**Sponsor Summary**

**Part II**


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## 10. CONSISTENCY OF SYNERGO TREATMENT EFFECT WITH HISTORICAL MMC AND BCG CONTROLS

A systematic review of the effect of MMC and BCG adjuvant treatment of STCCB based on reports available in the literature was conducted. A description of the methodology used to perform this analysis can be found in Appendix A.

The 1-year and 2-year probabilities of recurrence are compared between:

- Synergo group from Study 101.1 and MMC results from the literature;
- Synergo group from Study 102.1 and BCG results from the literature;
- Combined Synergo groups (Study 101.1 and Study 102.1) and MMC results from the literature; and
- Combined Synergo groups (Study 101.1 and Study 102.1) and BCG results from the literature.

Only the 2-year results are presented for comparisons with results from Study 101.1 and Study 102.1. As shown in **Table 52**, for MMC treatment, the literature-based estimate of recurrence is 41.5% at 2 years; for BCG treatment, the literature-based estimates of recurrence is 35.6% at 2 years.

***Table 52 – Summary of Efficacy Results – Kaplan-Meier estimated 2-year recurrence rates***

| | **Synergo** | **MMC** | **BCG** |
|---|---|---|---|
| Study 101.1* | 18.9% (6.3-31.5%)† | 61.6% (45.7-77.5%) | |
| Study 102.1 | 16.9% (2.1-31.7%) | -- | 31.7% (17.8-45.6%) |
| Combined Studies 101.1 + 102.1 | 17.1% (8.1-26.0%) | -- | -- |
| Meta-Analysis of Literature Reports | -- | 41.5% (36.8-46.3%) | 35.6% (32.4-38.7%) |

*Based on evaluable patients: Randomized As Treated cohort.
†95% confidence interval.

Note that the estimated 2-year recurrence rate for MMC treatment is higher in the MMC Control group in Study 101.1 (61.6%) compared to the literature-based meta-analysis estimate (41.5%). This difference in recurrence rates for MMC treatment is likely to be a reflection of the difference in patient populations, as Study 101.1 and Study 102.1 included only intermediate and high risk STCCB patients, whereas data reported in the literature included the overall STCCB patient population, including low risk patients. The estimated 2-year recurrence rate for BCG treatment from the meta-analysis (35.6%) is similar to that reported for the BCG Control group in Study 102.1 (31.7%), noting that BCG is usually given only to intermediate and high-risk patients.[1]

[1] It should also be noted here that the results of the current meta-analysis are similar to the results of the meta-analysis that the company presented in the PMA Amendment dated April 21, 2002. In that Amendment, the company reported an average, weighted 2-year recurrence rate of 41% for MMC. This rate is almost identical to the currently reported recurrence rate (41.5%) for the same patient population. Also, in the same Amendment, the company reported an average, weighted 2-year recurrence rate for the STCCB patient population at intermediate and high risk for recurrence of 55.5%. This rate is similar to the MMC Control group 2-year recurrence rate in Study 101.1 (61.6%) for the same patient population.

Importantly, as shown in **Table 52**, the estimated 2-year recurrence rates for the Synergo group from Study 101.1 (18.9%), Study 102.1 (16.9%), and the combined Study 101.1 and Study 102.1 (17.1%) are significantly lower than the 2-year recurrence rate for either BCG or MMC reported in the literature meta-analysis (35.6% and 41.5%, respectively).

# 11. CLINICAL INVESTIGATIONS – EUROPEAN PROPHYLACTIC PATIENTS (EPP)

## 11.1 Introduction

The Synergo system has been in commercial use in Europe and Israel since obtaining CE Certification in Europe and the Israeli Ministry of Health's approval for the product in August 2000. Synergo treatment is clinically indicated for use in Europe and Israel for intermediate and high-risk STCCB patients. Safety and efficacy data were obtained from patients treated in Europe and Israel with Synergo for prophylactic treatment of STCCB ("European Prophylactic Patients"(EPP)), and presented here as additional supportive data.

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. The clinical data for these patients was recorded on dedicated Case Report Forms in a prospective manner and systematically monitored by experienced monitors. Fifty out of 52 centers commercially using the Synergo device agreed to cooperate with the Sponsor and provide the clinical data.

## 11.2 Patient Population

The patient selection criteria employed for selecting the EPP group were essentially identical to the patient selection criteria employed in the previous studies. Although the EPP group was not screened according to strict inclusion and exclusion criteria set forth in a written protocol, each of the physicians received an intensive training course including patient selection and treatment procedures. This training was similar to that received by physicians in the Study 101.1 and Study 102.1.

Patients who did not meet the eligibility criteria for Synergo treatment and patients who have not yet reached the first follow-up cystoscopy examination were not included in the EPP efficacy analysis. All EPP patients treated with Synergo were included in the baseline analysis and in the safety analysis.

## 11.3 Treatment and Follow-up Procedures

The Synergo treatment sessions for the EPP group were similar to the treatment sessions in Study 101.1, that is, a total of 12 treatment sessions. Study 101.1 patients received 8 weekly inductive sessions followed by 4 monthly maintenance sessions, whereas the EPP group received 6-8 weekly inductive sessions followed by 4-6 monthly maintenance sessions.

The EPP group received identical Synergo treatment to Study 101.1 Synergo subjects, including 40 mg of MMC dissolved in 100 ml of sterile distilled water (delivered in two portions of 20 mg in 50 cc, at the start of treatment and after 30 minutes of treatment) and hyperthermia treatment delivered at 42 ± 2°C.

The follow-up evaluations for the EPP group were identical to the follow-up evaluations in Study 101.1, consisting of follow-up visits every three months beginning at the end of

the inductive treatment sessions, up to 24 months or until first recurrence, whichever came first and included cystoscopy, cytology, or biopsy, if required. As in Study 101.1, biopsies were performed only in the case of recurrence or suspicion of recurrence. As long as the patient remained tumor-free, no further adjuvant treatments, either local or systemic, were administered.

Although in most cases patients are followed-up at three month intervals over two years as part of routine medical treatment, in many cases patients who have completed a course of 1 year follow-up at the treating hospital and are tumor-free, are sent back to the referring physician at the community or private clinic for further follow-up. If the patient remains tumor free, then the data for the 1-2 year follow-up from the community or private clinics was not available to the Sponsor. In the case of tumor recurrence, the patient is referred back to the hospital for an additional TUR and in this case, the data was collected by the Sponsor. The lack of 1-2 year follow-up data for the tumor-free patients might have caused a bias in the estimated recurrence rate, resulting in a higher recurrence rate than would have been reported had this data been available.

## 11.4 Study Results

### 11.4.1 Analysis Population

The baseline data described here is based on all 186 subjects in the EPP group commercially treated with Synergo ("EPP All Patients").

The efficacy analysis is based on data from 122 patients ("EPP Evaluable cohort"). Sixty-four patients were not included for the following reasons:

- CIS patients (n=15);
- "Ongoing" patients (n=31); and
- Patients who did not meet eligibility criteria (n=18)

### 11.4.2 Baseline Characteristics

The descriptive evaluations presented in this section include all available data from all patients. **Table 53** presents the baseline demographic data, including patient gender, age, tumor characteristics and number of treatment sessions.

***Table 53 - Baseline demographics, tumor characteristics and number of treatment sessions (EPP All Patients)***

| **Baseline Demographics** | | **Synergo N=186** | |
|---|---|---|---|
| | | **N** | **%** |
| **Gender** | Female | 79 | 42.4% |
| | Male | 107 | 57.5% |
| **Age (yrs)** | ≤65 | 36 | 19.3% |
| | >65 | 150 | 80.6% |

| Baseline Tumor Characteristics | | N | % |
|---|---|---|---|
| **History of recurrence** | First Episode | 42 | 22.5% |
| | Recurrent | 33 | 17.7% |
| | High Recurrent | 111 | 59.6% |
| **Number of previous occurrences** | 0 | 42 | 22.5% |
| | 1 | 54 | 29.0% |
| | 2 | 30 | 16.1% |
| | 3+ | 60 | 32.2% |
| **Previous Tumor Stage** | Ta | 87 | 46.7% |
| | T1 | 74 | 39.7% |
| | CIS | 23 | 12.3% |
| | Unknown | 2 | 1.0% |
| **Previous Tumor Grade** | G1 | 39 | 20.9% |
| | G2 | 74 | 39.7% |
| | G3 | 67 | 36.0% |
| | Unknown | 6 | 3.2% |
| **Previous MMC treatment** | No | 142 | 76.3% |
| | Yes | 44 | 23.6% |
| **Previous BCG treatment** | No | 126 | 67.7% |
| | Yes | 60 | 32.2% |
| **Previous Epirubicin treatment** | No | 167 | 89.7% |
| | Yes | 19 | 10.2% |
| **Previous Therapy** | Prior Therapy | 105 | 56.4% |
| | None | 81 | 43.5% |
| **EAU Risk Group** | Low risk | - | - |
| | Intermediate risk | 77 | 41.3% |
| | High risk | 109 | 58.6% |

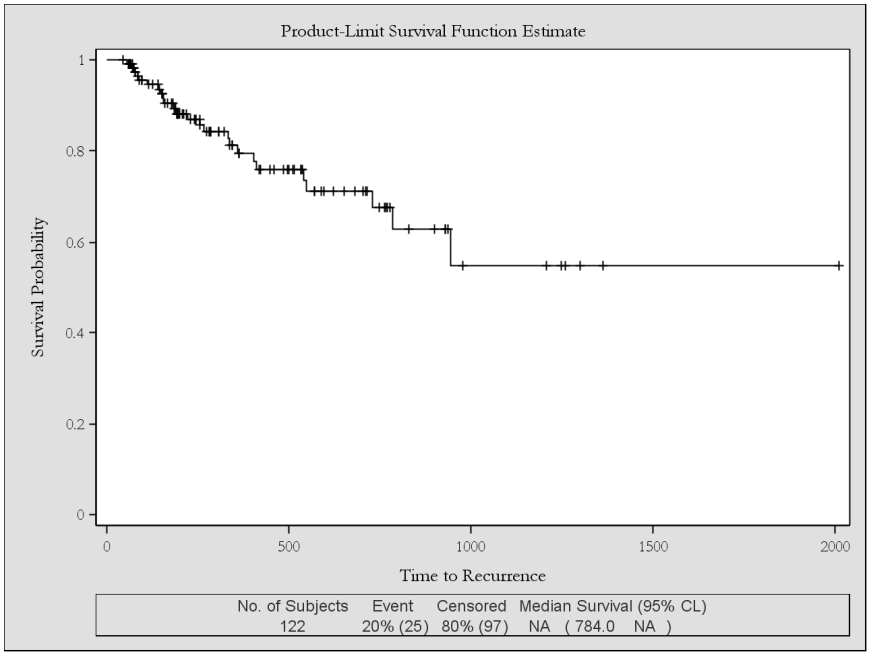
| **Number of treatments** | **Synergo N=186** | |
|---|---|---|
| | **N** | **%** |
| At least 12 sessions | 7 | 3.7% |
| 8-12 sessions | 105 | 56.4% |
| Less than 8 sessions | 74 | 39.7% |

### 11.4.3 Efficacy Analysis

Efficacy analysis results for recurrence free survival for EPP "Evaluable cohort" are provided in this section,.

**Table 54** presents the K-M Recurrence-Free Survival curve for the "EPP Evaluable cohort".

***Table 54 – Recurrence-free survival analysis results ("EPP Evaluable Patients")***




The efficacy results presented here demonstrate that 20.5% (25/122) of the patients suffered a tumor recurrence. The mean follow-up of recurrence free patients was 13.7 months and the median was 9.4 months. The Kaplan-Meier estimated 2-year recurrence rate is 32.2%. These results are slightly less favorable than the recurrence rates reported for Study 101.1 and Study 102.1 Synergo groups (19% and 17%, respectively). This difference may be due to higher risk patients included in the EPP compared to Study 101.1. Furthermore, the difference may also be due to the number of actual treatments the patients received and the bias due to the lack of follow-up data for tumor free patients, as explained below.

Higher Risk Patients

The EPP group was from commercial use of the Synergo device, and as can be expected from a new technology on the market, many of the patients referred for treatment were worse case patients. If we compare the patient baseline tumor characteristics, it is apparent that the EPP group constitutes a patient population with a <u>much</u> higher risk than the Study 101.1 subjects:

- First episode patients constitute 35.7% of the Study 101.1 patients, but only 22.6% of the EPP group.

- Average number of previous episodes is 2.3 in Study 101.1 and 3.3 in the EPP group.
- A larger percent of patients failed previous prophylactic treatment in the EPP group than in Study 101.1. 16.7% and 23.8% of patients in Study 101.1 failed MMC and BCG treatment, respectively, compared to 23.7% MMC treatment failures and 32.3% BCG treatment failures in the EPP group.

Number of Treatment Sessions:

As mentioned, the EPP group was from commercial use of the device. As a result, the patients were often subject to the influence of different factors, including re-imbursement policies. That is, if the patients' treatment was not covered by the appropriate insurance policy, then treatment was terminated and not administered. On the other hand, Study 101.1 was a controlled study, and protocol adherence was strictly maintained. To demonstrate these differences, the average number of treatment sessions was calculated for non-recurrent patients only. Non-recurrent patients should have continued their instillation programs, while recurring patient will undergo a TUR and be removed from Synergo treatment.

The average number of treatment sessions for non-recurrent patients was 11.5 in Study 101.1, but only 9.5 for the EPP group. In fact, 1 in 6 non-recurrent patients in the EPP group never received more than 6 treatment sessions. That is, these patients received only induction treatments and no maintenance treatments. The importance of administering maintenance instillations has been suggested in many articles as well as in the PMA.

The above differences demonstrate that the EPP group constitutes a higher risk group, and the clinical results were compromised by issues related to real-life, commercial use of a device, e.g., re-imbursement policies. This explains the slightly less favorable results compared to Study 101.1, though still surprisingly good for this high-risk patient population (more than 2/3 of patient still disease free at 2 years). Not withstanding all the above, a 2-year estimated recurrence rate of 32.2% for Synergo treatment is significantly better than the 2-year estimated recurrence rate of approximately 60% reported in the medical literature for a similar intermediate/high risk patient population treated with conventional treatment method of MMC.

Bias in the assessment of recurrence:

A bias in the EPP exists regarding the follow-up of tumor-free patients. The Synergo device is commercially used in fairly large hospitals or medical centers on patients that are referred to the hospital from community clinics or private doctors for transurethral resection (TUR) of their tumors and subsequent prophylactic treatment. The course of the Synergo prophylactic treatment and maximum follow-up of these patients is approximately 1 year, assuming the patient remains tumor free during this period. At this point, many of the tumor free patients are referred back to their community clinics or private doctors for further follow-up and the Sponsor has no access to this clinical data. Only if a patient suffers a tumor recurrence are they then referred back to the hospital for an additional TUR and this recurrence is recorded and collected by the Sponsor. As a result, there is a significant amount of 1-2 year follow-up data missing for recurrent-free

patients that are followed-up in the community or private clinics. For example, during the second year of follow-up, 61.5% of tumor-free patients were lost to follow-up.

**Conclusions**

The high risk EPP patient population combined with issues related to the real-life, commercial use of a device (e.g., re-imbursement policies), as well as the bias inherent in the follow-up of recurrence-free patients, may explain the somewhat less favorable efficacy results (recurrence) in the EPP compared to Study 101.1. Nevertheless, the results are still surprisingly good. The estimated 2-year recurrence rate of 32.2% for Synergo treatment is far better than standard conventional MMC treatments and at least as good as or in some cases better than today's gold standard, FDA approved BCG treatment.

### 11.4.4 Safety Analysis

As the EPP was an open, uncontrolled study, adverse event reporting may be incomplete. In order to encourage and improve adverse event reporting, the Sponsor used follow-up forms for the documentation of all clinical aspects of the Synergo treatment, including adverse events. The physicians and nurses in all the clinical centers, where the Synergo device is in commercial use, are repeatedly instructed by the sponsor's clinical experts regarding the comprehensive use of these forms. Consequently, under-reporting probably affects mainly common and well-documented side effects of Synergo, like pain and irritative symptoms, whereas unusual or severe adverse events are probably well documented.

#### 11.4.4.1 Expected Adverse Events

Expected adverse events are presented separately for those that change from session to session (e.g., pain) and are transient in nature ("per-session" adverse events), and for those that have a more sustained effect, i.e. those that persist over a few sessions ("per-patient" adverse events). **Table 55 and Table 56** present the frequency of expected adverse events for each of these types of adverse events.

***Table 55 "Per Session" adverse events ("EPP All Patients")***

| Adverse event | Frequency |
|---|---|
| Pain (including spasm) during session | 18.6% (297/1598) |
| Dysuria | 7.6% (122/1598) |
| Urge and/or incontinence during session | 2.1% (33/1598) |
| Hematuria | 2.8% (45/1598) |
| Traumatic catheter insertion | 1.1% (18/1598) |
| Urinary frequency/urgency | 1.3% (21/1598) |
| Nocturia | 0.5% (8/1598) |
| Urinary retention | 0.1% (2/1598) |
| Cystitis | 0.1% (2/1598) |
| Urinary tract infection | 0.4% (6/1598) |

*Table 56: "Per Patient" adverse events ("EPP All Patients")*

| Adverse event | Frequency |
|---|---|
| Posterior wall tissue reaction | 20.4 % (38/186) |
| Skin allergy | 5.4 % (10/186) |
| Urethral stenosis (edema / stricture) | 5.4% (10/186) |
| Bladder wall necrosis | 5.9% (11/186) |
| Bladder stone | 0.5% (1/186) |
| False passage | 0.5% (1/186) |

#### 11.4.4.2 Other Adverse Events

Two other adverse events have been observed as shown in **Table 57**.

*Table 57 Other adverse events ("EPP All Patients")*

| Adverse event | Frequency |
|---|---|
| Malaise | 0.5% (1/186) |
| Flu like symptoms with fever of 38 for 24h | 0.5% (1/186) |

#### 11.4.4.3 Serious Adverse Events

One 64-year old male patient was reported with a cerebrovascular accident (right hemiparesis and mild motor aphasia). He had a history of risk factors including hypertension, smoking, recurrent CVA in the past, and suspended antiplatelet aggregation therapy (prior to the transurethral tumor resection and did not resume this therapy afterwards). The patient arrived for his 2$^{nd}$ weekly treatment and complained about worsening of the weakness of right upper limb and dysarthria, which had started three days earlier. The treatment was canceled and the patient was hospitalized. The event was considered by the physician to be a serious adverse event unrelated to the drug (MMC) or to Synergo. The patient started the treatment with mild right hemiparesis due to a previous CVA. After the recent event the patient still suffered mild right hemiparesis that is regarded as a sequela of the two CVAs. The patient continued his remaining treatments as scheduled.

One 78-year old male patient experienced a coronary spasm and loss of consciousness during the 2$^{nd}$ half of treatment. He had a history of ischemic coronary disease prior to Synergo treatment. Despite repeated requests to the hospital, further information was not submitted to the sponsor. Since this adverse event occurred during an active treatment session, the Sponsor considers this probably related to the Synergo treatment.

### 11.4.5 EPP Conclusions

#### 11.4.5.1 Efficacy Conclusions

The high-risk EPP patient population combined with issues related to the real-life, commercial use of a device (e.g., re-imbursement policies), as well as the bias inherent in the follow-up of recurrence-free patients, may explain the somewhat less favorable efficacy results (recurrence) in the EPP compared to Study 101.1. Nevertheless, the results are still surprisingly good. The estimated 2-year recurrence rate of 32.2% for Synergo treatment is far better than standard conventional MMC treatments and at least as good as or in some cases better than today's gold standard, FDA approved BCG treatment.

#### 11.4.5.2 Safety Conclusions

When comparing the adverse events reported for the EPP group to the events reported in the PMA 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). Similar to Study 101.1 and Study 102.2, the most common adverse events observed in EPP are pain and posterior wall tissue reaction.

The additional EPP supportive data, consisting of an additional 122 patients treated with the Synergo device, supports Study 101.1, in part by presenting clinical outcomes that are far better than the conventional MMC treatment and at least as good as or better than BCG treatment.

# 12. BLADDER SALVAGE PATIENTS (BS)

## 12.1 Introduction

Bladder Salvage (BS) patients consisted of a cohort of 82 extremely high-risk patients. These patients were both highly recurrent (≥3 recurrences in last 24 months) and also had failed prior BCG treatment(s). They have traditionally been considered as obvious candidates for cystectomy and only in recent years have researchers tried alternative treatments, referred to as bladder salvage treatments.

The safety results presented in this section of the initial use of the Synergo treatment in this extreme high-risk group of Bladder Salvage patients have actually paved the way for the now routine, commercial use of the device in the intended patient population of all intermediate and high- risk STCCB patients. Only safety results are presented here since this extreme high-risk group does not represent the overall patient population (i.e., intermediate and high risk) indicated for Synergo treatment.

## 12.2 Safety

Expected adverse events are presented separately for those that change from session to session (e.g., pain) and are transient in nature ("per-session" adverse events), and for those that have a more sustained effect, i.e. those that persist over a few sessions ("per-patient" adverse events) **Table 58 and Table 59** present the frequency of expected adverse events for each of these types of adverse events.

***Table 58 "Per Session" adverse events ("All Study Patients")***

| Adverse event | Frequency |
|---|---|
| Pain (including spasm) during session | 7.1% (60/845) |
| Dysuria | 2.8% (24/845) |
| Urge and/or incontinence during session | 4.9% (41/845) |
| Hematuria | 1.3% (11/845) |
| Traumatic catheter insertion | 1.1% (9/845) |
| Urinary frequency/urgency | 0.9% (8/845) |
| Cystitis | 0.1 (1/845) |
| Urinary tract infection | 0.4% (3/845) |

***Table 59 "Per Patient" adverse events ("All Study Patients")***

| Adverse event | Frequency |
|---|---|
| Posterior wall tissue reaction | 35.4 % (29/82) |
| Skin allergy | 7.3 % (6/82) |
| Urethral stenosis (edema / stricture) | 7.3% (6/82) |
| Bladder wall necrosis | 8.5% (7/82) |

Four other adverse events have been observed and are shown in **Table 60.**

***Table 60 Other adverse events ("All Study Patients")***

| **Adverse event** | **Frequency** |
|---|---|
| Nausea, vomiting and heat flushes | 1.2% (1/82) |
| Vaso-vagal reaction | 1.2% (1/82) |
| Tremor (transient) | 1.2% (1/82) |
| Hyperventilation (transient) | 1.2% (1/82) |

One 84-year old female patient was reported with deep vein thrombosis (serious adverse event) approximately 6 months after she started treatments with Synergo, during the maintenance period. There is no indication that this event is related to Synergo treatment.

## 12.3 Conclusions

The Bladder Salvage patients were obtained from an open, uncontrolled study, hence adverse event reporting may be somewhat incomplete. This is especially true for common and well-documented side effects of Synergo, like pain and irritative symptoms. Unusual or severe adverse events are likely being well reported, due to the Sponsor's ongoing efforts encouraging adverse event reporting. Indeed, the frequency of common adverse event reported for the BS patients is, as expected, lower than that reported for the controlled Study 101.1 and Study 102.1.

When comparing the adverse events reported for the BS group to the events reported in the PMA pivotal Study 101.1, most of these types of events are the same. As in Study 101.1 and Study 102.2, the most common adverse events reported in BS are pain and posterior wall tissue reaction.

## 13. EUROPEAN ABLATION PATIENTS (EAP) - COMMERCIAL USE

The European Ablation Patients (EAP) are included here as additional supportive safety data from another 104 patients treated with Synergo, albeit for a different clinical indication for use. The Synergo treatment in the EAP group was indicated for ablative treatment of STCCB in patients for whom TUR was not possible or not recommended.

The EAP group included patients treated from August 2000 through July 2003, including 104 patients. The majority of these patients referred to Synergo treatment were the most difficult patients to treat, 85% of them high-risk according to EAU risk category and 65% of patients failed prior BCG therapy. The Synergo treatment for these patients was often offered as a last resort treatment.

It should be noted that the Synergo ablative treatments were administered with twice (i.e., 2 x 40mg) the dose used for prophylactic treatment of STCCB (2 x 20mg) .

**Table 61** presents the adverse events for EAP group. Note that the total number of events is more than the total number of patients (n=104, EAP All Study Patients), as a patient may have been reported with more than one adverse event during the treatment sessions. The 104 patients underwent a total of 764 treatment sessions.

***Table 61a "Per Session" adverse events ("All Study Patients")***

| Adverse event | Frequency |
|---|---|
| Pain (including spasm) during session | 9.3% (71/764) |
| Dysuria | 5.9% (45/764) |
| Hematuria | 1.8% (14/764) |
| Urinary tract infection | 0.1% (1/764) |
| Tissue Reaction | 1.3% (10/764) |

***Table 61b "Per Patient" adverse events ("All Study Patients")***

| Adverse event | Frequency |
|---|---|
| Posterior wall tissue reaction | 20.2% (21/104) |
| Skin allergy | 6.7% (7/104) |
| Urethral stenosis (edema / stricture) | 4.8% (5/104) |
| Bladder wall necrosis | 16.4% (17/104) |

***Table 61c Other adverse events ("All Study Patients")***

| Adverse event | Frequency |
|---|---|
| Other Adverse Events | 2.9% (3/104) |
| Serious Adverse Events | 1.9% (2/104) |

The expected adverse events are listed in the **Table 61**. Other adverse events include 2 patients with false passage or traumatic catheter insertion and 1 patient with reduced bladder capacity. Serious adverse events included two cases of hydronephrosis.

Note that in this ablative study, patients were recruited with viable tumors, therefore we expect to observe bladder wall necrosis as a result of bladder tumor eradication.

As can be seen from **Table 61**, the adverse events and serious adverse events reported for the EAP group are similar to the types of events reported in Studies 101.1 and 102.1. As in Study 101.1 and Study 102.2, pain and posterior wall tissue reaction are frequently reported in EAP.

## 14. STUDY 101.4 ABLATION PATIENTS

Study 101.4 data is included here as additional supportive safety data from another 42 patients treated with Synergo for ablative treatment of STCCB in patients for whom TUR was not possible or not recommended.

Safety evaluation for these patients was identical to the safety evaluation of Study 101.1 and included complete reporting of all adverse events and complete GCP monitoring of adverse event reporting by experienced monitors. Study 101.4 was conducted at two of the same clinical centers as Study 101.1.

It should be noted here that the Synergo treatments at one of the two clinical centers in Study 101.4 were administered with twice (i.e., 2 x 40mg) the dose used for prophylactic treatment of STCCB (2 x 20mg). Since this was an exploratory study, different doses were used. For most of the adverse events there was no difference in reporting of adverse events between the different treatment doses. The only side effect that presented a significant difference between the dosages was dysuria. There was also a suggestion of an increase in rates of hematuria, although formal statistical significance was not reached. However, there seems to be no clinical significance to the fact that there was a higher incidence of dysuria and hematuria in the patients treated with a lower dosage (20mg) of MMC.

**Table 62** presents the frequencies of expected adverse events, other adverse events and serious adverse events for all Study 101.4 patients. Note that the total number of events is more than the total number of patients (n=42, Study 101.4 All Study Patients), as a patient may have been reported with more than one event. The 42 patients underwent a total of 394 treatment sessions.

***Table 62a "Per Session" adverse events ("All Study Patients")***

| Adverse event | Frequency |
|---|---|
| Pain (including spasm) during session | 3.3% (13/394) |
| Dysuria | 2.5% (10/394) |
| Hematuria | 1.0% (4/394) |
| Urinary tract infection | 0.5% (2/394) |
| Tissue Reaction | 2.8% (11/394) |

***Table 62b "Per Patient" adverse events ("All Study Patients")***

| Adverse event | Frequency |
|---|---|
| Posterior wall tissue reaction | 64.3% (27/42) |
| Skin allergy | 9.5% (4/42) |
| Urethral stenosis (edema / stricture) | 2.4% (1/42) |
| Bladder wall necrosis | 14.3% (6/42) |

***Table 62c Other adverse events ("All Study Patients")***

| Adverse event | Frequency |
|---|---|
| Other Adverse Events | 14.3% (6/42) |
| Serious Adverse Events | 0% (0/42) |

The expected adverse events are listed in **Table 62**. Other adverse events include 3 patients with reduced bladder capacity, 1 patient with calculi and 2 patients with general weakness. No serious adverse events were reported in study 101.4.

As the EAP study, Study 101.4 is also an ablative study in which patients were recruited with viable tumors, therefore we expect to observe bladder wall necrosis as a result of bladder tumor eradication.

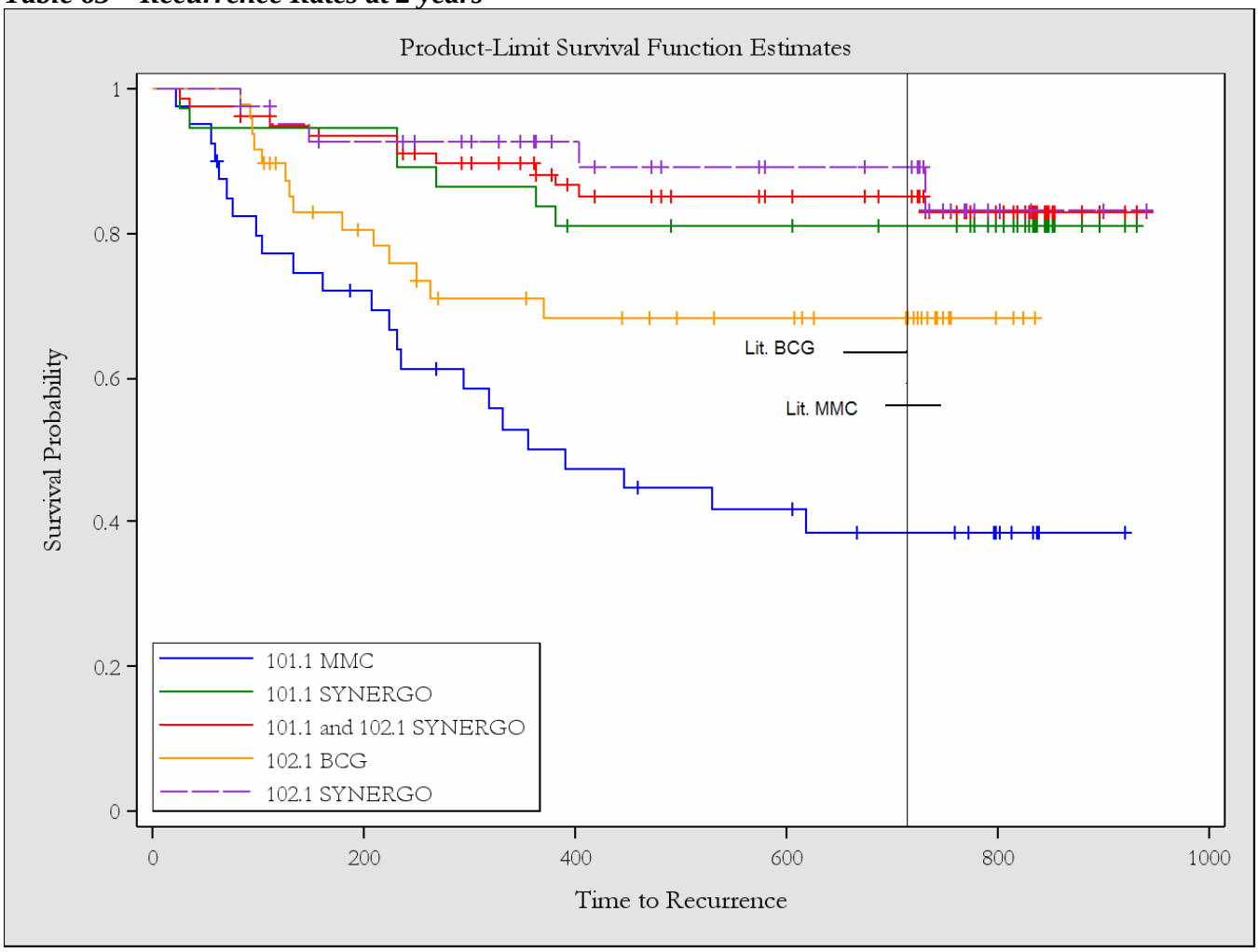
As can be seen from **Table 62**, the adverse events reported for Study 101.4 are similar to the events reported in Studies 101.1 and 102.1. As in Study 101.1 and Study 102.2, the most common adverse events are pain and posterior wall tissue reaction in Study 101.4.

## 15. OVERALL SUMMARY

### 15.1 EFFICACY

**Table 63** presents the Kaplan-Meier curves for the different studies conducted with the Synergo device. For comparison we super-imposed 2 horizontal lines at 2 years time which correspond to the results from the literature meta-analysis for BCG and MMC.

***Table 63 – Recurrence Rates at 2 years***




The clinical results of Study 101.1 clearly demonstrate a highly significant difference in tumor recurrence between groups, where the rate of tumor recurrence in the Synergo group is significantly lower than in the MMC Control group regardless of the patient populations analyzed. The PP analysis shows the largest reduction, almost an 80% reduction in the rate of recurrence in the Synergo group compared to the Control group (hazard ratio (HR)=0.21; 95% CI=0.08 to 0.51). Similarly, in the Evaluable Patients: Randomized As Treated, the Synergo group shows nearly 80% reduction in the rate of recurrence compared to the Control group (HR=0.23; 95% CI=0.09 to 0.54). Even in the worst-case scenario, the Synergo group shows more than 50% reduction in the rate of recurrence compared to the Control group (HR=0.46; 95% CI=0.23 to 0.91).

The long-term efficacy results show that even after over 10 years of follow-up, the treatment difference is still notable. The Kaplan-Meier estimates of recurrence rate at 10 years are 48% in the Synergo group and 85% in the Control group. The long-term results further support that the original findings of Study 101.1 were indeed unbiased even though the study was unblinded.

There were no significant differences between the treatment groups regarding the progression of stage or worsening of grade at tumor recurrence. There were also no significant differences in the occurrence of CIS and urothelial cell carcinoma in the upper tract or in the prostatic urethra, or the occurrence of distance metastasis. Study 101.1 is a randomized, controlled study, which demonstrated highly significant statistical results in reducing tumor recurrence. The low estimated 2-year probability of recurrence of 17.1% in the pivotal Study 101.1 was further supported by the 2-year probability of recurrence of 16.9 % observed in Study 102.1.

As Study 101.1 and Study 102.1 were similar in design and performance, except for the Control group, an analysis was considered in which the combined Synergo groups from the two studies was compared to the MMC Control group from Study 101.1 and the BCG Control group from Study 102.1. In this analysis, the estimated 2-year recurrence rates were 17.1% for the combined Study 101.1 and Study 102.1 Synergo group, 31.7% for the BCG Control group (Study 102.1), and 61.6% for the MMC Control group (Study 101.1). The combined analysis provides additional evidence that the Synergo treatment is significantly more efficacious than the conventionally available MMC or BCG treatments.

A systematic review of the literature was performed to evaluate the effect of conventionally available MMC and BCG prophylactic treatment for STCCB. Two-year recurrence rates were estimated from the literature for treatment with BCG or MMC. The estimated 2-year recurrence rate is 35.6% for BCG treatment and 41.5% for MMC treatment. In the Synergo studies, the estimated 2-year recurrence rates were 31.7% for the BCG Control group (Study 102.1) and 61.6% for the MMC Control group (Study 101.1). The recurrence rates for MMC treatment is higher in Study 101.1 compared to the literature-base estimates. The 2-year estimated recurrence rate for BCG treatment from the meta-analysis (35.6%) is similar to that reported for the BCG Control group in Study 102.1 (31.7%)[2].

In conclusion, the clinical results with Synergo treatment is far better than conventionally available MMC and at least as good if not better than BCG treatments for prophylactic treatment of STCCB in intermediate and high-risk patients.

Additional supportive data was also provided from the European Prophylactic Patient (EPP), with an estimated 2-year recurrence rate of 32.2%. Although the EPP Synergo results are somewhat less favorable compared to the controlled Synergo studies, this

[2] Note that the 2-year estimated recurrence rate for MMC treatment is higher in the MMC Control group in Study 101.1 (61.6%) compared to the literature-based meta-analysis estimate (41.5%). This difference in recurrence rates for MMC treatment is likely to be a reflection of the difference in patient populations, as Study 101.1 and Study 102.1 included only intermediate and high-risk STCCB patients, whereas data reported in the literature included the overall STCCB patient population, including low-risk patients as well as intermediate and high-risk patients.

difference may be due to the higher risk patients included in the EPP, including a larger number of previous episode and treatment failures and a higher proportion of "highly-recurrent" patients. Furthermore, a bias exists in the EPP regarding the available follow-up data of recurrent-free patients, or lack thereof, which considerably biased the clinical results when compared to the controlled Synergo studies with complete 2-year follow-up data as in Studies 101.1 and Study 102.1 studies.

It should also be noted that the MMC Control groups in both Study 101.1 and in the BCG NDA study report similar 2-year recurrence rates in the intermediate and high-risk STCCB patient population (i.e., 61.6% in Study 101.1 and 55% in the BCG NDA study). Also the BCG Control group in Study 102.1, the BCG group in the BCG NDA study and BCG treatment results reported in the literature meta-analysis report 2-year recurrence rates that are not very different (i.e., 31.7% in Study 102.1, 43% in the BCG NDA study and 36% in the literature meta-analysis). This suggests that the MMC and BCG Control arms in Study 101.1 and Study 102.1 are representative of the clinical outcomes as reported in the medical literature and other FDA submissions and strengthens their validity as reliable treatment controls.

In summary, the current PMA, including the pivotal Study 101.1 and the additional supportive data from the controlled Study 102.1 demonstrates that the Synergo treatment effect is consistent when administered in the intended patient population according to treatment protocol. The Synergo data from Studies 101.1 and 102.1 and the combined Synergo data for these studies demonstrate that the Synergo treatment is significantly better than the BCG and MMC Control groups from these controlled studies, and the BCG and MMC treatments reported in the literature meta-analysis. Furthermore, the Synergo data from these controlled studies and from the additional supportive EPP group are better than both the BCG and MMC clinical results provided for FDA approval of BCG treatment.

## 15.2 SAFETY

The Synergo PMA No. P010045 and its amendments present the safety results of 4502 treatment sessions in 506 patients, including 92 patients from controlled, randomized Studies 101.1 and 102.1, another 268 patients from real-life, commercial prophylactic use of the Synergo device (EPP and BS) and an additional 146 patients from two ablative (neo-adjuvant) studies using the Synergo device (Study 104.1 and EAP).

The only anticipated adverse events that were reported as significantly more frequent in the Synergo group were pain and posterior wall tissue reaction. However, out of a total of 426 treatment sessions performed in the Synergo group in Study 101.1, only 10 treatment sessions were shortened and 7 treatment sessions were performed without hyperthermia due to pain. In all occurrences of pain, the event was localized and transient during delivery of therapeutic heat during treatment and resolved without any residual effects. Furthermore, the above reported rates of pain per session in all the Synergo studies and patient groups shows a reasonable rate of this side effect.

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 of the study 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.

Although, urethral stenosis/stricture was not significantly more frequent in the Synergo group compared to the Control group in Study 101.1, there were more frequent reports of this event in the Synergo patients in Study 101.1, Study 102.1 and in the additional supportive patient groups. An actual 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 two patients were reported as having urethral stricture, but needed only urethral dilatation. In any case, urethral stenosis is generally expected in TCC patients, as they typically undergo multiple invasive trans-urethral procedures, such as resections, cystoscopies and catheterization. The higher incidence among Synergo patients compared to Control patients can be explained by the relatively larger diameter of the Synergo catheter (20F). However, in the majority of patients, it was mostly urethral edema which caused the stenosis and it was usually self-resolving.

The expected adverse events reported in the additional, controlled, randomized Study 102.1 were similar to those reported in Study 101.1, including dysuria, hematuria, tissue reaction, urinary tract infection, pain, posterior wall tissue reaction and bladder wall necrosis. Here too, the most common anticipated adverse events were pain and posterior wall tissue reaction. Furthermore, the additional supportive safety data presented for the additional study and patient groups (EPP, BS, EAP and Study 101.4) also reported similar expected adverse events with pain and posterior wall tissue reaction the most common. That is, all the studies and patient groups treated with Synergo showed the same side effects of the treatment in a consistent and repeatable manner.

There were a total of 7 patients reported with reduced bladder capacity out of 507 patients treated with Synergo treatment. In two patients in Study 101.1 this event was mild and required no medical intervention. In 4 patients (Study 101.4 and EAP) the Synergo treatments were administered with twice the indicated dose of MMC (2x40mg) compared to the prophylactic dose (2x20mg). 3 of these 4 patients underwent cystectomy in order to resolve this adverse event. The fourth patient dropped from the study as a result of transitional cell carcinoma in the renal pelvis after the 6-month follow-up and the outcome of this adverse event is unknown. In 1 patient in Study 102.1 this event resulted in cystectomy, but the patient had a reduced bladder volume of 150cc prior to receiving Synergo treatment, which is borderline for study inclusion. It is also important to note that reduced bladder capacity or bladder contraction has been reported in the literature for intravesical chemotherapy or immunotherapy as is noted later in this discussion.

Other adverse events that occurred in Study 102.1 or in the additional supportive data from the other studies and patient groups (EPP, BS, EAP and Study 101.4) were not related to the Synergo treatment. Therefore, the supportive safety results further demonstrate the consistent safety profile of the Synergo treatment.

The safety data presented for Study 101.1 and the supporting studies and patient groups are consistent, showing the same expected adverse events, some of them related to the use of hyperthermia, e.g., pain and posterior wall tissue reaction. Most of these events were mild, had minimal (or no) clinical significance and resolved without medical treatment or significant residual effects. The other adverse events and serious adverse events reported for the supporting studies and patient groups did not reveal new or different safety information regarding the Synergo treatment, thus strengthening the acceptable safety profile of the Synergo device presented in Study 101.1.

Furthermore, 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[7]. 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[3,4]. 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[5,6]. Furthermore, intravesical chemotherapy administration has led to severe bladder contracture[7,8].

The following table adapted from the AUA Bladder Cancer Guidelines[9] (1999) presents the rates of these common adverse events for intravesical agents:

***Table 65: Summary of Toxicity Reported for Common Intravesical Agents***

| **Toxicity** | **Thiotepa** | **MMC** | **Doxorubicin** | **BCG** |
|---|---|---|---|---|
| ***Local*** | | | | |
| Frequency/Nocturia | 11% (1-42%) | 42% (26-59%) | 27% (23-32%) | 63% (48-76%) |
| Dysuria | 30% (10-57%) | 35% (30-41%) | 20% (8-39%) | 75% (64-84%) |
| Irritative Symptoms | 13% (7-21%) | 18% (12-26%) | 21% (13-30%) | Too varied to calculate |
| Pain/Cramps | NR | 10% (6-14%) | 12% (4-25%) | 12% (7-18%) |
| Hematuria | 13% (4-23%) | 16% (7-28%) | 19% (12-29%) | 29% (22-36%) |
| Incontinence | NR | 1% (0.4-4%) | 9% (3-18%) | 4% (3-6%) |
| Bladder Contracture* | 3% (0.3-13%) | 5% (2-11%) | 3% (0.8-6%) | 3% (2-5%) |
| ***Systemic*** | | | | |
| Flu-like | 11% (4-23%) | 20% (4-48%) | 7% (3-13%) | 24% (18-31%) |
| Fever/Chills | 4% (1-10%) | 3% (1-7%) | 4% (2-9%) | 27% (22-32%) |
| Arthalgias | NR | 9% (0.1-47%) | 1% (0.1-5%) | 5% (1-13%) |
| Myelosuppression | 13% (8-19%) | 2% (0.3-7%) | 0.8% (0.2-2%) | 1% (0.1-4%) |
| Nausea/Vomiting* | 9% (0.8-31%) | 9% (1-26%) | 8% (4-13%) | 9% (6-14%) |
| Skin Rash | 2% (0.4-4%) | 13% (8-19%) | 2% (0.5-6%) | 6% (3-10%) |

| Toxicity | Thiotepa | MMC | Doxorubicin | BCG |
|---|---|---|---|---|
| Other | 0.2% (0-2%) | 3% (0.5-8%) | 0.2% (0-2%) | 23% (19-27%) |
| ***Infectious*** | | | | |
| Bacterial Cystitis* | 7% (2-16%) | 20% (17-23%) | 6% (2-12%) | 20% (13-8%) |
| Epid/Prost/Urethral | 0.4% (0-4%) | 4% (2-9%) | 2% (0.1-7%) | 5% (4-8%) |
| Pneumonia | NR | 0.2% (0-2%) | NR | 1% (0.2-3%) |
| Systemic | 0.3% (0-3%) | NR | NR | 4% (2-5%) |
| ***Treatment Continuation*** | | | | |
| Incomplete | 5% (2-11%) | 9% (2-14%) | 7% (2-16%) | 8% (5-10%) |
| Interruption | 6% (3-11%) | 11% (8-16%) | 2% (0.1-8%) | 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.

In summary, the safety profile of the Synergo treatment is not significantly 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 BCG vs. MMC study from the BCG NDA and 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.

Thus, we believe that the data from the various studies described demonstrate that Synergo is a safe and effective prophylactic treatment for superficial transitional carcinoma of the bladder.

## 16. RISK BENEFIT ANALYSIS

The clinical data for the PMA pivotal Study 101.1 shows findings of improved efficacy for the Synergo treatment over the MMC Control treatment. The results for the Synergo treatment are better than the results commonly accepted as performance benchmark criteria for prevention of recurrence in intermediate and high-risk STCCB patients. Moreover, the highly significant statistical results that are maintained over a 5 and 10-year period. Study 101.1 is supported by Study 102.1, another randomized, controlled study, and by the combined Synergo results of both Study 101.1 and Study 102.1. Additional data regarding the commercial use of Synergo treatment in the European Prophylactic Patients (EPP) provides further support. The combined controlled Synergo studies were compared to the MMC and BCG Control groups from each of the Synergo controlled studies, to the MMC and BCG treatment results published in the literature meta-analysis and to the BCG and MMC Control groups from the FDA approved BCG NDA (92-0306).

The safety profile of the Synergo treatment is not significantly different than what has been generally reported in the literature for intravesical prophylactic treatment. The same types of adverse events occurred and with similar frequencies. Use of the Synergo treatment generated consistent side effects related to the use of hyperthermia and MMC in all the controlled studies and patient groups. Most events were mild, had minimal (or no) clinical significance, resolved without medical treatment and without any residual effects or with mild, clinically insignificant effects. This kind of safety profile should be considered acceptable for cancer treatments with the level of efficacy reported.

It is worthwhile to compare the Synergo safety profile to that of the other treatments approved by FDA for prevention of intermediate and high-risk STCCB, namely TICE-BCG. The safety discussions showed the adverse events reported in the BCG study submitted in support of the BCG NDA (92-0306) compared to the events reported in the Synergo studies. These rates of occurrence of these events for BCG treatment were similar or sometimes even higher than for Synergo treatment. In general, it can be seen that the Synergo treatment has a safety profile that is at least as good as if not better than BCG or MMC treatment. This is true even without discussing the potentially fatal adverse events of BCG treatment.

When evaluating the risk/benefit tradeoff for the new Synergo treatment, whose benefit was shown to be clearly greater than the acceptable risk it presents, it is important to consider the number of recurrences that may be prevented, the number of cystectomies that may be avoided, and the accompanying savings both in cost and in quality of life for the diseased patients and the health care system.

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## APPENDIX A – META-ANALYSIS METHODOLOGY

### Introduction

A systematic review of the effect of MMC and BCG adjuvant treatment of STCCB based on reports available in the literature was conducted. The criteria for inclusion of literature in the review were pre-specified and are described here within.

The 1-year and 2-year recurrence free survival probabilities (S(1yr), S(2yrs)) and standard errors from each of the studies were estimated from the Kaplan-Meier curves published in the papers using the methods of Parmar et al.[3], unless the data were presented in a straightforward manner in the paper. Once the 1-year and 2-year recurrence free survival probabilities and standard errors were obtained the overall one and two-year probabilities of recurrence and their respective confidence intervals were calculated separately for MMC or BCG treated patients, using a weighted average of the individual study results.

The 1-year and 2-year probabilities of recurrence are compared between:

- Synergo group from Study 101.1 and MMC results from the literature;
- Synergo group from Study 102.1 and BCG results from the literature;
- Combined Synergo groups (Study 101.1 and Study 102.1) and MMC results from the literature; and
- Combined Synergo groups (Study 101.1 and Study 102.1) and BCG results from the literature.

Meta-Analysis of MMC in Literature

Search term used:*

| Search | Most Recent Queries | Time | Result |
|---|---|---|---|
| #4 | Search "meta analysis"[Publication Type] AND "mitomycin/therapeutic use"[MeSH Terms] AND "urinary bladder neoplasms/therapy"[MeSH Terms] | 04:08:40 | 6 |

*Search was performed on March 13, 2007.

The term “Meta-analysis”[Publication Type] was used in order to select data from specific articles, which were already tested for quality and found to be appropriate for use in meta-analyses. The 6 results generated by the search key included the following:

1. Bohle A, Bock PR. Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology. 2004 Apr;63(4):682-6; discussion 686-7.

2. Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk

[3] Parmar MKB, Torri V and Stewart L. Extracting summary statistics to perform meta-analysis of the published literature for survival end-points. Statistics in Medicine 1988;17:2815-2834.

superficial bladder cancer: a meta-analysis of randomized trials. BJU Int. 2004 Mar;93(4):485-90. Review.

3. Shelley MD, Court JB, Kynaston H, Wilt TJ, Coles B, Mason M. Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2003;(3):CD003231. Review.

4. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol. 2003 Jan;169(1):90-5.

5. Huncharek M, Kupelnick B. Chemotherapeutic prophylaxis of superficial bladder tumors. Oncology (Williston Park). 2001 Sep;15(9):1106.

6. Huncharek M, McGarry R, Kupelnick B. Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. Anticancer Res. 2001 Jan-Feb;21(1B):765-9.

Since Article No. 5 made several references to another article by the same authors (see below), it was included in the analysis as well:

7. Huncharek M, Geschwind JF, Witherspoon B, McGarry R, Adcock D. Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trials. J Clin Epidemiol. 2000 Jul;53(7):676-80.

Articles 1, 3, and 5 were excluded for the following reasons:

- Article 1: focuses on tumor progression only
- Article 3: is the Cochrane library adaptation of article No. 4
- Article 5: is an editorial letter with insufficient data

This leaves articles 2, 4, 6, and 7 as meta-analysis that may be analyzed for our purpose.

Meta-Analysis of BCG in Literature

Search term used:*

| Search | Most Recent Queries | Time | Result |
|---|---|---|---|
| #1 | Search "meta analysis"[Publication Type] AND "bcg vaccine"[MeSH Terms] AND "urinary bladder neoplasms/therapy"[MeSH Terms] | 08:05:40 | 9 |

*Search was performed on March 8, 2007.

Same approach used for the selection of MMC articles was used to identify BCG articles in the literature. The 9 results generated by the search key included the following:

1. Sylvester RJ, van der Meijden AP, Witjes JA, Kurth K. Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. J Urol. 2005 Jul;174(1):86-91; discussion 91-2.

2. Huncharek M, Kupelnick B. The influence of intravesical therapy on progression of superficial transitional cell carcinoma of the bladder: a metaanalytic comparison of chemotherapy versus bacilli Calmette-Guerin immunotherapy. Am J Clin Oncol. 2004 Oct;27(5):522-8.

3. Bohle A, Bock PR. Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology. 2004 Apr;63(4):682-6; discussion 686-7.

4. Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int. 2004 Mar;93(4):485-90. Review.

5. Shelley MD, Court JB, Kynaston H, Wilt TJ, Coles B, Mason M. Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2003;(3):CD003231. Review.

6. Huncharek M, Kupelnick B. Impact of intravesical chemotherapy versus BCG immunotherapy on recurrence of superficial transitional cell carcinoma of the bladder: metaanalytic reevaluation. Am J Clin Oncol. 2003 Aug;26(4):402-7.

7. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol. 2003 Jan;169(1):90-5.

8. Sylvester RJ, van der MEIJDEN AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol. 2002 Nov;168(5):1964-70.

9. Lamm DL. Comparison of BCG with other intravesical agents. Urology. 1991;37(5 Suppl):30-2. No abstract available.

Article 1, 2, 3, 5, 8, 9 were excluded for the following reasons:

- Article 1: deals with carcinoma in situ tumors only
- Article 2, 3, 8: focuses on tumor progression only
- Article 5: is the Cochrane library adaptation of article No. 4
- Article 9: is 16 years old

This leaves articles 4, 6, and 7 as meta-analysis articles that may be analyzed for our purpose.

Article Selection Methodology

Some meta-analysis articles appeared in both searches. Therefore, it was decided to select all unique meta-analyses directly comparing BCG to MMC. This left us with the following 3 meta-analytic articles:

1. Shelley MD, Wilt TJ, Court J, Coles B, Kynaston H, Mason MD. Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int. 2004 Mar;93(4):485-90. Review.

2. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol. 2003 Jan;169(1):90-5.

3. Huncharek M, Kupelnick B. Impact of intravesical chemotherapy versus BCG immunotherapy on recurrence of superficial transitional cell carcinoma of the bladder: metaanalytic reevaluation. Am J Clin Oncol. 2003 Aug;26(4):402-7.

The purpose of this exercise is to compare the Kaplan-Meier estimates of disease free survival rates of different treatments in Study 101.1 and Study 102.1 to those of the corresponding treatments in the literature. Since these rates are not cited in the meta-analysis articles, they have to be extracted directly from all the original articles (n=19) cited in the meta-analysis articles.

Of the 19 original articles, 9 were excluded from the analysis for the following reasons:

- One article was in Korean and was unavailable for the purpose of data extraction (Lee et al. Korean J Urol 1992;33:1014), and another in Italian (Pagano et al. Acta Urol Ital 1987; suppl.1:4).
- Two articles had no Kaplan-Meier data, and therefore could not be used for the present analysis (Nufueria et al. Eur Urol 2000;37, suppl 2:1-175 and Debruyne et al. Urology 1992; suppl., 40:11).
- Two articles had Kaplan-Meier data only for subsets and were thus not used for the analysis (Melekos et al. Intl Urol and Nephro 1996;28 (4):499-509 and Melekos et al. Oncology 1996;53:281-288).

Another three articles were removed as they represented preliminary results of other papers that are included in the analysis (Ludholm et al. J Urol 1996;156:372-376, Jauhiainen et al. In; Immunotherapy of Urological Tumors 1990:13-26, and Vegt et al. J Urol 1995;153:929-933).

The remaining 10 articles were included in the analysis. The following data were extracted from the articles:

- Kaplan-Meier estimates of disease free survival at 1 year;
- Kaplan-Meier estimates of disease free survival at 2 year.
- Total number of patients used for Kaplan-Meier analysis in each treatment arm;
- The minimum and maximum length of follow-up;

- The identification of any special groups analyzed in the Kaplan-Meier curves (*e.g.*, T1 patient, high-risk patients, etc.).

Statistical Methodology

Estimated recurrence free survival probabilities were obtained using the method of Parmar et al.[3]. Survival probabilities were extracted from the survival curves or from data available in the text. The effective number of patients at risk before time t was calculated using the method from the paper and was used to calculate the standard errors of the survival probabilities.

The standard errors were calculated using the method of Peto:

$$s.e._p[S(t)] = \left\{ \frac{S(t)[1-S(t)]}{R_t} \right\}^2$$

where $R_t$ is the effective number of patients at risk before time t.

Once these estimates were extracted and calculated, the weighted average was calculated as detailed in Fleiss[4]:

$$\bar{S}(t) = \frac{\sum_{i=1}^{N} w_i S_i(t)}{\sum_{i=1}^{N} w_i}$$

where $w_i = 1 / (s.e.(S_i(t)))^2$ and N is the number of studies included.

The weighted mean and its 95% confidence interval were calculated with the PROC MEANS procedure in SAS v9.1 (SAS Institute, Cary NC) weighted by $w_i$.

The weighted average of the probability of recurrence was subsequently calculated as $1-\bar{S}(t)$.

Results

The 1-year and 2-year estimates of probability of recurrence were extracted or calculated from the original articles cited in the meta-analysis articles identified in the literature as these data were not directly reported in the meta-analysis articles (*i.e.*, only hazard ratios between treatment arms were reported).

Table 1 presents the extracted 1-year and 2-year probabilities of recurrence and their respective calculated standard errors.

[4] Fleiss J.L., Statistical methods for rates and proportions, second edition 1981, Wiley.

***Table 1 - Kaplan-Meier Estimates of 1-year and 2-year probability of Recurrence Extracted from the Literature***

| | BCG | | | | | | MMC | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Article** | **N** | **1-year** | **s.e.** | **2-year** | **s.e.** | **comment** | **N** | **1-year** | **s.e.** | **2-year** | **s.e.** |
| Lamm 1991 | 63 | 75.00% | 6.30% | 56.00% | 8.36% | Cis | | | | | |
| Lamm 1991 | 64 | 62.00% | 7.71% | 50.00% | 8.84% | Ta T1 G1-G3 | | | | | |
| Ayed 1998 | 81 | 80.00% | 3.48% | 65.00% | 5.04% | | 189 | 61.00% | 7.42% | 53.00% | 8.92% |
| Witjes 1998 | 159 | 67.00% | 4.68% | 59.00% | 5.85% | BCG RIVM | 168 | 74.00% | 4.04% | 63.00% | 5.36% |
| Witjes 1996 | 140 | 66.00% | 5.00% | 53.00% | 5.00% | BCG TICE | 148 | 73.00% | 4.00% | 61.00% | 5.00% |
| Witjes 1996 | 149 | 70.00% | 4.00% | 61.00% | 5.00% | BCG RIVM | | | | | |
| Rintala 1991 | 45 | 74.00% | 8.04% | 66.00% | 9.89% | | 46 | 40.00% | 12.07% | 32.00% | 13.81% |
| Lamm 1995 | 191 | 70.00% | 4.27% | 59.00% | 5.57% | | 186 | 59.00% | 5.06% | 48.00% | 6.35% |
| Malstorm1999 | 125 | 67.00% | 5.32% | 59.00% | 6.15% | | 125 | 59.00% | 5.92% | 49.00% | 6.86% |
| Krege1996 | 48 | 85.00% | 5.85% | 68.00% | 9.05% | primary | 56 | 86.00% | 5.24% | 70.00% | 8.11% |
| Krege 1996 | 54 | 71.00% | 7.76% | 51.00% | 10.56% | recurrent | 57 | 85.00% | 5.37% | 74.00% | 7.49% |
| Martinez 1990 | 67 | 95.00% | 2.83% | 88.00% | 4.58% | | | | | | |
| Rodriguez 2000 | 229 | 78.00% | 3.19% | 69.00% | 3.91% | | | | | | |

Table 2 presents the weighted estimates of 1-year and 2-year probability of recurrence based on data extracted from the literature. As shown in Table 52, for BCG treatment, the literature-based estimates of probability of recurrence are 22.5% at 1 year and 35.6% at 2 years; for MMC treatment, the literature-based estimates of probability of recurrence are 28.5% at 1 year and 41.5% at 2 years.

***Table 2 - Weighted 1-year and 2-year Probabilities of Recurrence for Treatment with BCG or MMC, Based on Data Reported in the Literature***

| | **1-year Recurrence** | | **2-year Recurrence** | |
|---|---|---|---|---|
| **Treatment** | **KM estimate** | **95% CI** | **KM estimate** | **95% CI** |
| BCG | 22.5% | 20.1%-25.0% | **35.6%** | 32.4%-38.7% |
| MMC | 28.5% | 24.9%-32.2% | **41.5%** | 36.8%-46.3% |

Table 3 presents a summary of the estimated probabilities of recurrence for BCG and MMC in Study 101.1 and Study 102.1. In Study 102.1, the estimated probabilities of recurrence for BCG were 28.9% at 1 year and 31.7% at 2 years. The estimated probabilities of recurrence for MMC were 49.8% at 1 year and 61.5% at 2 years. The estimated probabilities of recurrence for the Synergo groups in these studies are also presented in Table 55.

***Table 3 - Kaplan-Meier Estimates of 1-year and 2-year Probability of Recurrence in Study 101.1 and Study 102.1***

| **Study** | **N** | **1-year Recurrence** | | **2-year Recurrence** | |
|---|---|---|---|---|---|
| | | **KM estimate** | **95% CI** | **KM estimate** | **95% CI** |
| **101.1** | | | | | |
| Synergo | 37 | 16.2% | 4.3%-28.1% | **18.9%** | 6.3%-31.5% |
| MMC | 40 | 49.8% | 33.8%-65.8% | **61.6%** | 45.67%-77.5% |
| **102.1** | | | | | |
| Synergo | 42 | 7.4% | 0.0%-15.5% | **16. 9%** | 2.07%-31.7% |
| BCG | 48 | 29.0% | 15.6%-42.4% | **31.7%** | 17.83%-45.6% |
| **Combined 101.1 & 102.1** | | | | | |
| Combined Synergo | 79 | 11.9% | 4.6%-19.2% | **17.1%** | 8.1%-26.0% |

*Patients who had at least one cystoscopy evaluation were included in the analysis. Results based on “as randomized - as treated” analysis for Synergo Study 101.1 patients.