table 24**, there were no significant effects of demographic factors (e.g., age and gender), number of previous tumor occurrences, number of pre-treatment tumor sites, previous tumor size (>2 vs. <2 cm), previous multifocal tumors (>5 vs. ≤5), previous

tumor stage and grade, previous prophylactic treatments, and clinical center (P >0.05) on the rate of recurrence.

The factors that showed a significant effect on the rate of recurrence included history of tumor recurrence (first episode, recurrent or high recurrent) and EAU risk group. For these significant prognostic factors, further analyses were performed to determine whether the treatment difference persists after adjusting for these factors. The results are shown in **Table 25**. As shown, the recurrence rate remained significantly lower in the Synergo group than in the MMC group even after adjusting for these prognostic factors.

Table 25 - Analysis for Recurrence Adjusting for Significant Prognostic Factors

Treatment Effect for Recurrence	Synergo vs. MMC Hazard Ratio (95% CI)	P-value*
Unadjusted	0.231 [0.099-0.541]	0.0007
Adjusted for type of recurrence	0.174 [0.073-0.417]	<0.0001
Adjusted for EAU risk group	0.160 [0.066-0.386]	<0.0001

*P-value for treatment effect after adjusting for each prognostic factor based on stratified log-rank test.

7.3.9 Safety Analysis

The safety analysis for Study 101.1 is based on All Study Patients (n=83) grouped according to the treatment that they actually received (*i.e.*, "Randomized As Treated"). Safety evaluation includes analysis of the following events:

- Expected adverse events
- Other adverse events
- Serious adverse events
- Systemic adverse events

The expected adverse events include the following events: tissue reaction to the treatment (this may include inflammatory changes, hyperemia, cystitis, etc.), dysuria (including urgency and frequency), urethral stenosis, hematuria, posterior wall tissue reaction, urinary tract infection, bladder wall necrosis, skin allergy and pain.

Posterior wall tissue reaction is classified as an expected adverse event since it may be anticipated either as a result of eradication of unintentional residual bladder tumors in this area, or as an event related to the application of the Synergo. Occasionally, the cumulative effect of the dissipated heat in the area around the location of the RF antenna in the bladder may result in a small, localized area of necrosis in the posterior wall of the bladder. There have been reports of necrotic areas in the bladder with MMC treatment and therefore, the MMC administered in conjunction with the hyperthermia treatment may also contribute to the formation of the posterior wall tissue reaction[13].

Note that posterior bladder wall necrosis is only a transient, expected adverse event involving a focally located yellow medallion and is normally small in size. It is usually noted during follow-up cystoscopy. In the event of occurrence, posterior wall tissue reaction is superficial (no muscle involvement), asymptomatic, and resolves without medical intervention and without residual effects. This adverse event is anticipated due to the nature of the hyperthermia device.

Other adverse events reported in this study (101.1) included false passage, hypotonic bladder, reduced bladder capacity, transient amnesia, anxiety, weakness, fever and urgency.

Serious adverse events reported during the study included bronchial bleeding, suspected myocardial infarction (MI), nephrolithiasis, hydronephrosis cerebrovascular accident (CVA) and leukemia.

7.3.9.1 Expected Adverse Events

The expected adverse events include the following events: tissue reaction to the treatment (e.g., inflammatory changes, hyperemia, cystitis), dysuria (including urgency and frequency), urethral stenosis, hematuria, posterior wall tissue reaction, urinary tract infection, bladder wall necrosis, skin allergy and pain.

The following tables present each of the expected adverse events reported during the study according to the number of patients reporting that event.

Table 26 –Expected Adverse Events by Treatment Group (All Study Patients)

Adverse Events	**MMC N=41**		**Synergo N=42**		**P-Value***
	N	**%**	**N**	**%**	
Dysuria	4	9.8	10	23.8	0.141
Hematuria	2	4.9	3	7.1	1.000
Tissue Reaction	20	48.8	21	50	1.000
Urethral Stenosis	2	4.9	3	7.1	1.000
Skin Allergy	2	4.9	5	11.9	0.433
Pain	-	-	17	40.5	0.000
Posterior Wall Tissue reaction	1	2.4	27	64.3	0.000
Urinary Tract Infection	-	-	3	7.1	0.241
Bladder Wall Necrosis	2	4.9	2	4.8	1.000

*Fisher's exact test.

<u>Dysuria</u>
There was an increase in the rates of dysuria in the Synergo group (10/42, 24%) compared to the MMC group (4/41, 10%), although the difference was not statistically significant. All cases of dysuria were reported as mild, except for 2 cases reported as moderate (1 in the MMC group and 1 in the Synergo group) and 1 case reported as severe (Synergo group). In all cases, dysuria required no treatment intervention, was a transient event that spontaneously resolved within a few days of the inciting treatment. Furthermore, dysuria may occur in both treatment groups as a result of the multiple catheterization procedures and is not specifically related to the hyperthermia treatment.

Hematuria
Few cases of hematuria occurred in both treatment groups (3/42, 7% in the Synergo group and 2/41, 5% in the MMC group). Hematuria may occur as a result of the multiple catheterization procedures and is not specifically related to the hyperthermia treatment.

Tissue Reaction
Tissue reaction includes events such as hyperemia, inflammation, and cystitis. These events are mild tissue reactions to the treatment whether it be MMC or Synergo treatment. These events are anticipated adverse events of the treatments and occurred in about 50% of the patients in both treatment groups.

Urethral Stenosis
Few cases of urethral stenosis occurred in both treatment groups (3/42, 7% in the Synergo group and 2/41, 5% in the MMC group). Urethral stenosis may occur as a result of the multiple catheterization procedures, or as a result of repeated transurethral surgeries or co-morbidity.

Skin Allergy
Seven cases (7/83, 8%) of skin allergy were reported. Five cases (5/42, 12%) in the Synergo group and two cases (2/41, 5%) in the MMC group. Allergic reaction to MMC is an anticipated adverse event and may occur in both treatment groups receiving the drug. In two cases (one in each group), the investigator terminated the patients' study participation due to moderate allergic reaction to MMC. Both events resolved with no residual effect.

Urinary Tract Infection
Three cases (3/42, 7%) of urinary tract infection were reported in the Synergo group. Urinary tract infection may occur as a result of the Synergo treatment or similar treatments requiring insertion of a catheter or may be due to patient co-morbidity. All three cases responded to antibiotic treatment and the events were resolved. The rate of urinary tract infection (7%) reported here is considered low for a procedure involving multiple insertions of an intravesical catheter or instrument.

Bladder Wall Necrosis
Four cases of bladder wall necrosis occurred in both treatment groups (2/42, 5% in the Synergo group and 2/41, 5% in the MMC group). Necrosis may be related either to the Synergo treatment or to patient co-morbidity. In the prophylactic patients, unintentional small residual tumor areas left in the bladder (following tumor eradication) may result in necrosis following Synergo and/or MMC treatment.

These results compare favorably to a meta-analysis on MMC side effects reported by the AUA 1999 guidelines panel (e.g., cystitis rate 20%) and by another independent analysis (Boehle, J Urol 2003).

Since pain and posterior wall tissue reaction were the only adverse event categories found to be significantly different between the two treatment groups, a further analysis of the specific events in these adverse event categories in the Synergo group was conducted and

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described below. Both pain and posterior wall tissue reaction are anticipated adverse events.

Pain/spasms

Table 27 presents the specific events included in the adverse event category for pain according to severity.

Table 27 - Pain according to Severity in the Synergo Group

Pain	**Severity**			
	Mild	**Moderate**	**Severe**	**Total**
	N	**N**	**N**	**N**
Bladder spasms	3	3	1	7
Intolerability to treatment	-	2	-	2
Pain	4	1	2	7
Urethral pain	-	1	-	1
Total no. of patients	7	7	3	17

Bladder spasms were reported in 7 patients. Bladder spasms are contractions of the bladder muscles as a result of the bladder irritation. Treatment solution may leak out of the bladder as a result of these contractions. Bladder spasms were usually associated with mild patient discomfort, and therefore were grouped with pain, although discomfort would be considered a very mild form of pain. In one patient bladder spasms were severe and this patient withdrew from further the hyperthermia treatment after two treatments. Bladder spasms were moderate in three patients. In these 3 patients, bladder spasms occurred during 1-3 (out of 12) treatment sessions and the treatment time during these sessions was shortened by 10-30 minutes. In the remaining three patients bladder spasms were mild and did not affect the treatment in any way.

Intolerability to treatment was reported in 2 patients. Intolerability to treatment may be associated with some pain or discomfort of the treatment procedure. In both patients the event occurred during one treatment session (out of 12) and the treatment time was shortened due to the event.

Pain other than spasms and intolerability was reported in 8 patients (7 patients reported pain and 1 patient reported urethral pain). Two patients reported severe pain. In one patient, 5 treatment sessions were shortened by 10-30 minutes, 2 treatment sessions were administered without heat, and 3 treatment sessions were performed per protocol, for a total of 11 treatment sessions. This patient refused the last treatment session. In the second patient with severe pain, the third treatment session was shortened by 10 minutes and the patient only received a total of 6 treatment sessions. Two patients reported moderate pain. One patient reported moderate pain and anxiety 5 minutes into the treatment procedure. This patient withdrew consent and continued treatment without hyperthermia. The second patient reported moderate urethral pain. For this patient, 2 treatment sessions were shortened by 10-15 minutes, 5 treatment sessions were performed per protocol, and the last 5 treatment sessions were administered without heat due to pain.

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Four patients reported mild pain. In one patient, two treatment sessions were shortened by 20-30 minutes, one treatment session was administered without heat, 3 treatment sessions were not performed at the request of the patient and 6 treatment sessions were performed per protocol, for a total of 12 treatment sessions. In another patient, no treatment sessions were shortened, but the patient only received eight treatment sessions due to the pain. The other 2 patients reported mild pain during only 1 of 12 treatment sessions, and this event did not affect the treatment in any way (i.e., treatment sessions were not shortened).

Out of a total of 426 treatments sessions in the Synergo group, there were only 10 treatment sessions (4 patients) that were shortened and 7 treatment sessions (3 patients) performed without hyperthermia due to pain. There was only one patient that terminated the study due to pain who also experienced anxiety along with the pain and withdrew consent.

In summary, 24% (10/42) of the patients in the Synergo group reported pain or intolerability to treatment in only 22 of 426 (5%) of the total treatment sessions performed. Severe pain occurred in only 2 patients in 4 treatment sessions. Seventeen percent (7/42) of the patients in the Synergo group experienced bladder spasms in 5% (21/426) of the total treatment sessions performed. Severe bladder spasms occurred in only 1 patient during 2 treatment sessions. In all occurrences, the events were localized and transient during treatment and resolved without any residual effects, except for the one patient who experienced severe bladder spasms in 2 treatment sessions, who received treatment the second time the event occurred and who eventually withdrew consent.

No serious adverse events were reported concerning pain or bladder spasms. Hospitalization was not extended. No extra treatment was required, and there were no sequela from these events.

Posterior Wall Tissue Reaction

Table 28 presents the specific events included in the adverse event category for posterior wall tissue reaction according to severity. The specific events are posterior wall hyperemia, posterior wall inflammation, posterior wall eschar, and posterior wall ulceration. These events occurred due to the location of the RF antenna in the bladder. In some cases there was a cumulative effect of the dissipated heat in the area around the antenna causing a small, localized area of superficial tissue reaction (hyperemia, inflammation, necrosis, or ulceration) in the posterior wall.

Table 28 - Posterior Wall Tissue Reaction according to Severity in the Synergo Group

Posterior Wall Tissue Reaction	**Severity**			
	Mild	**Moderate**	**Severe**	**Total**
	n	**n**	**n**	**n**
Posterior wall hyperemia	1	1		2
Posterior wall inflammation	1			1
Posterior wall eschar	15	4	4	23
Posterior wall ulcer	1			1
Total number of patients	18	5	4	27

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As shown in **Table 28**, 2 patients reported posterior wall hyperemia and 1 patient reported posterior wall inflammation. These events were mild tissue reactions in the posterior wall of the bladder. There were a total of 23 patients with posterior wall eschar and 1 patient with posterior wall ulceration (with no evidence of muscle involvement). The majority of these events were mild (18/42, 43%) or moderate (5/42, 12%). Overall, there were only 4 (4/42, 10%) Synergo patients who experienced severe posterior wall eschar.

All of these events were noted during follow-up cystoscopy, superficial (no muscle involvement), and resolved without medical intervention. It is important to note that none of the patients with these findings were symptomatic and none reported any complaints relating to these findings. These events resolved without any residual effects in 22 patients. In 5 patients, these events resolved with only residual signs of hyperemia.

Posterior wall tissue reaction (all degrees of severity) is an anticipated side effect of the device. This device side effect is not the same as the more severe side effects seen with other hyperthermia devices, for example burns, as it is much less severe, superficial (no muscle involvement), asymptomatic, resolved without medical intervention and without significant residual effects.

Conclusions

The safety analysis demonstrates that most of the expected adverse events were common amongst both treatment groups. The only adverse events that presented significant difference between the treatment groups were pain and posterior wall tissue reaction, which were higher in patients treated with Synergo treatment than in patients treated with MMC treatment. These findings are anticipated due to the nature of the hyperthermia device. All these events were localized, transient and resolved without any significant residual effects.

7.3.9.2 Other Adverse Events

Other adverse events reported in Study 101.1 included false passage, hypotonic bladder, reduced bladder capacity, transient amnesia, anxiety, weakness, fever and urgency. **Table 29** is a cross-tabulation of other adverse events observed by treatment group.

Table 29 – Other Adverse Events (All Study Patients)

Adverse Events	MMC N=41		Synergo N=42		P-Value*
	N	%	N	%	
Anxiety	-	-	1	2.4%	1.000
Amnesia	-	-	1	2.4%	1.000
Hypotonic bladder	-	-	1	2.4%	1.000
Reduced bladder capacity	-	-	2	4.8%	0.494
False passage	-	-	1	2.4%	1.000
Fever & Urgency	1	2.4%	-	-	1.000
General weakness	1	2.4%	-	-	1.000

*Fisher's exact test.

Anxiety
One patient from the Synergo group reported anxiety (1/42, 2%). This event resulted in the patient withdrawing his consent to receive the Synergo treatment.

Amnesia
One patient from the Synergo group reported transient amnesia (1/42, 2%). This patient reported transient amnesia a day after the third treatment. This event was reported as unrelated to treatment. The event resolved with no residual effect after the patient received treatment.

Hypotonic Bladder
One patient from the Synergo group was reported with hypotonic bladder (1/42, 2%). The event of hypotonic bladder was discovered in a routine uroflowmetry examination. The patient had a high bladder volume (937cc) and no change in the bladder wall pressure was observed during the filling part of the examination. No significant urinary residual volume was witnessed post voiding. The patient resumed his treatment and no medical intervention or treatment was required. This clinically non-significant event was reported as unrelated to treatment.

Reduced Bladder Capacity
Two patients from the Synergo group were reported with reduced bladder capacity. Both events were considered treatment related and reported as ongoing during the study. The two patients had bladder volumes of 313 ml and 250 ml, measured by uroflowmetry. Since these cases were considered relatively mild reductions in bladder capacity no medical intervention or treatment were required. This adverse event has been reported in the literature for intravesical chemotherapy or immunotherapy.

False Passage
One patient from the Synergo group was reported with false passage (1/42, 2%). False passage was related to the treatment procedure involving multiple insertions of a Foley like catheter, albeit somewhat larger (20F). The investigator reported that the event was related to the device. The event may also be related to either multiple catheter insertions, patient co-morbidity, or unknown causes.

Fever and Urgency
One patient from the MMC group reported fever and urgency (1/41, 2%). The event fever and urgency did not occur during a treatment session and can be related to the MMC treatment, patient co-morbidity or unknown causes. This event resolved without residual effects.

Weakness
One patient from the MMC group reported weakness (1/41, 2%). The event of weakness was reported during a treatment session. The event was transient and resolved with no residual effects.

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Conclusions

The safety analyses demonstrate that there is no significant difference in the incidence of other adverse events between the treatment groups. All these adverse events, other than the reduced bladder capacity and the false passage (although these adverse events did not pose a serious risk to the patients), resolved with no residual effects.

7.3.9.3 Serious Adverse Events

Serious adverse events reported during the study included bronchial bleeding, suspected myocardial infarction (MI), nephrolithiasis, hydronephrosis, cerebrovascular accident (CVA) and leukemia.

As shown in **Table 30**, 3 SAEs were reported in each study group. As can be seen from the discussion below, none of the 3 SAEs in the Synergo group were related to the Synergo treatment.

Table 30 –Serious Adverse Events by Treatment Group (All Study Patients)

Adverse Events	MMC N=41		Synergo N=42		P-Value
	N	%	N	%	
Bronchial bleeding	-	-	1	2.4%	1.000
Nephrolithiasis	-	-	1	2.4%	1.000
Hydronephrosis	1	2.4%	-	-	1.000
Suspicious MI	-	-	1	2.4%	1.000
CVA	1	2.4%	-	-	1.000
Leukemia	1	2.4%	-	-	1.000

Bronchial bleeding
One 60 yr old male patient in the Synergo group was reported with bronchial bleeding. He suffered from severe chronic lung disease (COPD) and was treated with broncho-dilators (by inhalation and P.O.) as well as prolonged steroid and antibiotic treatments. The patients' medical history also included upper lobectomy due to adenocarcinoma of the lung, hypertension and cardiac arrhythmia. He suffered few episodes of hemoptysis prior to the Synergo treatment. The patient complained of hemoptysis between the 10th and 11th treatments and was treated outside the country (in the clinical center that had treated his lung disease). The event was considered by the physician to be a serious adverse event unrelated to the drug (MMC) or to the Synergo device. After the event resolved he continued his remaining treatments as scheduled.

Nephrolithiasis
One 35 yr old female patient in the Synergo group was reported with nephrolithiasis. The patient was diagnosed with nephrolithiasis during the study. She was hospitalized and required only conservative treatment (no surgical procedure was needed). The patient remained asymptomatic during the rest of her treatments and follow- up. The event was considered by the physician to be a serious adverse event unrelated to the treatment. She continued her remaining treatments as scheduled.

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Hydronephrosis
One 81 yr old female patient in the MMC group was reported with hydronephrosis. The patient was diagnosed with hydronephrosis during the study. The event was moderate in severity and was considered by the physician to be a serious adverse event related to the patient's co-morbidity and unrelated to the treatment. The event required hospitalization and treatment and resolved with a residual effect. The patient had a previous scar of the right ureter meatus, which has been subsequently submitted to a resection.

Suspected myocardial infarction (MI)
One 70 yr old male patient in the Synergo group was reported with suspected MI. The patient suffered from hypertension and was treated with calcium channel blockers and ACE inhibitors. Before starting his 7th Synergo treatment he complained of chest pain and blood tests revealed mild CPK elevation with no other related cardiac enzymes elevation. He was hospitalized for observation and the CPK levels returned to normal values. He was discharged from the hospital after 5 days and continued his remaining treatments as scheduled. The event was considered by the physician to be a serious adverse event unrelated to the drug (MMC) or to Synergo.

Cerebrovascular Accident (CVA)
One 74 yr old male patient in the MMC group was reported with cerebral vascular accident (CVA). The patient received the full treatment course (12 sessions) and died as a result of this CVA or stroke during the course of the study follow-up (after the six month follow-up visit). This patient had no adverse event recorded during treatment or follow-up and complied with the study protocol until the six-month follow-up visit. The event and death were considered by the physician to be a serious adverse event unrelated to the drug (MMC).

Leukemia
One 72 yr old male patient in the MMC group was reported with Leukemia. The patient received the full treatment course (12 sessions). The patient was diagnosed with leukemia a short time after study entry, although the disease and death as a result of the leukemia were considered by the physician to be a serious adverse event unrelated to the drug (MMC). The only event recorded for this patient during the course of the clinical study was an anticipated and transient adverse event consisting of mild tissue reaction (in the bladder), which spontaneously resolved following treatment. The tissue reaction was related to the MMC treatment, mild, required no treatment and resolved without any residual effect.

Conclusions

None of aforementioned serious adverse events occurred during a treatment session or as a result of the treatment session. All events in the Synergo group resolved with no residual effects. In the MMC group, the event of hydronephrosis resolved with a residual effect and the two deaths (CVA and Leukemia) were considered by the physician to be serious adverse events unrelated to the Control treatment.

All serious adverse events were reported by the physicians (investigators) as not related to the MMC or to the Synergo treatments.

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7.4 Efficacy Conclusions

The efficacy analysis results demonstrated that the Synergo treatment was significantly superior to MMC treatment. Kaplan-Meier estimated 2-year recurrence rates are presented in **Table 31** for all patient cohorts.

Table 31 - Kaplan-Meier estimated 2 year recurrence rate, Study 101.1 (all patient groups)

Patient Population	**MMC**	**Synergo**	**Log-Rank P**
Evaluable Patients: Randomized As Treated (N=77)	61.6% (n=40)	18.9% (n=37)	0.0002
Evaluable Patients: Randomized As Intended (N=77)	54.4% (n=41)	25.0% (n=36)	0.0097
Per-Protocol cohort (N=75)	61.6% (n=40)	17.1% (n=35)	0.0002
All Study Patients “Worst Case Scenario” (N=83)	59.9% (n=41)	30.9% (n=42)	0.0219

The efficacy results demonstrate a highly statistically significant difference between the Synergo treatment and the MMC treatment for all patient cohorts, including the All Study Patients “worst case scenario” analysis.

The superior result of the Synergo treatment was also maintained for long-term follow-up, with 39% and 48% recurrence rates compared to 78% and 84% recurrence rates for MMC treatment, at 5 and 10 years follow-up, respectively.

The efficacy analysis also revealed no patients with progression in tumor stage in the Synergo group. Furthermore, only one (1) patient was reported to have a worsening in grade, and that patient was in the MMC group. Although at 3 month follow-up the patient completed the study protocol due to recurrence, he had progression in stage (Ta to T2) 4 months later, and then developed metastasis in the lungs and pelvis 3 months later, and soon after that the patient died.

The efficacy analysis demonstrates that there was no significant difference between the treatment groups regarding the incidence of distant metastasis. Although not statistically significant, it is noteworthy that all 3 cases of metastasis occurred in the MMC group. The three patients in the MMC group reported with distant metastasis, included one patient with a positive finding of distant metastasis on CT examination at tumor recurrence. The other two patients had positive findings of distant metastasis on pelvic-abdominal ultrasound examination.

The prognostic factors that showed a significant effect on the rate of recurrence included history of tumor recurrence (first episode, recurrent or high recurrent) and EAU risk group. For these significant prognostic factors, further analyses were performed to determine whether the treatment difference persists after adjusting for these factors. The results showed that the recurrence rate remained significantly lower in the Synergo group than in the MMC group after adjusting for these prognostic factors.

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7.5 Safety Conclusions

The expected adverse events that were reported for the Synergo and MMC treatment groups in Study 101.1 included: dysuria (24% vs. 10%, respectively), hematuria (7% vs. 5%, respectively), tissue reaction (50% vs. 49%, respectively), urethral stenosis (7% vs. 5%, respectively), skin allergy (12% vs. 5%, respectively), pain and bladder spasms (41% vs. 0%, respectively), posterior wall tissue reaction (64% vs. 2%, respectively), bladder wall necrosis (5% vs. 5%, respectively) and urinary tract infection (7% vs. 0%, respectively).

The safety analysis demonstrates that most of the expected adverse events were common amongst both treatment groups. The only adverse events that presented significant difference between the treatment groups were pain and posterior wall tissue reaction, which were higher in patients treated with Synergo. These findings are anticipated due to the nature of the hyperthermia device. Both pain and posterior wall tissue reaction were transient, and the latter was totally asymptomatic.

Other adverse events that were reported in Study 101.1 included: one patient each in the Synergo group with false passage, hypotonic bladder, transient amnesia and anxiety, and 2 patients with reduced bladder capacity. One patient with weakness and one with fever and urgency (2%) were reported in the MMC group. There is no significant difference in the incidence of other adverse events between the treatment groups. All events had no sequalae and were not device related, expect for false passage and reduced bladder capacity.

Similar adverse events as reported with the Synergo device have been reported with chemotherapy intravesical instillations, as well. The most frequently observed immediate symptoms are irritative lower urinary tract problems, including dysuria, frequency/nocturia, urgency, pain and cramping and passing of debris in the urine, including blood or clots. Patients also experience bacterial cystitis, urinary incontinence and bladder perforation[7]. Intravesical instillation of mitomycin in patients who have undergone resection of superficial bladder tumors had led to the development of indolent asymptomatic ulcers at the resection site which may persist for months before healing[3,4]. Severe eczematous symptoms in patients receiving intravesical mitomycin appear to be due to delayed hypersensitivity reaction, which also appears to be responsible for the bladder irritation and cystitis, which follow intravesical MMC[5,6]. Intravesical chemotherapy administration has also led to severe bladder contracture[7,8].

Table 32 adapted from the AUA bladder Cancer Guidelines (1999) presents the rates of commonly reported adverse events for other intravesical agents for prophylactic treatment of STCCB:

Table 32: Summary of Toxicity Reported for Common Intravesical Agents

Toxicity	**MMC**	**BCG**
Local		
Frequency/Nocturia	42% (26-59%)	63% (48-76%)
Dysuria	35% (30-41%)	75% (64-84%)
Irritative Symptoms	18% (12-26%)	Too varied to calculate
Pain/Cramps	10% (6-14%)	12% (7-18%)
Hematuria	16% (7-28%)	29% (22-36%)
Incontinence	1% (0.4-4%)	4% (3-6%)
Bladder Contracture*	5% (2-11%)	3% (2-5%)
Systemic		
Flu-like	20% (4-48%)	24% (18-31%)
Fever/Chills	3% (1-7%)	27% (22-32%)
Arthalgias	9% (0.1-47%)	5% (1-13%)
Myelosuppression	2% (0.3-7%)	1% (0.1-4%)
Nausea/Vomiting*	9% (1-26%)	9% (6-14%)
Skin Rash	13% (8-19%)	6% (3-10%)
Other	3% (0.5-8%)	23% (19-27%)
Infectious		
Bacterial Cystitis*	20% (17-23%)	20% (13-8%)
Epid/Prost/Urethral	4% (2-9%)	5% (4-8%)
Pneumonia	0.2% (0-2%)	1% (0.2-3%)
Systemic	NR	4% (2-5%)
Treatment Continuation		
Incomplete	9% (2-14%)	8% (5-10%)
Interruption	11% (8-16%)	7% (5-11%)

*Corresponding rates for TUR alone (without chemotherapy) are 0.8% for bladder contracture, 0.9% for nausea/vomiting and 20% for bacterial cystitis. NR = not reported.
Adapted from the AUA Bladder Cancer Guidelines Panel Report on the Management of Non-Muscle-Invasive Bladder Cancer, 1999.

Thus, the potential complications caused by the Synergo treatment are known and previously reported in the literature with chemotherapy or immunotherapy treatments.

Six serious adverse events were reported in Study 101.1 included: bronchial bleeding, suspected myocardial infarction (MI), nephrolithiasis, hydronephrosis cerebrovascular accident and leukemia. Three SAEs were reported in each study group and none of the 3 SAEs were related to the Synergo treatment.

None of aforementioned serious adverse events occurred during a treatment session or as a result of the treatment session. All events in the Synergo group resolved with no residual effects. In the MMC group, the event of hydronephrosis resolved with a residual effect and the two deaths (CVA and Leukemia) were considered by the physician to be serious adverse events unrelated to the MMC.

All serious adverse events were reported by the physicians (investigators) as not related to the MMC or to the Synergo treatments.

In summary, the safety analysis of adverse events demonstrate that the benefits offered by Synergo treatment as demonstrated by the efficacy results, outweigh the risks of these potential adverse events.

7.6 Overall Conclusions

The AUA Bladder Cancer Clinical Guidelines[2] (Journal of Urology, Dec. 2007) report that Mitomycin or BCG is appropriate for patients with "multifocal and/or large volume, histologically confirmed, low grade Ta or with recurrent low grade Ta bladder cancer." For these same patients, maintenance BCG or MMC may be considered. Furthermore, the Guidelines recommend only BCG (with maintenance) for CIS and high-grade Ta or T1 tumors. Adjuvant intravesical chemotherapy or immunotherapy is therefore an acceptable prophylactic treatment for STCCB. Furthermore, hyperthermia is used in the treatment of cancer, both alone and in conjunction with other established methods of treatment, e.g., radiation, chemotherapy and immunotherapy[10]. It is also well established that cytotoxic action of many chemotherapeutic agents may be enhanced by moderate elevation of tissue temperature[11,12].

The Synergo device combines both these aspects of treatment by delivering hyperthermia treatment simultaneously with intravesical MMC instillations. The current study compared the Synergo treatment to the traditional intravesical MMC treatment for the risk of tumor recurrence (primary efficacy endpoint), risk of tumor progression (secondary efficacy endpoint) and adverse events (safety endpoint).

The results of the PMA pivotal Study 101.1, comparing Synergo treatment to MMC treatment, demonstrated a significantly lower estimated 2-year recurrence rate in the Synergo group compared to the MMC group (19% vs., 62%, respectively), for the Evaluable Patients: Randomized As Treated population. The superior result of the Synergo treatment was also maintained for long-term follow-up, with 39% and 48% recurrence rates compared to 78% and 84% recurrence rates for MMC treatment, at 5 and 10 years follow-up, respectively.

The safety analysis demonstrates that most of the expected adverse events were common among both treatment groups. The only expected adverse events that presented significant difference between the treatment groups were pain and posterior wall tissue reaction, which were higher in patients treated with Synergo compared to MMC. These findings are anticipated due to the nature of the hyperthermia device. Both pain and posterior wall tissue reaction were transient, and the latter was totally asymptomatic. Other adverse events other than the reduced bladder capacity and false passage (although these adverse events did not pose a serious risk to the patients) resolved with no residual effects. Similar adverse events have been known to be reported with chemotherapy or immunotherapy intravesical instillations, as well. All serious adverse events were reported by the physicians (investigators) as not related to MMC or to the Synergo treatments.

Results from pivotal Study 101.1 are further supported by another randomized, controlled study comparing the Synergo treatment to BCG (Study 102.1). This study is summarized in the next section. Furthermore, the Synergo results from Study 101.1 and Study 102.1 were combined and compared to the control arm of Study 101.1 (MMC) and the control

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arm of Study 102.1 (BCG) and to a systematic meta-analysis review of the scientific literature reported for these conventional treatments (i.e., MMC and BCG). The supportive data are provided in the following sections.

In summary, the potential adverse events caused by the Synergo are known and previously reported in the literature with other similar devices and chemo or immuno-therapy treatments. It is also reasonable to conclude that in a significant portion of the intended patient population, the use of the Synergo system will produce clinically significant results. Consequently, the benefits offered by the Synergo system as demonstrated by the clinical effectiveness results, outweigh the risks of potential complications.

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8 CLINICAL INVESTIGATIONS – SYNERGO vs. BCG STUDY 102.1

8.1 General Information

Study 102.1 (Synergo vs. BCG) is a controlled, randomized and ongoing study, provided in support of the pivotal Study 101.1 results. The purpose of the study is to compare Synergo treatment to intravesical instillation of BCG immunotherapy, for prophylactic treatment in patients with intermediate high risk STCCB. At data lock, a total of 104 patients were enrolled in the clinical study. Of these, 51 patients were treated with Synergo.

The study was designed with a sample size of 300 patients. Since only 104 patients have been enrolled at data lock in this ongoing study, it is not anticipated to observe a statistically significant difference in efficacy (or safety). Furthermore, it should be stressed here that the purpose of submitting the results of Study 102.1 is not to conclusively evaluate the endpoints of the study. Rather, the purpose of submitting the results of Study 102.1 is to demonstrate the consistency of the safety and efficacy results for the Synergo treatment in a second randomized, controlled, clinical study.

8.2 Summary of Study Protocol

Both studies 101.1 and 102.1 were designed to compare Synergo with two different prophylactic treatments for the treatment of STCCB.

The eligibility criteria were very similar between Study 102.1 and Study 101.1, requiring inclusion of intermediate or high-risk STCCB patients. The similarities and differences in the eligibility criteria are summarized in **Table 33**.

Table 33 – Comparison of Eligibility Criteria

Study 101.1 Inclusion Criteria	**Study 102.1 Inclusion Criteria**
STCCB pathology findings with resected Stage Ta or T1 and Grade G1-G3 (Patients with Ta primary and solitary lesions will be excluded.)	STCCB pathology findings with any G3 or any T1 or Multifocal (>1) Ta lesions and/or multiple recurrences (>2) of Ta lesions in the last 24 months. (Note: This study protocol also includes positive CIS patients – although they had a different endpoint and were analyzed separately.)
Complete tumor eradication must be possible	Complete tumor eradication must be possible
Life expectancy of >24 months	Life expectancy of >24 months
(specified in exclusion criteria below)	WHO performance status 0-2
Able to understand the study	(not specifically stated but part of informed consent)
Willing to sign informed consent	Willing to sign informed consent
Study 101.1 Exclusion Criteria	**Study 102.1 Exclusion Criteria**
Ta, G1, single transitional tumors at first episode of disease	(not specifically stated – but indicated in above inclusion criteria)
T> T1 transitional tumors	Previous history of Transitional Cell Carcinoma of the bladder stage T2 or higher
Bladder tumors other than transitional tumors	Bladder tumors other than transitional cell carcinoma

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Study 101.1 Inclusion Criteria	Study 102.1 Inclusion Criteria
Transitional tumors of the bladder involving the prostatic urethra and primary transitional tumors of the prostatic urethra	Transitional cell carcinoma of the bladder involving the urethra or upper urinary tract
Solitary, multifocal or associated carcinoma in situ (CIS) at entry on-study	(CIS patients are included – although they are analyzed separately)
Clinical presence of distant or lymphatic metastasis	Clinical presence or previous history of regional spreading or distant metastases
Performance status WHO > 2	(specified in above inclusion criteria)
Patients who cannot be followed-up properly	Patients who cannot be followed up properly or are unable to collaborate
Presence of another tumor	Coexistence of another primary malignant tumor other than BCC of the skin
Well known allergy to topical or systemic Mitomycin C administration	Known allergy to MMC or BCG
Previous intravesical instillations within 3 months before the first session of their treatment is scheduled or systemic cancer treatment with immunotherapy, cytotoxic drugs or radiotherapy	- Intravesical MMC treatments during the last 12 months - Previous intravesical BCG therapy: - Any intravesical BCG therapy in the last 24 months prior to the present TURBT. - More than 6 intravesical instillations in the last 48 months prior to the present TURBT.
Untreated urinary tract infection or recurrent severe bacterial cystitis	Active intractable or uncontrollable UTI
Patients suffering from large BPH	(not specified)
Neurogenic bladder	Urinary incontinence
Persistent hematuria not due to known tumor	Urethral bleeding or persistent hematuria
Urethrorragia	(not specified)
Urethral strictures or other urethral pathology	Urethral stricture impeding 20F catheterization
Patients mentally unable to collaborate	(not specified but included in inclusion criteria)
(Not specified)	Additional criteria learning from the first study: - Previous pelvic radiotherapy or systemic chemotherapy - Partial cystectomy - Diverticulum of bladder larger than 1cm in diameter - Residual urine (>100cc) and bladder volume (<150cc) are measured by ultrasound and/or uroflowmetry - Pregnant or lactating women
(Not Relevant)	Additional criteria relevant to BCG treatment: - Active tuberculosis or BCG infection - Patients who experienced BCG life threatening sepsis - Known impaired immune response, positive HIV serology, patients receiving systemic steroids or immunosuppressive therapy - Hematological disorders; leukocytes < 3500, platelets < 100,000 - Kidney or liver function disorders (more than 1.5 times upper normal limit)

The Synergo treatment consists of 6 weekly induction sessions and 6 maintenance sessions. The Control group includes one vial of BCG administered in 6 weekly induction sessions and 3 weekly repeated maintenance sessions (3x3). Both groups included induction and maintenance treatment phases administered over a period of one year.

The difference between the Synergo treatment and follow up in Study 101.1 and Study 102.1 is shown in **Table 34**.

Table 34 – Comparison of Synergo treatment and Follow-up

Study 101.1 Synergo Treatment	**Study 102.1 Synergo Treatment**
- 40 mg of MMC in 100 ml delivered as 2 x 20 mg MMC in 50 ml portions/ 0.5 hr, with hyperthermia 42±2°C - 8 weekly inductive sessions - 4 monthly maintenance sessions	- 40 mg of MMC in 100 ml delivered as 2 x 20 mg MMC in 50 ml portions/ 0.5 hr, with hyperthermia 42±2°C - 6 weekly inductive sessions - 6 maintenance sessions at 6-8 weeks intervals
Study 101.1 Follow-up	**Study 102.1 Follow-up**
Every 3 months up to 24 months	Every 3 months up to 24 months
Urine cytology Cystoscopy with biopsies from any suspected areas Periodic blood tests Uroflowmetry recommended quarterly I.V.P. after 1 year, as needed Abd-pelvic US after 1 year, as needed Bone scan after 2 years, as needed Chest X-ray after 2 years, as needed	Urine cytology Cystoscopy with biopsies from any suspected areas and in cases of positive urine cytology Mandatory biopsies of pre-treatment diagnosis of T1G3 or any tumor with concomitant CIS Periodic blood tests and urinalysis Uroflowmetry recommended at 1 year Pelvic CT recommended at 1 year

Study 102.1 patients were randomized to either Synergo ("Synergo Treatment" or "Synergo Group") or BCG ("BCG Treatment" or "Control Group") in a similar manner to Study 101.1 in which the patients were randomized to either Synergo or MMC.

The primary efficacy endpoint in both studies was to compare recurrence rates (recurrence-free survival) between the Synergo treatment and a Control group. As in Study 101.1, the primary endpoint assessment of tumor recurrence is determined based on a positive histology report from a cold-cup or TUR biopsy in Study 102.1. Study 102.1 also included CIS patients with a separate efficacy endpoint and analyzed separately. The efficacy analysis for the CIS patients is not provided here.

The secondary efficacy endpoints in both studies was to compare tumor progression rate and/or metastatic disease between the study groups. The assessment of tumor progression is also determined based on the tumor grade and stage reported in the histology report from a cold-cup or TUR biopsy and distant metastasis is determined based on pelvic CT.

Safety assessment of the study included evaluation of adverse events during the course of treatment and follow-up.

8.2.1.1 Statistical Methods Planned in Protocol

8.2.1.1.1 Determination of Sample Size

The primary endpoint of the study is time to recurrence of STCCB. The null hypothesis is that there is no difference in the rate of recurrence between the study groups. The

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alternative hypothesis is that the rate of recurrence is lower in the Synergo group. The log rank test was used to test the null hypothesis.

In previous studies of the Synergo treatment, approximately 75% of the patients remained recurrence free at two years. According to the literature, approximately 60% of the patients treated with BCG are expected to be recurrence free at two years. Using these estimates for expected efficacy, for 5% type I error and 80% power, with 2 years of follow-up, a total of 237 patients are required. Assuming a drop-out rate of 20%, a total of 300 patients will be randomized, 150 in each study group.

8.2.1.1.2 Statistical Analysis Planned in Protocol

The statistical analyses planned for Study 102.1 are similar to the statistical analyses performed for Study 101.1. For comparison of time to event data, the log rank test will be used. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the Chi-square test or Fisher's exact test will be used as appropriate. Stratified analyses will be performed to explore any potential subgroup differences in terms of safety and efficacy. No adjustment for multiple comparisons will be made. Regression models will be used to evaluate baseline covariates that may be prognostic of STCCB or other secondary endpoints, or to adjust for baseline imbalance.

The analysis of all adverse events will include incidence tables calculated both on per-patient and per-session basis, and will include incidence tables by severity, relationship to treatment and baseline parameters.

8.2.1.2 Interim Analysis

While the Company intends to perform a limited analysis of data from Study 102.1 prior to conclusion of the study, we do not believe a formal interim analysis plan is necessary since the company does not intend to stop the trial based on the interim results. In addition to the primary goal of this study, it is our intent to utilize the results obtained from the ongoing Study 102.1 as supportive data for the PMA submission, where Study 101.1 is the pivotal study. For the interim looks at the data, only the point estimate and the confidence intervals will be produced to evaluate the treatment effect and no significance testing will be performed. These interim results will not be disclosed to the clinical investigators or the staff, unless the safety data demands such disclosure for ethical reasons.

8.3 Study Results

8.3.1 Introduction

At the end of this study, a difference in efficacy between the treatment groups is anticipated in favor of the Synergo treatment group. Since only 104 patients have been enrolled at data lock date in this ongoing study, it is not anticipated that a statistically significant difference in efficacy (or safety) would be observed. No statistical tests were performed for differences between treatment groups.

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8.3.2 Analysis Population

The efficacy analysis described here is based on data from the study sample consisting of 104 patients (53 BCG group and 51 Synergo group) who were enrolled in the study as of database closure.

Table 35 displays the number of patients that were included in the patient cohorts.

Table 35 – Number of patients included in study cohorts

	BCG n (%)	**Synergo n (%)**
All Study Patients	53 (51%)	51 (49%)
Evaluable Patients (for efficacy analysis)	48 (53%)	42 (47%)

Safety data is presented for all patients for whom safety data was available as of database closure (n=98) and efficacy data is presented for 90 Evaluable Patients who completed at least 6 treatment sessions and had at least the first cystoscopy follow-up examination.

8.3.3 Baseline Characteristics

The descriptive statistical evaluations presented in this section include all available data from all patients.

8.3.3.1 Demographics

Table 36 presents the baseline demographic data, including patient gender and age, according to treatment group. It can be seen that there does not exist a significant difference between the treatment groups regarding age or gender.

Table 36 – Baseline demographics (All Study Patients)

Baseline Demographics		**BCG N=53**		**Synergo N=51**		**P-Value**
		N	%	N	%	
Age	≤65	24	45.2%	26	50.9%	0.374
	>65	29	54.7%	25	49.0%	
Gender	Female	7	13.2%	4	7.8%	0.561
	Male	46	86.7%	47	92.1%	

8.3.3.2 Tumor Characteristics by Group

Table 37 presents the baseline tumor characteristics data, according to treatment group:

- History of tumor recurrence (first episode, recurrent, or high recurrent)
- Previous tumor stage (T)
- Previous tumor grade (G)
- Previous therapy (BCG, MMC, other)
- Number of previous tumors occurrences

These baseline tumor characteristics were evaluated as they are indicative of the severity of STCCB disease. It can be seen that there is no difference between the treatment groups regarding gender or age. Additionally, there does not exist a significant difference between the treatment groups regarding all baseline tumor characteristics, except for previous therapy. The baseline demographic and tumor characteristics analyses were also performed for the Evaluable Patients (n=90) and there were also no differences between treatment groups, except for pervious therapy.

The only tumor characteristic which appears to be different between treatment arms is previous therapy: 14 (26.4%) patients in the BCG group and 4 (7.8%) in the Synergo group. Since patients were randomly assigned to one of the treatment groups there can be no doubt this is an incidental finding. The study's design is specifically planned to avoid any influence of previous treatments, as it excludes any patient with a recent history of MMC or BCG treatments. Thus, these represent patients with a remote (>2 year) history of prior therapy. The hazard ratio for risk of recurrence in the Synergo group versus the BCG group is 0.36 [95% CI: 0.13-1.00]. When stratifying by prior therapy (any versus none), the hazard ratio is insignificantly modified to 0.41 [95% CI: 0.14-1.15].

Table 37 – Baseline Tumor Characteristics (All Study Patients)

Baseline Tumor Characteristics		**BCG N=53**		**Synergo N=51**	
		N	**%**	**N**	**%**
History of Recurrence	First Episode	28	52.8%	32	62.7%
	Recurrent	10	18.8%	7	13.7%
	High Recurrent	14	26.4%	11	21.5%
	Unknown	1	1.8%	1	1.9%
Number of Previous Occurrences	0	28	52.8%	32	62.7%
	1	9	16.9%	4	7.8%
	2	7	13.2%	8	15.6%
	3+	9	16.9%	6	11.7%
	Unknown	0	0	1	1.9%
Current Tumor Stage	Ta	29	54.7%	27	52.9%
	T1	24	45.2%	24	47.0%
Current Tumor Grade	G1	12	22.6%	11	21.5%
	G2	27	50.9%	19	37.2%
	G3	14	26.4%	21	41.1%

Baseline Tumor Characteristics		BCG N=53		Synergo N=51	
		N	%	N	%
Previous MMC treatment	No	46	86.7%	50	98.0%
	Yes	7	13.2%	1	1.9%
Previous BCG treatment	No	50	94.3%	50	98.0%
	Yes	3	5.6%	1	1.9%
Previous Therapy	None	39	73.5%	47	92.1%
	Prior Therapy	14	26.4%	4	7.8%
EAU Risk Group	Intermediate	30	56.6%	23	45.0%
	High	23	43.3%	28	54.9%

8.3.4 Primary Efficacy Analysis

8.3.4.1 Primary Efficacy Endpoint

Currently, data are available on 90 patients who underwent at least 6 treatment sessions and at least one cystoscopy follow-up examination. Follow-up times and time to recurrence are presented in **Table 38**.

Table 38 – Follow-up time and time to recurrence

	BCG (N=48)		Synergo (N=42)	
Follow-up (in months)	**n**	**Mean (Median)**	**n**	**Mean (Median)**
Follow-up to recurrence in patients who recurred	14	5.5 (4.3)	5	9.7 (4.9)
Follow-up of recurrence-free patients	34	18.6 (23.5)	37	18.5 (22.2)

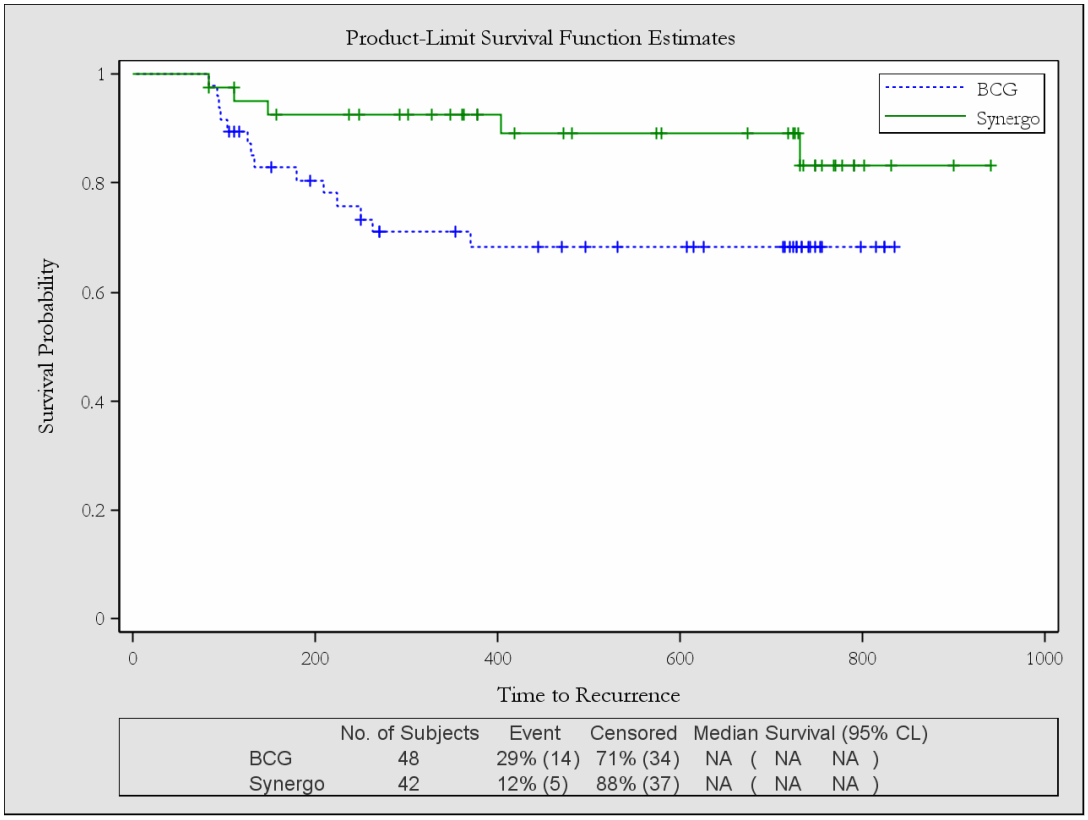
Primary efficacy endpoint in Study 102.1 was defined as tumor recurrence. In case a patient has a recurrence other than T1G3 during the first year of study (treatment period), the tumor was resected and the patient was returned to treatment. Some of these patients had a second tumor recurrence. **Table 39** presents the number of patients with ≥1 (i.e., any recurrence) and 2 tumor recurrences by treatment group.

Table 39 – Number of tumor recurrences and crude recurrence rate

	BCG n (%)	Synergo n (%)	Total n (%)
Total “Per protocol” patients	48	42	90
No recurrence	34 (70.8%)	37 (88.1%)	71 (78.9%)
≥1 tumor recurrence	14 (29.2%)	5 (11.9%)	19 (21.1%)
2 tumor recurrences	5 (10.4%)	1 (2.4%)	6 (6.7%)

Table 40 presents the analysis results of time to recurrence by treatment group using Kaplan-Meier survival analysis.

Table 40 – Primary Efficacy Analysis (Synergo vs. BCG)



Estimated 2-year probability of recurrence: Control – 31.7% Synergo – 16.9%

The results show an estimated 2-year recurrence rate of 16.9% in the Synergo group, and 31.7% in the BCG group.

The results of the Synergo treatment in Study 102.1 are indeed similar to the results of the Synergo treatment in Study 101.1 (i.e., an estimated 2-year recurrence rate of 16.9% compared to 18.9%, respectively).

8.3.5 Secondary Endpoint Analysis

Only one event of progression was recorded in a single patient in the BCG group, with progression in stage from Ta to T1 and progression in grade from G2 to G3.

8.3.6 Safety Analysis

8.3.7 Expected Adverse Events

As of April 2007, treatment information and adverse events data were available for 98 patients of the 104 patients enrolled. All 98 patients had been exposed to at least one

treatment of either BCG or Synergo. The expected adverse events observed during the course of the study included some form of tissue reaction to the treatment (this may include inflammatory changes, hyperemia or cystitis), dysuria (including urgency and/or frequency), hematuria, posterior wall tissue reaction, bladder wall necrosis, skin allergy, urinary tract infection and pain. All of these events resolved spontaneously, with no long-term sequela and did not pose a serious risk to the patient.

The anticipated adverse events were analyzed in 2 ways: (1) adverse events that are transient (usually no more than 48 hours) and may vary from treatment session to treatment session (e.g., pain) were analyzed on a-per-treatment session basis ("per-session"); and (2) the more sustained adverse events that persist over a few sessions were analyzed on a per-patient basis ("per-patient").

8.3.8 Treatment-related "Per-session" Adverse Events

Table 42 presents frequency of "per-session" adverse events. The table is sorted by ascending "odds ratio" comparing the Synergo group to the BCG Control group.

Table 42 –"Per-session" Adverse Events

	# of Sessions with AE Reported (Percent) [#, percentage of Patients with AE]		
Adverse Events	**BCG 828 Sessions 48 Patients**	**Synergo* 722 Sessions 50 Patients**	**Odds Ratio**
Arthralgia	43 (5.2%) [11, 22.9%]	2 (0.3%) [2, 4.0%]	0.051
Fever (in the absence of neutropenia)	68 (8.2%) [17, 35.4%]	4 (0.6%) [3, 6.0%]	0.062
Fatigue (lethargy, malaise, asthenia)	91 (11.0%) [17, 35.4%]	6 (0.8%) [5, 10.0%]	0.068
Incontinence	76 (9.2%) [13, 27.1%]	19 (2.6%) [9, 18.0%]	0.27
Residual urine (≥100cc)	23 (2.8%) [6, 12.5%]	11 (1.5%) [6, 12.0%]	0.54
Urinary tract infection	13 (1.6%) [9, 18.8%]	9 (1.3%) [7, 14.0%]	0.79
Urinary Frequency / Urgency	282 (34.1%) [37, 77.1%]	219 (30.3%) [28, 56.0%]	0.84
Dysuria	236 (28.5%) [35, 72.9%]	182 (25.2%) [31, 62.0%]	0.85
Hematuria	117 (14.1%) [28, 58.3%]	91 (12.6%) [29, 58.0%]	0.88
Nocturia	260 (31.4%) [32, 66.7%]	273 (37.8%) [29, 58.0%]	1.33
Pain between sessions (not dysuria)	31 (3.7%) [12, 25.0%]	39 (5.4%) [13, 26.0%]	1.47
Urinary retention	4 (0.5%) [2, 4.2%]	6 (0.8%) [4, 8.0%]	1.78
Vomiting	2 (0.2%) [2, 4.2%]	7 (1.0%) [5, 10.0%]	4.17

	# of Sessions with AE Reported (Percent) [#, percentage of Patients with AE]		
Adverse Events	**BCG 828 Sessions 48 Patients**	**Synergo* 722 Sessions 50 Patients**	**Odds Ratio**
Bladder spasms	13 (1.6%) [6, 12.5%]	134 (18.6%) [32, 64.0%]	14.3
Pain during session	7 (0.90%) [1, 2.1%]	130 (18.0%) [27, 54.0%]	25.8

(*) At the beginning of Study 102.1 side effects in the Synergo arm were recorded during the session, unlike the BCG arm where it was done a week later. This was amended later on, but is still reflected in the side effect rates.

As can be seen in **Table 42**, systemic symptoms (arthralgia, fever, and fatigue) and urinary incontinence were significantly more frequent in the BCG group, while pain and bladder spasms were significantly more frequent in the Synergo group (18.0% vs. 0.9% and 18.6% vs. 1.6%, for pain and bladder spasms, respectively). This is explained by the nature of the hyperthermia treatment, where heat is the direct cause for these symptoms.

Despite the significantly higher frequency of pain and bladder spasm in the Synergo group than in the BCG group, the vast majority of treatment sessions were accompanied by no or mild pain only. Moderate pain was observed in 5.7% of Synergo treatment sessions and severe pain in 1.1% of treatment sessions. Similar result was observed for bladder spasms as well. Bladder spasms are caused by the increased local temperature which is a part of the Synergo treatment. In all occurrences these events were localized and transient during delivery of therapeutic heat during treatment and resolved without any residual effects.

8.3.9 Treatment-related "Per-patient" Adverse Events

Table 43 presents frequency of "per-patient" adverse events.

Table 43 "Per-Patient" Adverse Events.

Adverse Events	**BCG N=48**	**Synergo N=50**	**Odds ratio**	**95% confidence interval**	
				Lower	**Upper**
Hypotonic Bladder	4 (8.3%)	0 (0.0%)	N/A	N/A	N/A
Cystitis	14 (29.2%)	5 (10.0%)	0.27	0.09	0.82
Granulomatous Changes of Bladder Wall	2 (4.2%)	4 (8.0%)	2.00	0.35	11.5
Bladder Tissue Reaction	12 (25.0%)	24 (48.0%)	2.77	1.18	6.53
Allergic Reaction/ Hypersensitivity	3(6.3%)	8 (16.0%)	2.86	0.71	11.5
Urethral Stricture/ Stenosis	4 (8.3%)	11 (22.0%)	3.10	0.91	10.5
Posterior wall tissue reaction	0 (0.0%)	20 (40.0%)	N/A	N/A	N/A

Among the adverse events, cystitis and hypotonic bladder were more frequent in the BCG group, while bladder tissue reaction, posterior wall tissue reaction and urethral stricture or

stenosis were significantly more frequent in the Synergo group. The higher incidence of posterior wall tissue reaction in the Synergo group compared to the BCG group was also anticipated due to the nature of the hyperthermia treatment. This event occurs due to the location of the RF antenna in the bladder, and in some cases there is a cumulative effect of the dissipated heat in the area around the antenna causing a small, localized area of superficial tissue reaction (hyperemia, inflammation, ulceration or necrosis) in the posterior wall. The posterior wall tissue reaction was seen at follow-up cystoscopies and was asymptomatic. Furthermore, posterior wall tissue reaction resolved without medical intervention or significant residual effects.

A total of 11 patients in the Synergo group reported stricture or stenosis, graded as follows:

5 patients - Grade 1 (No need for action)
2 patients - Grade 2 (Needed dilatation)
4 patients - Grade 3 (Needed surgical intervention: urethrotomy cuts)
0 patients - Grade 4 (Needed surgical intervention: urethroplasty)

All 4 patients in the BCG group had grade 1 (no need for action) stricture or stenosis.

A true urethral stricture requires urethrotomy or urethroplasty, while urethral stenosis may resolve spontaneously, or require simple urethral dilatations. Despite this clear distinction, stricture and stenosis are often used interchangeably, even by senior urologists. This is well demonstrated in Study 102.1, in which investigators reported 5 patients as having urethral stricture, but state that no treatment was required and another 2 patients were reported as having urethral stricture, but needed only urethral dilatation. This is also true for the European studies (EPP, BS, EAP), in which reporting may be a bit more lax, due the nature of the uncontrolled studies. Moreover, in the Italian language, there is only one word for both stenosis and stricture. In any case, urethral stenosis is generally expected in TCC patients, as they typically undergo multiple invasive transurethral procedures, such as resections, cystoscopies and catheterization. The higher incidence among Synergo patients compared to BCG patients can be explained by the relatively larger diameter of the Synergo catheter (20Fr). However, in the majority of patients, it was mostly urethral edema which caused the stenosis and it was usually self-resolving.

The adverse events reported in Study 102.1 for the Synergo group are very similar to those reported in the pivotal Study 101.1 and include dysuria, hematuria, tissue reaction, urinary tract infection, pain, posterior wall tissue reaction, and bladder wall necrosis. The most common adverse events are pain and posterior wall tissue reaction in both Study 101.1 and Study 102.2.

8.3.10 Other Adverse Events

Other adverse events that were reported during the study are presented in **Table 44**. The results demonstrate similar occurrences of other adverse events reported in the patients undergoing the Synergo treatment compared to the patients undergoing BCG treatment.

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Table 44 – Other adverse events

Adverse Events	**BCG N=48**	**Synergo N=50**	**Total N=98**
Meatitis	-	2 (4.0%)	2 (2.0%)
Nausea	3 (6.3%)	7 (14.0%)	10 (10.2%)
Vomiting	2 (4.3%)	5 (10.0%)	7 (7.1%)
Pneumonia	-	2 (4.0%)	2 (2.0%)
Epididymitis	-	1 (2.0 %)	1 (1.0%)
Granulomatous prostatitis	1 (2.1%)	-	1 (1.0%)
Bilateral Ing hernia	1 (2.1%)	-	1 (1.0%)
Conjunctivitis	1 (2.1%)	-	2 (2.0%)
Knee pain	1 (2.1%)	-	1 (1.0%)
Stomach pain	1 (2.1%)	2 (4.0%)	2 (2.0%)
Muscle ache	1 (2.1%)	-	1 (1.0%)
Blepharitis	2 (4.2%)	-	2 (2.0%)
Constipation	1 (2.1%)	-	1 (1.0%)
Elevated blood pressure	1 (2.1%)	-	1 (1.0%)
Decreased libido	1 (2.1%)	-	1 (1.0%)
Erectile insufficiency	1 (2.1%)	-	1 (1.0%)
Fainting	1 (2.1%)	-	1 (1.0%)
Gonarthrosis (arthritic pains in the knee)	1 (2.1%)	-	1 (1.0%)
Foot skin inflammation	1 (2.1%)	-	1 (1.0%)
Intercostal pain	1 (2.1%)	-	1 (1.0%)
Meatal stricture	1 (2.1%)	-	1 (1.0%)
Shivering	2 (4.2%)	-	2 (2.0%)
Traumatic catheterization	1 (2.1%)	-	1 (1.0%)
Groin pain	-	1 (2.0 %)	1 (1.0%)
Malaise	-	1 (2.0 %)	1 (1.0%)
Weakness of arm	-	1 (2.0 %)	1 (1.0%)
Speech difficulties	-	1 (2.0 %)	1 (1.0%)
Hydroureteronephrosis	-	1 (2.0 %)	1 (1.0%)
Palpitations	-	1 (2.0 %)	1 (1.0%)
Perforation (during TUR)	-	1 (2.0 %)	1 (1.0%)
Carcinoma of the pancreas	1 (2.1%)	-	1 (1.0%)
Poor bladder function	-	1 (2.0 %)	1 (1.0%)
False urethral passage	-	1 (2.0 %)	1 (1.0%)

8.3.11 Serious Adverse Events

Serious adverse events reported in Study 102.1 are detailed in **Table 45**.

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Table 45 –Serious Adverse Events

BCG Group (N=48)	**n (%)**	**Relationship to Treatment***
Cerebrovascular Accident (CVA)	2 (4.17%)	Definitely not related
Macrohematuria and Urinary Retention	1 (2.08%)	Probably related
Hematuria	1 (2.08%)	Definitely not related
Pulmonary Edema (prior to start of treatment)	1 (2.08%)	Definitely not related
Infected Wound of Rt. Foot	1 (2.08%)	Definitely not related
Unstable Angina	1 (2.08%)	Definitely not related
Rt. Bacterial Bronchopneumonia along with Ischemic Sigmoiditis	1 (2.08%)	Definitely not related
Ascending Cholangitis	1 (2.08%)	Definitely not related
Urinary Tract Infection	2 (4.17%)	1 possibly related, 1 definitely not related
Total	11	
Synergo Group (N=50)	**n (%)**	**Relationship to Treatment***
Cerebrovascular Accident (CVA)	1 (2.00%)	Definitely not related
Urethral Stricture	1 (2.00%)	Probably related
Small Contracted Bladder and Severe irritative Symptoms	1 (2.00%)	Probably related
Urethral Bleeding	1 (2.00%)	Definitely related
Synovial Popliteal Cyst on Knee Prosthesis	1 (2.00%)	Definitely not related
Fever but no Other Irritative Symptoms	1 (2.00%)	Probably related
Fever and Irritative Symptoms but a Negative Urine Culture	1 (2.00%)	Probably related
Total	7	

*As determined by each site's local investigator

The serious adverse events in the Synergo group reported in the above table included one patient with Cerebrovascular Accident (CVA), one patient with Urethral Stricture, one patient with small contracted bladder and severe irritative symptoms, one patient who suffered urethral bleeding and one with fever and irritative symptoms but a negative urine culture.

Case 1

One 64 yr old male patient was reported with a cerebrovascular accident (right hemiparesis and mild motor aphasia). This patient had a history of risk factors including hypertension, smoking and recurrent CVA in the past. His anti-platelet-aggregation therapy was suspended prior to the transurethral tumor resection, and not resumed afterwards. The patient arrived for his 2nd weekly treatment and complained about worsening of the weakness of Rt. upper limb and dysarthria, which had started three days earlier. The treatment was canceled; the patient was referred to the emergency room and hospitalized in the neurological department. The event was considered by the physician to be a serious adverse event definitely not related to the drug (MMC) or to the Synergo. The patient started the treatment with mild Rt. hemiparesis due to a previous CVA. After the recent event the patient still suffered mild Rt. hemiparesis that is regarded as a sequela of the two CVAs. The patient continued his remaining treatments as scheduled.

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Case 2

One 58 yr old male patient was hospitalized following his 15 months follow-up, when Urethral Stricture was diagnosed during an attempted cystoscopy. The patient underwent endoscopy under anesthesia and bladder neck cuts were performed to relieve the stricture. The event was considered by the investigator to be a serious adverse event, definitely related to the Synergo device, and definitely not related to the drug (MMC). The patient was discharged and the SAE resolved with unknown sequela (not reported on CRF). The patient continued his follow up procedures as scheduled.

The same patient was hospitalized 2 months later and underwent radical cysto-prostatectomy despite being tumor free, due to small contracted bladder with severe irritative symptoms (Frequency, Urgency, Dysuria, Nocturia every 15-30 minutes). The event was considered by the physician to be a serious adverse event probably related to the drug (MMC) or to the Synergo and was resolved by surgery with sequela. The patient was withdrawn from the study. Histopathology of the removed bladder showed no evidence of a bladder tumor.

Case 3

One 54 yr old male was hospitalized after he suffered urethral bleeding following catheter insertion during his second Synergo treatment. Previous hematuria between sessions was reported. The event was considered by the physician to be a serious adverse event definitely related to the Device (Synergo) and possibly related to the drug (MMC), and was spontaneously and completely resolved overnight. A control cystoscopy could not reveal any reason for the event. The patient withdrew his informed consent shortly thereafter and dropped out of the study.

Case 4

One 58 yr old male was hospitalized for dysuria, urinary urgency and fever lasting 3 days following treatment. He was treated with IV antibiotics, but urine culture was negative. The event was considered by the physician to be a serious adverse event possibly related to the Device (Synergo) and probably related to the drug (MMC).

8.3.12 Study 102.1 Conclusions

8.3.12.1 Efficacy Conclusions

The efficacy results in Study 102.1 demonstrate a substantially lower estimated 2-year recurrence rate of 16.9% in the Synergo group compared to 31.7% in the BCG group. The efficacy results of the Synergo treatment in Study 102.1 are similar to the results of the Synergo treatment in Study 101.1 (16.9% estimated recurrence rate compared to 18.9%, respectively).

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8.3.12.2 Safety Conclusions

Although most of the adverse events were similar between the Synergo group and the BCG group, some systemic symptoms (arthralgia, fever, and fatigue) and urinary incontinence were notably more frequent in the BCG group, while pain and bladder spasms were more frequent in the Synergo group. Among the sustained adverse events, cystitis and hypotonic bladder were more frequent in the BCG group, while bladder tissue reaction, posterior wall tissue reaction and urethral stricture/stenosis were more frequent in the Synergo group. The higher incidence of pain and posterior wall tissue reaction in the Synergo group compared to the BCG group was also anticipated due to the nature of the hyperthermia treatment.

When comparing the adverse events reported for the Synergo patient population in Study 102.1 to the events reported in the pivotal Study 101.1, most of these events are the same (dysuria, hematuria, tissue reaction, urinary tract infection, pain, posterior wall tissue reaction and bladder wall necrosis). This group of intermediate and high-risk STCCB patients (after having numerous tumor occurrences, TUR's and previous bladder instillations) is prone to develop a higher rate of adverse events. The most common adverse events are pain and posterior wall tissue reaction in both Study 101.1 and Study 102.2.

8.4 Overall Conclusions

The interim results of Study 102.1 provides additional supportive evidence that Synergo is a safe and effective treatment for intermediate to high risk STCCB patients. Efficacy and safety data from this study are similar to those of the pivotal Study 101.1. The Synergo data from Study 101.1 and Study 102.1 are combined to provide additional supportive data and the results are presented in the next section.

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9 COMBINED ANALYSIS OF STUDIES 101.1 and 102.1

9.1 Introduction

Synergo data from Studies 101.1 and 102.1 were combined to provide additional comparison to the control arms in each of these studies (Section 9) and to historical meta-analysis data from the published literature for MMC and BCG treatments (Section 10).

In this combined analysis, the efficacy outcomes are compared between: (1) Combined Synergo group (Study 101.1 and Study 102.1) vs. MMC (Control group) from Study 101.1; and (2) Combined Synergo group (Study 101.1 and Study 102.1) vs. BCG (Control group) from Study 102.1.

9.2 Justification of Poolability of Synergo Arms from Study 101.1 and Study 102.1

The combined analysis of Synergo data of Study 101.1 and Study 102.1 is justified as both studies are randomized, controlled studies conducted using the Synergo treatment in patients with intermediate to high risk STCCB. Both studies are similar in their design and conduct, i.e., patient inclusion and exclusion criteria, treatment protocol, and assessment of efficacy measures. The two studies are different principally in the treatment used in the control groups.

Prior to combining the Synergo arms from Study 101.1 and Study 102.1, the baseline demographics and tumor characteristics between the two arms were compared, as were the treatment effects (i.e., time to recurrence) to evaluate the poolability of the two Synergo arms. **Table 46** presents the baseline demographics and tumor characteristics of the Synergo groups by study based on the All Study Patients population in both studies.

Table 46 - Baseline Characteristics of Synergo Arms in Study 101.1 and Study 102.1

Baseline Characteristics	**Synergo Arm**				
	Study 101.1 N=42		**Study 102.1 N=51**		
	N	**%**	**N**	**%**	**P-value***
Age					
Age ≤65	25	59.5%	26	50.9%	0.410
Age >65	17	40.4%	25	49.0%	
Gender					
Female	7	16.6%	4	7.8%	0.214
Male	35	83.3%	47	92.1%	
History of Tumor Recurrence					
First Episode	15	35.7%	32	62.7%	0.015
Recurrent	12	28.5%	11	21.5%	
High Recurrent	15	35.7%	7	13.7%	
Number of Previous Occurrence					
0	15	35.7%	32	62.7%	0.012
1	7	16.6%	4	7.8%	
2	5	11.9%	8	15.6%	
3+	15	35.7%	6	11.7%	

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Baseline Characteristics	Synergo Arm				P-value*
	Study 101.1 N=42		Study 102.1 N=51		
	N	%	N	%	
Previous Stage					
Ta	15	35.7%	25	49.0%	0.245
T1	26	61.9%	26	50.9%	
CIS	1	2.3%	0	0	
Previous Grade					
G1	4	9.5%	8	15.6%	0.055
G2	27	64.2%	20	39.2%	
G3	11	26.1%	23	45.0%	
Current Stage					
Ta	24	57.1%	27	52.9%	0.685
T1	18	42.8%	24	47.0%	
Current Grade					
G1	7	16.6%	11	21.5%	0.091
G2	25	59.5%	19	37.2%	
G3	10	23.8%	21	41.1%	

*Chi-square or Fisher's exact test.
Note: 1 subject in study 102.1 had missing tumor characteristics data.

As shown in **Table 46**, there were no statistically significant differences between the two Synergo groups with respect to age, gender, previous tumor stage and grade and current tumor stage and grade. Statistically significant differences were found between the Synergo groups only for history of tumor recurrence and number of previous occurrences with more Synergo patients in Study 102.1 having their first episode of STCCB (no prior occurrence). However, as can be seen in **Table 47**, there was no evidence that these factors were prognostic for tumor recurrence (stratified log rank test p >0.05).

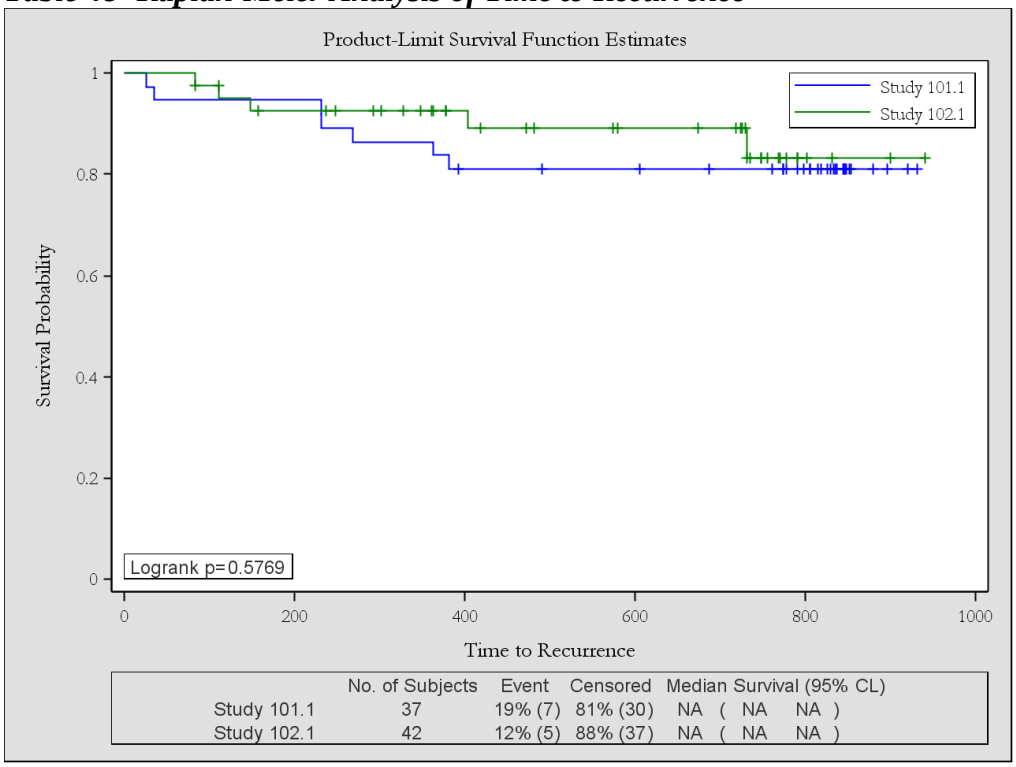
Table 47 - Prognostic Factor Analysis for Recurrence

Baseline Characteristic	P-value*
History of Tumor Recurrence	0.487
Number of previous occurrences	0.272

*Log-rank test for time to recurrence stratified by study.

Time to recurrence between the Synergo groups was compared by Kaplan–Meier curves and the log rank test. All randomized patients who had at least one cystoscopy evaluation were included in the analysis (37 patients in Study 101.1 and 42 patients in Study 102.1). The analysis was performed according to treatment received ("Randomized, As treated" for the Study 101.1 Synergo group). As can be seen in **Table 48**, the two Synergo groups are quite similar with respect to time to recurrence (log rank p=0.58).

Table 48 -Kaplan-Meier Analysis of Time to Recurrence



In conclusion, there is substantial similarity between the two Synergo groups with respect to baseline characteristics and time to recurrence.

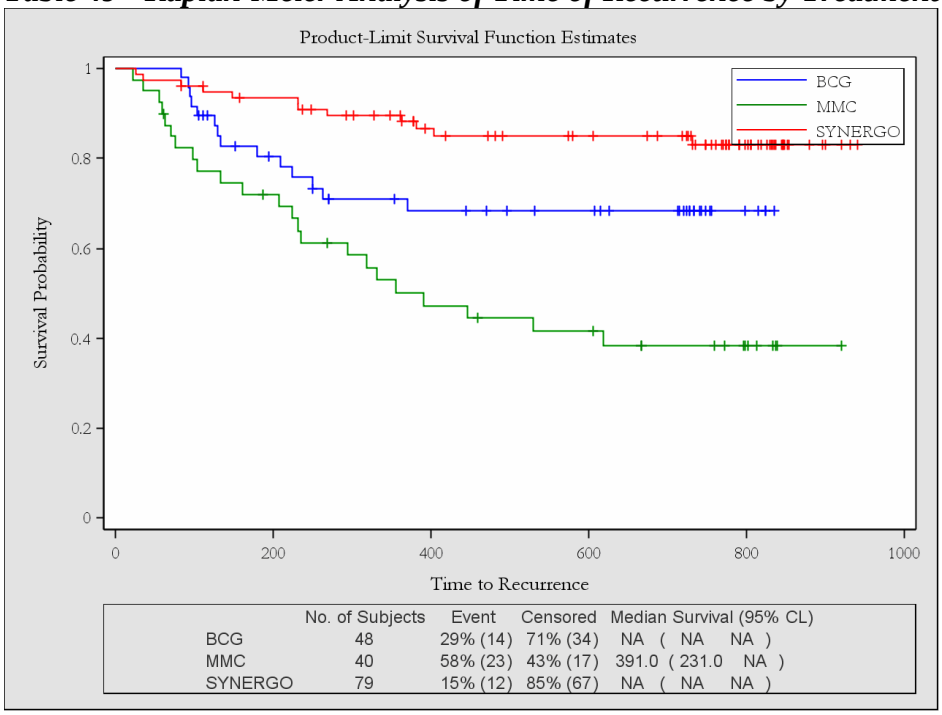
9.3 Combined Study 101.1 and Study 102.1 Synergo Arm Results

Three study groups are compared:

- Combined Study 101.1 and Study 102.1 Synergo group (N=79)
- MMC Control group (N=40)
- BCG Control Group (N=48)

All randomized patients who had at least one cystoscopy evaluation were included in the analysis. The analysis was performed according to treatment received ("Randomized, As Treated" for the Study 101.1 patients). The estimated 2-year recurrence rate are 17.1% (s.e.=4.6%) for Synergo (combined Studies 101.1 and 102.1), 61.6% (s.e.=8.1%) for MMC Control group, and 31.7% (s.e.=7.1%) for BCG Control group. A clear difference in time to recurrence can be seen between the three different treatment groups in **Table 49**.

Table 49 - Kaplan-Meier Analysis of Time of Recurrence by Treatment Groups



	No. of Subjects	Event	Censored	Median Survival (95% CL)
BCG	48	29% (14)	71% (34)	NA (NA NA)
MMC	40	58% (23)	43% (17)	391.0 (231.0 NA)
SYNERGO	79	15% (12)	85% (67)	NA (NA NA)

The combined Study 101.1 and Study 102.1 Synergo analysis provides additional supportive evidence that the Synergo treatment is significantly more efficacious than MMC treatment and BCG treatment.