Safety and Performance of Metastatic Tumor Cell Trap Device in Patients with Advanced Ovarian Cancer

Statistical Analysis Plan

Versions	Date	Documents used	Author	Validation
Version 2.0	10SEP2019	Protocol MTRAP Version 3.0 (12SEP2017) CRF V4.0 (30AUG2018)	[redacted]	[redacted]
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SIGNATURE PAGE

Safety and Performance of Metastatic Tumor Cell Trap Device in Patients with Advanced Ovarian Cancer

Version 2.0

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CRO

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AT	As-Treated
CRF	Case Report Form
DTC	Disseminated tumor cells
IDS	Interval Debulking Surgery
ITT	Intention To Treat
MAE	Major Adverse Events
MTRAP	Metastatic Tumor Cell Trap Device
PCI	Peritoneal Carcinomatosis Index
PCPU	Polycarbonate Polyurethane
PDS	Primary Debulking Surgery
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

1. OVERVIEW

This statistical analysis plan (SAP) describes the planned statistical analyses of the data collected in the course of the clinical study of the M-Trap device.

This SAP provides additional details concerning the statistical analyses outlined in the protocol (version 3.0 dated 12 September 2017). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data.

1.1. Study Objectives

The objective of this study is to assess the safety and the performance of the M-Trap device in the capture of metastatic tumor cells in Stage IIIC and IV ovarian cancer patients to support CE-marking of the device.

Safety objectives:

The primary objective is to demonstrate that the safety of M-Trap, as measured by freedom from device- and procedure-related major adverse events (MAE) through 6-months post-implantation, is non-inferior to historical controls.

The secondary objective is to collect long-term safety data to support device safety and post-market surveillance. Safety will be evaluated to demonstrate acceptable levels of device-related and procedure-related complications.

Performance objectives:

The primary objective is to confirm M-Trap performance, as determined by histological evidence of tumor cell capture.

The secondary objective is to assess disease focalization with use of the M-Trap device.

1.2. Study Design

This study is a prospective, multi-center, non-blinded, single arm study to evaluate the safety of the M-Trap device in Stage IIIC and IV ovarian cancer patients in comparison to historical controls in which up to 22 patients will be enrolled from up to 8 sites located in Spain.

Patients with one of the following outcomes after debulking surgery will be targeted in this study:

- Residual visible tumor ≤1 cm after primary debulking or
- Complete resection or residual visible tumor ≤1 cm after interval debulking surgery.

Up to twenty-two (22) patients will be treated in the clinical investigation to obtain twenty (20) evaluable patients.

Once patients have received the study treatment, they will be evaluated at 1 month, 3 months, 6 months, 9 months, 12 months, 15 months, and 18 months post-operatively.

This study will be conducted in a two-phase approach, as follows:

(1) The first phase will enroll five (5) patients. Safety data at the 1-month time point will be collected, including physical examination, ultrasound, adverse events, and concomitant medications.

(2) The second phase will enroll the remaining seventeen (17) patients and will commence upon approval by AEMPS to proceed with a continuation of the study.

1.3. Study Plan

1.3.1. Patient's Follow-up

Nine (9) visits are scheduled:

- Visit 0: Screening within 21 days
- Visit 1: Procedure (D0)
- Visit 2: 1 Month (±1 week)
- Visit 3: 3 Months (±2 weeks)
- Visit 4: 6 Months (±2 weeks)
- Visit 5: 9 Months (±1 month)
- Visit 6: 12 Months (±1 month)
- Visit 7: 15 Months (±1 month)
- Visit 8: 18 Months (±1 month)

1.3.2. Study Device Use

The M-Trap Device (Metastatic Tumor Cell Trap Device) represents a breakthrough therapeutic strategy that provides a preferential site for the capture of disseminating tumor cells, transforming a systemic disease into a focalized disease where surgery, radiation, and chemotherapy have proven efficacy. M-Trap is an implantable surgical mesh comprised of a non-resorbable, polycarbonate polyurethane (PCPU) scaffold with a Type I collagen coating.

M-Trap is intended to be implanted into the peritoneal cavity during the tumor debulking procedure to capture disseminating tumor cells. Up to three (3) M-Trap devices will be surgically implanted via laparotomy in the right and left paracolic (pelvic) gutters and behind segment 6 of the liver within the peritoneal cavity of the patient at the time of surgical resection. Patients will receive standard platinum-based chemotherapy. If the cancer is diagnosed to have recurred, M-Trap devices with captured tumor cells will be removed via minimally invasive surgery (laparoscopy).

1.3.3. Study Assessments

The following flowchart applies to the study:

Examination/ Assessment	Visit 0 Screening Within 21 days	Visit 1 Procedure (D0)	Visit 2 1M (±1W)	Visit 3 3M[1] (±2W)	Visit 4 6M[2] (±2W)	Visit 5 9M (±1M)	Visit 6 12M (±1M)	Visit 7 15M (±1M)	Visit 8 18M (±1M)
Signed Informed Consent	X								
Eligibility criteria check	X	X							
Demographics, medical history	X								
Physical examination	X	X	X	X	X	X	X	X	X
Biomarker CA-125	X			X	X	X	X	X	X
CT scan	X			X	X	X	X	X	X
Ultrasound		X	X	X	X	X	X	X	X
PCI[3]	X	X							
Cytology/biopsy									X[4]
Pathology (explant)									X[4]
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X

2. STATISTICAL METHODS

2.1. General Statistical Considerations

2.1.1. Time Points Definition

Baseline/Screening data is defined as the last available observation recorded before the first study device implantation for the patient.

Visit(n) data is defined as the last available observation on or before the Visit(n) time point following the first study device implantation for the patient.

2.1.2. Handling Missing Data

In order to provide unbiased and informative findings, no replacement of missing values is planned for any parameters.

2.1.3. Descriptive Statistics in Summary Tables

- *Continuous variables* will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations will also be specified.

[1] 3M visit must occur after the final chemotherapy infusion in interval debulking patients. The 3M CT scan will serve as the baseline for assessing disease progression for purposes of device removal.
[2] 6M visit must occur after the final chemotherapy infusion in primary debulking patients. The 6M CT scan will serve as the baseline for assessing disease progression for purposes of device removal.
[3] Peritoneal Carcinomatosis Index.
[4] To be performed at time of device removal. Device removal may occur earlier if conditions for device removal described in Section 6.2 of the protocol are met.

- *Categorical variables* will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Percentages will be calculated on the number of non-missing observations, and will be displayed using one decimal. The number of missing observations will also be specified.

2.1.4. Inferential Analysis

- Confidence intervals:

The 95% bilateral confidence interval of the mean will be calculated for continuous variable if pertinent.

For categorical variables, if pertinent, the 95% asymptotic confidence interval will be calculated if theoretical assumptions are verified. If this is not the case, and the corresponding proportion is 0% or 100%, then the Agresti-Coull confidence interval will be calculated instead. In all other cases, the exact confidence interval will be calculated.

2.1.5. Interim Analysis

An interim analysis will be performed after all patients reach the 6-month time point to support the CE-marking application.

2.1.6. Data Listings

Patient data listings will be selected data supportive of summary statistical tables, including derived/calculated data from statistical process. These key data listings will be performed on selected analysis sets according to the focus of the listings.

2.2. Sample size calculation

The primary objective is to demonstrate that the safety of M-Trap, as measured by freedom from device- and procedure-related major adverse events (see Primary Endpoint for definition) through 6-months post-implantation, is non-inferior to historical controls. Using a success rate of 90% (freedom from device- and procedure-related major adverse events), a non-inferiority margin of 25%, >85% power, and one-sided alpha=0.05, a sample size of n=20 patients is needed to demonstrate that M-Trap is as safe as current standard-of-care through 6-months post-surgery. Assuming a 10% dropout rate, up to 22 patients will be treated to have 20 evaluable patients.

2.3. Analysis Sets

2.3.1. Definition of patient populations

Two (02) analysis sets populations will be defined:

- The Intent-to-Treat (ITT) population will comprise all patients who signed their informed consent, have been judged suitable for index procedure and are compliant with all inclusion/exclusion criteria.
- The As-Treated (AT) population will include all subjects from the ITT population implanted with at least one (1) M-Trap device.

2.3.2. Protocol Deviations

Protocol deviations are defined as instances where the protocol requirements are not followed in such a manner whereby data is unusable or unavailable. Protocol deviations are less serious in nature as long as they do not have an effect on the rights, safety or welfare of the study subject.

Protocol deviations include, but are not limited to:

- Examinations/test/assessment not performed within the allowed follow-up window
- Required data not obtained

The study site should report the protocol deviation on the applicable CRF page.

2.4. Statistical Analyses

2.4.1. Patient Disposition and Follow-up

The number and percentage of patients included in each population and the reasons of non-inclusion in each subsequent population will be presented on the ITT population. The distribution of populations by site will be presented as well.

The number and percentage of patients present at each visit will be presented on the ITT and the As-treated population with the study exit reasons.

The average time of patient follow-up will be given on the ITT and on the As-treated population.

2.4.2. Baseline (Screening) Patient Characteristics

Descriptive statistical data will be used to draw up a recapitulation of the characteristics of the patients at the time of Enrollment/Screening visit.

The following data will be presented on the ITT and the As-treated populations:

- Demographics and Physical Exam: Age at Enrollment, Height (cm), Weight (kg), BMI (kg/m^2), Temperature (°C), Blood pressure (Systolic and Diastolic in mmHg), Heart rate (bpm), Pregnancy test performed (Yes/No), the result if Yes and the reason if No or Not applicable, Specific abdominal examination performed (Yes/No), Presence of nodules or bumps if Yes (Yes/No) and How many nodules or bumps if Yes, Specific gynecologic examination performed (Yes/No), Presence of nodules or bumps in the cul-de-sac if Yes (Yes/No) and How many nodules or bumps in the cul-de-sac if Yes, Ovarian cancer stage, ECOG performance status.
- Medical History: Neurological, Respiratory, Smoker or past smoker (Yes/No), if Yes Current/Past and if Yes the number of years smoking, Arrhythmia, Symptomatic congestive heart failure, Unstable angina pectoris, Myocardial infraction, Ischemic heart disease, Pulmonary embolism, Deep vein thrombosis, Genitourinary, Allergy/Immunologic, Psychiatric, Current active infection and At least one other medical history.
- Specific Cancer History: Prior treatment with abdominal and/or pelvic radiotherapy, Presence of central nervous system or cerebral metastases, Recurrent ovarian cancer, History of other cancer, Hypersensitivity to carboplatin or paclitaxel, Current treatment using other antineoplastic agents, Type of debulking surgery planned, Three or four rounds of chemotherapy given prior to surgery if interval (Yes/No) and specification of the number if Yes.
- Peritoneal Carcinomatosis Index (PCI): Peritoneal Carcinomatosis Index (PCI) performed (Yes/No), PCI score if Yes, Detail of PCI scores (Region, Maximum lesion size (cm) and Lesion size score).
- Biomarker CA-125: Biomarker CA-125 (test performed Yes/No) and the Biomarker CA-125 result (U/mL). The analysis of the Biomarker CA-125 will be performed on primary debulking surgery (PDS) patients, interval debulking surgery (IDS) patients and overall.
- CT Scan: Abdominal CT Scan obtained, Pelvic CT Scan obtained, Chest CT Scan obtained, Lesions Sites, Lesions location, Lesions measurable (Yes/No), Lesions Measurements (mm) if measurable.
- Medications: Patient receiving any concomitant medication (Yes/No).

2.4.3. Procedure (D0) Patients characteristics

Descriptive statistical data will be used to draw up a recapitulation of the intervention details at the time of the operation.

The following data will be presented on the ITT and the As-Treated populations:

- Physical exam: Weight (kg), BMI (kg/m^2), Temperature (°C), Blood pressure (Systolic and Diastolic in mmHg), Heart rate (bpm), Specific abdominal examination performed (Yes/No), Presence of nodules or bumps if Yes (Yes/No) and How many nodules or bumps if Yes, Specific gynecologic examination performed (Yes/No), Presence of nodules or bumps in the cul-de-sac if Yes (Yes/No) and How many nodules or bumps in the cul-de-sac if Yes, Pre-operative serum albumin (g/dL) and Pre-operative hemoglobin (g/dL).
- Procedural Information: Type of debulking surgery, Debulking surgery duration (HH:MM), Pre-debulking PCI performed (Yes/No), PCI score if Yes, Detail of PCI scores (Region, Maximum lesion size (cm) and Lesion size score), Post-debulking PCI performed (Yes/No), PCI score if Yes, Detail of PCI scores (Region, Maximum lesion size (cm) and Lesion size score), Extensive upper abdominal surgical procedures (Diaphragm peritonectomy, Splenectomy, Full-thickness diaphragm resection, Partial hepatectomy, Distal pancreatectomy, Cholecystectomy), Other surgical procedures (Unilateral/bilateral salpingo-oophorectomy, Hysterectomy, Omentectomy, Large bowel resection, Pelvic lymph node dissection, Para-aortic lymph node dissection, Appendectomy, Thoracoscopy, Small bowel resection, Ileostomy, Colostomy, Inguinal lymph node dissection, Other), total number of extensive procedures, total number of other surgical procedures, total number of extended procedures (Patankar definition).Residual Tumor Characterization: Residual tumor observed after debulking (Yes/No), Can the patient be treated with M-Trap and the reasons if No, Device implant procedure duration (HH:MM), Suture used diameter (USP designation).
- Device: Successful implantation (Yes/No), The reason if No, Localization of implant.
- Post-Procedure Ultrasound: Abdominal ultrasound obtained (Yes/No), Reasons if No.
- Device deficiencies: Device malfunction occur during the procedure (Yes/No), If Yes Device deficiency description.

  The analysis of the PCI and the residual tumor observed after debulking will be performed on PDS patients, IDS patients and overall.

2.4.4. Follow-up Patients characteristics

Descriptive statistical data will be used to draw up a recapitulation of patients' follow-up visit characteristics.

The following data will be presented on the as-treated population at 1Month, 3Months, 6Months, 9Months, 12Months, 15Months and 18Months follow-up visits:

- Physical exam: Weight (kg), BMI (kg/m^2), Temperature (°C), Blood pressure (Systolic and Diastolic in mmHg), Heart rate (bpm), Specific abdominal examination performed (Yes/No), Presence of nodules or bumps if Yes (Yes/No) and How many nodules or bumps if Yes, Specific gynecologic examination performed (Yes/No), Presence of nodules or bumps in the cul-de-sac if Yes (Yes/No) and How many nodules or bumps in the cul-de-sac if Yes.
- Chemotherapy: Is chemotherapy complete (Yes/No), Number of IDS patients complete chemotherapy by the 3-month visit, Number of PDS patients complete chemotherapy by the 6-month visit, Number of cycles received since last visit, Is this visit the first one since the completion of chemotherapy (Yes/No), The reasons if chemotherapy is not completed
- Biomarker CA-125: CA-125 test performed (Yes/No), CA-125 results (U/mL), Disease progression as defined by CA-125 criteria (Yes/No).
- CT Scan: Abdominal CT Scan obtained, Pelvic CT Scan obtained, Chest CT Scan obtained, Target lesions site, Target Lesion location, Target Lesion Measurement (mm), New Target lesion, Evaluation of Target Lesions after chemotherapy completion, Non-Target Lesion Sites, Non-Target

lesion location, Measurement of Non-Target lesion if measurable (mm), New Non-Target lesion, Evaluation of Non-Target Lesions after chemotherapy completion, Objective Subject Response.

CT Scan is not performed at 1Month visit.

- Device(s) Removal: Device(s) removal planned during this visit (Yes/No)
- Ultrasound: Abdominal Ultrasound obtained (Yes/No), The reason specification if No
- Medications: Medication(s) change since last visit (Yes/No)
- Adverse Event: New adverse events occur since last visit (Yes/No)

2.4.5. Primary Analysis

Primary analysis of safety will be performed on the ITT population and the As-Treated populations.

The primary safety endpoint is freedom from device and procedure-related major adverse events through 6-months post-implantation, including shock, cardiac arrest, myocardial infarction, pulmonary embolism, prolonged intubation, unplanned reintubation, or adverse events leading to removal of the device, including infection, seroma formation, mesh migration, bowel obstruction, adhesions, and local cancer progression through the abdominal wall at M-Trap suture sites.

The primary safety endpoint will be analyzed using a unilateral one sample test for binomial proportion at the 5% level. In addition, the exact bilateral 95% confidence interval will also be given. The statistical test for the primary safety endpoint is given by:

- H0: M-Trap freedom MAE incidence <= 90% - Non-inferiority margin (25%)

Versus

- HA: M-Trap freedom MAE incidence > 90% - Non-inferiority margin (25%)

A modified primary analysis will also be performed that uses a freedom from MAE incidence rate that is adjusted for the surgical complexity of the study population, as compared to the Patankar study population, which is the basis of the statistical rationale for this study (repeated in the table below). The total number of extended procedures will be split in four classes: 0, 1, 2, 3 and more.

Procedures	0	1	2	3 or more	AVG
Total patients	1352	1214	254	50	2870
Severe complications, n	51	92	44	9	196
Severe complications, %	3.8%	7.6%	17.3%	18.0%	6.8%

A further modified primary analysis will also be performed that only includes procedure-related events through 30 days, as this is the comparable population to the Patankar study population, which is the basis of the statistical rationale for this study.

Primary analysis of performance will be performed on the As-Treated population and by device location. This analysis will be also performed using these 3 following sub-populations: (1) platinum resistant, recurrent patients; (2) platinum sensitive, recurrent patients; (3) non-recurrent patients (see definition in part 2.5).

The primary performance endpoint is histopathologic evidence of tumor cell capture (see 2.5). Histopathology will be performed after device explant.

The primary performance endpoint will be assessed with exact one-sided 90% confidence intervals.

2.4.6. Secondary analysis

Secondary analysis of safety will be performed on the ITT population and the As-Treated populations.

Secondary safety endpoints include incidence of other device-related adverse events and all other adverse events long-term. Patients will be evaluated by physical examination, CT scan, ultrasound, and biomarker cancer antigen CA-125.

A medical coding will be done on the adverse events using the MedDRA dictionary. All adverse events (AEs) will be categorized by system organ class (SOC) and preferred term (PT). A complete description will be done for the following AEs:

- Total number of AEs/SAEs and corresponding number and percentage of patients
- Total number of device-related AEs/SAEs and corresponding number and percentage of patients
- Total number of unanticipated device-related AEs/SAEs and corresponding number and percentage of patients
- Total number of procedure-related AEs/SAEs and corresponding number and percentage of patients
- Total number of device deficiencies and corresponding number and percentage of patients
- The overall mortality rate will also be presented

Secondary analysis of performance will be performed on the As-Treated population.

Secondary performance endpoints include semi-quantitative scoring of disease focalization based on direct visual assessment, CT scan and ultrasound at the time of device removal. In addition, a microscopic assessment will be performed during explant, including cytological assessment of any ascites present, cytological assessment of peritoneal washings, if indicated, and a minimum of two (2) peritoneal biopsies from designated locations, if indicated.

The secondary performance endpoints are the percentages of recurrent patients with disease focalization scores of: 1) I, 2) I or II, 3) I, II or III, and 4) I, II, III or IV. This analysis will be also performed using the 3 sub-populations defined below ((1), (2), (3)), and using the populations (1) and (2) combined and overall.

The secondary performance endpoints will be assessed with exact one-sided 90% confidence intervals.

2.4.7. Device Removal

Descriptive statistical data will be used to draw up a recapitulation of the device removal details at the time of the removal operation.

The following data will be presented on the As-Treated population on patients number:

- Duration until device removal (days), Reason for removal, All devices removed (Yes/No), The number of devices removed if No. Duration until device removal (days) if the reason for removal is recurrence.
- The time to recurrence will be described using a Kaplan Meier curve. Patients lost to follow-up before the removal will be censored at the date of last follow-up. Patients who have removal for another reason than recurrence before the 18 months will be censored at the date of the removal.
- Disease Focalization: Disease focalization score, Modalities used for the assessment of disease focalization, If a peritoneal wash performed, were malignant cells present (Yes/No)

  Disease Focalization will be also analyzed using the 3 sub-populations defined below ((1), (2), (3)), and using the populations (1) and (2) combined and overall.
- Adverse Event: New adverse event(s) occur during removal procedure (Yes/No)
- Cytology (Done with final device removal): Where ascites present (Yes/No), Were malignant cells present in the ascites (Yes/No), Was a peritoneal wash performed (Yes/No), From which area was the wash obtained if “Yes”, Were malignant cells present in the peritoneal wash.

- Biopsies (Done with final device removal): Biopsy location, Biopsy taken (Yes/No), Is visible tumor present (Yes/No), Is microscopic disease present (Yes/No)

  If Biopsy location is Adhesive bands, abnormally scarred areas or Retroperitoneum the further details given will be described by the mean of listing.

The following data will be presented on the As-Treated population on devices number:

- Location of Device, Attachment of the device to the surrounding tissues
- Assessment of device removal: Ease of locating M-Trap device, Did the M-Trap device remain securely fixed in its original location, Ease of removing M-Trap device, Endobag used, Trocar size (mm)
- Core Lab: Device(s) sent to the core laboratory (Yes/No), the Reasons and the Location if No
- Data Entered by Core Lab: Device size (Length (mm) and Width (mm)), Immunohistochemistry (CD3, CD20, CD68, CKAE1/AE3, CK7, ER, P53, WT1 (Key: (0)=nil, (1)=mild, (2)=moderate, (3)=marked)), CD31 and D240 (Yes/No), Tumor cell infiltration (%), Gross photo taken (Yes/No), Images from a microscope obtained (Yes/No).

2.5. Derived Criteria Calculation

If at least one of the items needed to calculate a derived criterion is missing then the corresponding derived criterion will be considered as missing.

- Derived criterion “ITT population” will be defined as follows:

If “Signed Informed Consent” = “Yes” and the date of signature of the consent form is filled and all inclusion/exclusion criteria are compliant and “Can the patient be treated with M-Trap” = “Yes” then “ITT population” = “YES”, else “ITT population” = “NO”.

- Derived criterion “As-Treated population” will be defined as follows:

If the date of signature of the consent form is filled and are compliant with all inclusion/exclusion criteria and “Can the patient be treated with M-Trap” = “Yes” and at least one device successfully implanted then “As-Treated population” = “YES”, else “As-Treated population” = “NO”.

- Derived criterion “Age at Enrollment” will be calculated as follows:

“Age at Enrollment” = “Date of signature of Informed Consent” – “Birth date” in years

- Derived criterion “Duration of patients Follow-up” will be calculated as follows:

“Duration of patients Follow-up” = “Last patient follow-up date” – “Procedure patient date”

If patient procedure date is missing Baseline/Screening date will be used (for ITT population)

- Derived criterion “Duration debulking surgery” will be calculated as follows:

“Duration debulking surgery” = “end time of debulking surgery” – “start time of debulking surgery”

- Derived criterion “Duration of implantation” will be calculated as follows:

“Duration of implantation” = “end time of implantation” – “start time of implantation”

- Derived criterion “Total number of procedures” will be equal to the number of checked boxes for “Extensive upper abdominal” and “Other procedures”.
- Derived criterion “Total number of extensive procedures” will be equal to the number of checked boxes for “Extensive upper abdominal”.
- Derived criterion “Total number of other surgical procedures” will be equal to the number of checked boxes for “Other procedures” and the count of procedures listed in the free text field “Other”.

  CRO will send to MTrap an Excel file with the list of all other surgical procedures to count their number.

- Derived criterion “Number of extended procedures (Patankar definition)” will be calculated as follows:

All patients start with a score of 1, since all patients had cytoreduction surgery.
Add 1 to the score if Pelvic or Para-aortic or Inguinal lymph node dissection are ticked or if any other procedure includes lymph node dissection (lymphadenectomy).

Add 1 to the score if Small bowel resection is ticked.
Add 1 to the score if Large bowel resection is ticked (colectomy, rectosigmoid resection).
Add 1 to the score if Diaphragm peritonectomy or Full-thickness diaphragm resection (diaphragm resection) is ticked.
Add 1 to the score if Partial hepatectomy (hepatic resection) is ticked.

- Derived criterion "freedom of device- and procedure-related major adverse events through 6 months post-implantation, including shock, cardiac arrest, myocardial infarction, pulmonary embolism, prolonged intubation, unplanned reintubation, or adverse events leading to removal of the device, including infection, seroma formation, mesh migration, bowel obstruction, adhesions, and local cancer progression through the abdominal wall at M-Trap suture sites" which is the primary endpoint will be calculated as follows:

  If a MAE occurred in a patient within 6 months ± 2W post implantation and "Does this event meet the definition of a major adverse event for the primary endpoint?" = "Yes" then "freedom of device- and procedure-related major adverse events through 6-months post-implantation" = "No" else "freedom of device- and procedure-related major adverse events through 6-months post-implantation" = "Yes".
- Derived criterion "recurrent patients" will be defined as patients with device removal reason "Disease progression as defined by objective RECIST 1.1 and CA-125 criteria" or device removal reason "other" that indicates recurrence. Derived criteria "non-recurrent patients" are the remaining patients. CRO will send to MTrap an excel file with the list of all other reason of device removal to identify the reason that indicates "recurrence".
- Derived criterion "time to recurrence" will equal to the date of the follow-up visit when "Device removal planned for this visit" is yes minus the procedure date.
- Derived criterion "platinum resistant, recurrent patients" will be defined as "recurrent patients" where the difference between the date of the follow-up visit when "Device removal planned for this visit" is yes and the date of the most recent chemotherapy medication treatment is less than or equal to 180 days.
- CRO will send to MTrap an excel file with the list of the concomitant medication to identify the chemotherapy medication treatment. Derived criterion "platinum sensitive, recurrent patients" will be defined as "recurrent patients" that are not "platinum resistant, recurrent patients".
- Histopathologic evidence of tumor cell capture is "Yes" if Tumor cell infiltration for at least one device is >0 in a patient. Otherwise, Histopathological evidence of tumor cell capture is "No".
- An AE will be considered as an SAE if "Serious Adverse event" = "Yes".
- An AE will be considered "Unanticipated" if "Anticipated adverse event" = "No".
- An AE will be considered as device related if "Relationship to device(s)" is "possible", "probable" or "definite".
- An AE will be considered as procedure related if "Relationship to procedure" is "possible", "probable" or "definite".
- At least one other medical history will be calculated as follows:

  If at least one variable of other medical history is equal to "Yes" then "At least one other medical history" = "Yes",

  If no variable of other medical history is equal to "Yes" then:

  - If all variables of other medical history are equal to "No" then "At least one other medical history" = "No",
  - If at least one variable of other medical history is equal to "Missing" then "At least one other medical history" = "Missing",

  If all variables of other medical history are equal to "Missing" then "At least one other medical history" = "Missing".

3. STATISTICAL SOFTWARE

All statistical outputs (summary tables and data listings) will be generated using SAS® version 9.4.

4. STATISTICAL TABLES, LISTINGS AND GRAPHS (TABLE OF CONTENTS)

4.1. Statistical Tables

Patients dispositions and Follow-up

Table 1: Patients disposition (Type 1)
Table 2: Patients follow-up by population (Type 2)
Table 3: Sites by population (Type 2)
Table 4: Patients follow-up time by population (Type 3)

Baseline (Screening) patients Characteristics

Demographics and Physical Exam

Table 5: Demographics by population (Type 4)
Table 6: Physical Exam by population (Type 3)
Table 7: Specific Test Performed by population (Type 5)

Medical History

Table 8: Medical History by population (Type 5)

Specific Cancer History

Table 9: Specific Cancer History by population (Type 5)

Peritoneal Carcinomatosis Index (PCI)

Table 10: PCI performed by population (PCI) (Type 4)
Table 11: Detail of PCI score by population (Type 3)

Biomarker CA-125

Table 12: Biomarker CA-125 by population (PDS, IDS and overall) (Type 4)

CT Scan

Table 13: CT Scan by population (Type 4)
Table 14: Type of Lesion by CT Scan on ITT population (Type 6)
Table 15: Type of Lesion by CT Scan on AT population (Type 6)
Table 16: Lesion Measurement (mm) by Lesion site (Type 3)

Medications

Table 17: Patient receiving any concomitant medication by population (Type 5)

Procedure patients Characteristics

Physical Exam

Table 18: Physical Exam at procedure by population (Type 3)
Table 19: Specific Test Performed at procedure by population (Type 5)

Procedural Information

Residual Tumor Characterization

Device

Post-Procedure Ultrasound

Device Deficiency

Follow-up patients Characteristics

Physical Exam

Chemotherapy

Biomarker CA-125

CT Scan

Target lesions

Table 45: Evaluation of Target Lesions after chemotherapy completion by follow-up visit on AT population (Type 5)

Non-Target lesions

Table 46: Non-Target Lesions by follow-up visit on AT population (Type 5)
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Table 50: Objective Subject Response by follow-up visit on AT population (Type 5)

Device removal

Table 51: Device removal during the planned visit by follow-up visit on AT population (Type 5)

Ultrasound

Table 52: Abdominal Ultrasound by follow-up visit on AT population (Type 5)

Medications

Table 53: Medication(s) change since last visit by follow-up visit on As-Treated population (Type 5)

Adverse Events

Table 54: New adverse events occur since last visit by follow-up visit on As-Treated population (Type 5)

Primary Analysis

Primary Safety analysis

Table 55: Non-inferiority on Freedom of device and procedure related MAE through 6-months on AT population (Type 5)

Table 56: Freedom of device and procedure related MAE through 6-months on AT population using MAE expected incidence adjusted for the study population number of extended procedures (Patankar definition) (Type 8)

Table 57: Freedom of device and procedure related MAE through 30 days on AT population using MAE expected incidence adjusted for the study population number of extended procedures (Patankar definition) (Type 5)

Primary Performance analysis

Table 58: Histological evidence of tumor cell capture in at least one M-Trap device after device explant on AT population by device location (Type 2)

Table 59: Histological evidence of tumor cell capture in at least one M-Trap device after device explant on AT population with sub-analysis of histological evidence of tumor cell capture by device location and recurrence status (Type 2)

Secondary Analysis

Secondary Safety analysis

Table 60: AEs on ITT population (Type 6)

Table 61: AEs on AT population (Type 6)

Table 62: SAEs on ITT population (Type 6)

Secondary performance analysis

Device(s) removal

Device removal information

Device location

Assessment of device removal

Disease Focalization

Table 100: Disease focalization score (Type 5)
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Adverse Events

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Cytology

Table 103: Cytology at device removal (Type 5)

Biopsy (Done with final device removal)

Table 104: Biopsy taken at final device removal (Type 4)
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Pathology analysis
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Table 108: Device Length (mm) and Width (mm) by location device (Type 7)
Table 109: Immunohistochemistry (Type 7)
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4.2. Listings

Study Patients

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Baseline Patient Characteristics

Listing 3: Demographics and physical exams
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Listing 5: Specific cancer history
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Procedure Patient Characteristics

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Listing 12: Surgical procedure
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Follow-up Patient Characteristics

Listing 18: Physical exams, specific test performed and biomarker CA-125
Listing 19: Chemotherapy result
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Primary analysis

Listing 22: Primary performance endpoint
Listing 23: Primary safety endpoint

Secondary analysis

Listing 24: Secondary safety endpoint (adverse event)
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Device Removal

Listing 26: Device removal information
Listing 27: Biopsy at final device removal
Listing 28: Pathology data
Listing 29: Unscheduled visits

5. LAYOUT OF THE STATISTICAL TABLES

5.1. Qualitative variables

5.1.1. Qualitative variable (Type 1)

Var 1 / Var 2	Var 1 (N=XX)
Var 1	XX (XX.X %)
Mod 1	XX (XX.X %)
Mod 2	XX (XX.X %)
Mod 3	XX (XX.X %)
Var 2	XX (XX.X %)
Mod 1	XX (XX.X %)
Group 3	XX (XX.X %)

5.1.2. Qualitative variable by population or by visit (Type 5)

		Pop 1 or Visit 1 (N=XX)	Pop 2 or Visit 2 (N=XX)	P-value*
Var 1	N	XX	XX	XX.XXXX
	Mod 1	XX (XX.X%)	XX (XX.X%)	
	Mod 2	XX (XX.X%)	XX (XX.X%)	

		Pop 1 or Visit 1 (N=XX)	Pop 2 or Visit 2 (N=XX)	P-value*
	Missing	XX	XX	

*if needed

5.1.3. Qualitative variable by population or Visit (Type 2)

Var 1 / Var 2	Pop 1 or Visit 1 (N=XX)	Pop 2 or Visit 2 (N=XX)
Group 1	XX (XX.X %)	XX (XX.X %)
Mod 1	XX (XX.X %)	XX (XX.X %)
Mod 2	XX (XX.X %)	XX (XX.X %)
Mod 3	XX (XX.X %)	XX (XX.X %)
Group 2	XX (XX.X %)	XX (XX.X %)
Mod 1	XX (XX.X %)	XX (XX.X %)
Group 3	XX (XX.X %)	XX (XX.X %)

5.2. Quantitative variables

5.2.1. Quantitative variables without group (Type 7)

	N	Missing	Mean	S.D.	Median	Min,Max	Q1-Q3
Var 1	XX	XX	XX.X	XX.X	XX.X	XX.X, XX.X	XX.X - XX.X

5.2.2. Quantitative variables by population or by visit (Type 3)

			N	Missing	Mean	S.D.	Median	Min,Max	Q1-Q3
Var 1	Pop 1 or Visit 1*	Mod 1*	XX	XX	XX.X	XX.X	XX.X	XX.X, XX.X	XX.X - XX.X
		Mod 2*	XX	XX	XX.X	XX.X	XX.X	XX.X, XX.X	XX.X - XX.X
		Total*	XX	XX	XX.X	XX.X	XX.X	XX.X, XX.X	XX.X - XX.X
	Pop 2 or Visit 2*	Mod 1*	XX	XX	XX.X	XX.X	XX.X	XX.X, XX.X	XX.X - XX.X
		Mod 2*	XX	XX	XX.X	XX.X	XX.X	XX.X, XX.X	XX.X - XX.X
		Total*	XX	XX	XX.X	XX.X	XX.X	XX.X, XX.X	XX.X - XX.X

*if needed

5.3. Others / Adverse Event / Medications

5.3.1. Qualitative and quantitative variables by population or by visit (Type 4)

		Pop 1 or Visit 1 (N=XX)	Pop 2 or Visit 2 (N=XX)
Var 1	N	XX	XX
	Mean	XX.X	XX.X
	S.D.	XX.X	XX.X
	Median	XX.X	XX.X
	Min,Max	XX.X, XX.X	XX.X, XX.X

		Pop 1 or Visit 1 (N=XX)	Pop 2 or Visit 2 (N=XX)
	Q1-Q3	XX.X- XX.X	XX.X- XX.X
	Missing	XX	XX
Var 2	N	XX	XX
	NO	XX (XX.X%)	XX (XX.X%)
	YES	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX

5.3.2. Qualitative variable by event/patient (Type 6)

	n event (1)	n (2)	% (3)
ALL	XX	XX	XX.X
Var1 –Mod 1	XX	XX	XX.X
Var 2 – Mod 1	XX	XX	XX.X
Var 2 – Mod 2	XX	XX	XX.X
Var 2 – Mod 3	XX	XX	XX.X
Var2 –Mod 1	XX	XX	XX.X
Var 2 – Mod 1	XX	XX	XX.X
Var 2 – Mod 2	XX	XX	XX.X
Var 2 – Mod 3	XX	XX	XX.X

(1) number of events
(2) number of patients with at least one event
(3) n/total number of patients

5.3.3. Qualitative variable by class (Type 8)

	Var2	Class 1	Class 2	Class 3	Class 4	Total
Var 1	N	XX	XX	XX	XX	XX
	Mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mod 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX	XX