

GASTROENTEROLOGY & UROLOGY DEVICES PANEL

Gaithersburg, Maryland

June 25, 2008

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

PMA P010045

Proposed Post Approval Study Protocol

Sponsor Comments on Attached Proposed Post Approval Study Protocol

The post approval study (PAS) synopsis presented in this Panel Pack is based a PAS protocol the company submitted to FDA in February, 2007. Since that time, the company has had additional thoughts on the design of the PAS. The company has considered revising the study design primarily relating to the initially proposed hypothesis testing. Many aspects of the study will remain largely the same, with expanded data collection on additional adverse events.

The following reflects the company's current thoughts regarding the attached PAS proposal:

- Upon further review of its prior proposal, the company does not believe that eight separate hypothesis tests for non-inferiority for each of the primary safety endpoints, as originally proposed, is clinically sensible or statistically reasonable. The company believes that estimated adverse event rates will provide adequate safety information on the device to practicing clinicians.
- All adverse events will be collected and analyzed regardless of their relationship with the device.
- All device-related adverse events will be collected and analyzed regardless of their clinical significance. Pain and dysuria will be added to the list of originally proposed device related adverse events. These adverse events will be analyzed using point estimates and 95% confidence intervals. The estimated event rates will be compared qualitatively with those reported in Study 101.1.
- The sample size of 211 was originally proposed to support the hypothesis testing approach. However, the company believes that such hypothesis testing is no longer required and that a substantially smaller sample size will be sufficient to estimate the adverse event rates with appropriate precisions. The company now believes that the previously proposed hypothesis testing should not be required.

May 8, 2008

Proposed Post Approval Study Protocol Synopsis

Sponsor/ Sponsor Contact	Medical Enterprises Ltd. 6 Odem St., POB 7166 Petah Tikva 49170 Israel Tel: +972 3 924 48 30
Study Title/ Protocol Number	Synergo Post Approval Study
Device Name	Synergo® SB-TS 101.1
Intended Use	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.
Objective	The objective of this study is to evaluate the safety of the Synergo system in a U.S. population.
Type of Study	Multi-center clinical study
Study Group	Single arm study of Synergo treatment only
Treatment Regimen	All patients will be treated with the Synergo in conjunction with Mitomycin C instillations. The treatment regimen will consist of an induction phase of eight weekly sessions, followed by maintenance treatment consisting of four monthly sessions, for a total of 12 treatment sessions over a six-month period. Recurrence evaluation using cystoscopy with biopsies of any suspected areas, and cytology will be performed every three months beginning one month after the inductive phase.
Key Eligibility Criteria	
<u>Inclusion Criteria</u>	<ul style="list-style-type: none"> • Subjects with resected Stage Ta or T1 and Grade G1-G3, STCCB, intermediate or high risk (according to the European Urology Association definitions) • Complete tumor eradication must be possible • Subjects with a life expectancy > 12 months • Subjects able to understand the characteristics, the purpose and the procedures of the study • Subjects willing to sign informed consent
<u>Exclusion Criteria</u>	<ul style="list-style-type: none"> • Subjects with Ta, G1 single transitional tumors at first episode of disease • Subjects with tumor stage > T1 • Subjects with Tis transitional tumor (pure or concomitant to a papillary tumor) • 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

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	<ul style="list-style-type: none"> • 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 > two • Presence of another active malignancy • Well known allergy to Mitomycin-C • Subjects who have been treated with chemotherapy instillations during the last three month • Subjects treated with immunotherapy, cytotoxic agents or radiotherapy during the last three months • Subjects with an active 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, false passage, or any condition that will not allow the insertion of a 20F bladder catheter • Subjects mentally unable to collaborate • Subjects not willing to sign informed consent
<p>Safety Endpoints</p>	<p>Primary:</p> <ul style="list-style-type: none"> • Device-related adverse events <ul style="list-style-type: none"> - Posterior wall tissue reaction - Urethral stenosis / stricture - Hematuria - False passage - Hypotonic bladder - Reduced bladder capacity - Urinary tract infection - Bladder wall necrosis <p>Secondary:</p> <ul style="list-style-type: none"> • Any unanticipated adverse event not previously reported with the Synergo device
<p>Visit Schedule</p>	<p>Patients will be interviewed regarding their health, symptoms, complaints and adverse events in all patient visits, throughout the study period. Visits will be held according to the following schedule:</p> <ul style="list-style-type: none"> • Pre study visit for evaluation of eligibility criteria • Baseline visit for collection of demographic and baseline clinical information, cystoscopy, and cytology. Baseline signs and symptoms will be evaluated for pre-existing conditions that may later be interpreted as treatment related • Eight weekly inductive treatment sessions • Four monthly maintenance treatment sessions • Four follow-up visits at 3, 6, 9, 12 months after study enrollment, including evaluation exams for recurrence (i.e., cystoscopy,

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	cytology and possibly biopsies) • Additional visits as needed
Duration of Investigation	The total duration of a subject's participation in the trial will be approximately 12 months from the time of enrollment until the final follow-up visit.
Sample Size	A total of 211 subjects will be enrolled from three to five U.S. sites. The sample size is calculated using a non-inferiority approach, comparing the event rates of each primary safety endpoint to those observed in the pivotal study. The maximum sample size required for each individual comparison is chosen as the study sample size.
Statistical Analysis	The incidence of each primary safety endpoint will be reported as a percentage together with a 90% exact binomial confidence interval. The null hypothesis of non-inferiority will be rejected in favor of the alternative hypothesis if the upper confidence limit does not exceed the pre-specified upper bound for each event.