EARLY FEASIBILITY STUDY FOR EVALUATION OF THE TRACEIT® TISSUE SPACER FOR CREATING SPACE BETWEEN THE DUODENUM AND PANCREAS IN PATIENTS WITH LOCALIZED PANCREATIC CANCER UNDERGOING RADIATION THERAPY

THE TIPS PILOT STUDY
STATISTICAL ANALYSIS PLAN

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TIPS Study Statistical Analysis Plan

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THE TIPS PILOT STUDY

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1 PROTOCOL SUMMARY

TraceIT Tissue Spacer consists of a pre-filled glass syringe containing the absorbable radiopaque cross-linked polyethylene glycol (PEG) hydrogel spacer and a delivery mechanism (syringe and needle) packaged in a single use kit. TraceIT Tissue Spacer is a radiopaque hydrogel material intended to temporarily position the duodenum away from the pancreas in subjects undergoing Radiation Therapy (RT) for treatment of pancreatic cancer and in creating this space. It is the intent of TraceIT Tissue Spacer to reduce the radiation dose delivered to the duodenum during radiotherapy. When used as a spacer, the TraceIT hydrogel radiographically marks the area for radiotherapy planning and localization.

The TIPS Pilot Study is a multicenter prospective, single-arm early feasibility study, with up to 18-month follow-up. The objective is to evaluate the feasibility, radiotherapy benefits, and safety when using TraceIT Tissue Spacer to create space between the pancreas and duodenum. The study will be conducted at up to four (4) investigational sites in the United States to enroll six (6) subjects with localized (resectable, borderline resectable, or locally advanced) pancreatic cancer (defined per NCCN guidelines) having completed induction chemotherapy if required and for whom a course of radiotherapy (RT) is indicated.

2 INTRODUCTION

Despite improvements in therapy, pancreatic adenocarcinoma remains a deadly disease with an extremely dismal prognosis. Indeed, the disease is now the third leading cause of cancer-related death. The aggressive nature of this cancer is partly due to its late presentation and the intimate anatomic relationship between the pancreas and adjacent structures, namely the duodenum, stomach, liver, bile ducts, spleen, and the great vessels and their branches.

The current guidelines for the management of patients with borderline resectable pancreatic cancer (BRPC) and locally advanced unresectable disease (LAPC) include single- or multi-agent chemotherapy or chemoradiation (CRT) in sequence with chemotherapy. Patients with borderline resectable disease are likely to ultimately undergo resection, and thus there is a strong rationale for use of local therapy radiation in addition to chemotherapy in these patients.

Thus, in BRPC/LAPC cases, advanced radiation therapy techniques using dose-escalation with intensity modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) are potential strategies to improve local control. However, the tolerance of the surrounding gastrointestinal (GI) tract has historically limited delivering higher doses of radiation therapy to the gross tumor.

The majority of pancreatic tumors are in the head of the pancreas. The primary RT dose limiting structure for tumors in the head of the pancreas is the duodenum. The intimate relationship between the head of the pancreas and the duodenum puts this organ at risk

for significant radiation toxicity, particularly in consideration that chemotherapy regimens used in conjunction with RT serve the purpose of increasing radio sensitivity, not just to the tumor, but normal GI tissues as well. Potential complications include duodenal stricture, duodenitis, bleeding, obstructive jaundice, duodenal hemorrhage and diarrhea among others. Indeed, when delivering stereotactic doses of radiation in multiple fractions, as is the current convention, and when adhering to contemporary duodenal dose constraints, the rates of medically significant grade ≥3 duodenal toxicity continues to be a problem reported in up to 15% of patients.

As radiation dose from stereotactic radiation drops off very quickly, displacement of the duodenum from the pancreas by only a few millimeters would be expected to significantly diminish duodenal toxicity. A similar product, SpaceOAR, was cleared by the FDA in 2015 specifically for use to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer. Based on the SpaceOAR study it is believed that incorporation of application of the TraceIT Tissue Spacer into the regimen of radiotherapy treatment can allow for improvement in RT delivery in multiple aspects including:

1) allowing for safe duodenal dose constraints to be achieved at the target prescription dose;
2) allow for an increase in tumor volume coverage while maintaining acceptable duodenal dose constraints or
3) allow for an individualized dose escalation prescription while maintaining acceptable duodenal dose constraints. Space creation between the duodenum and the head of the pancreas (HOP) may also provide a benefit in reducing incidental radiation to the duodenum due to intra and inter fraction motion.

Success in any one of the parameters noted above would make TraceIT Tissue Spacer an important tool for the radiation oncologist as they plan and treat patients with cancer of the pancreatic head.

This document details the analysis plan for the effectiveness and safety endpoints in the TIPS pilot study.

3 ENDPOINT ANALYSIS

All data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum, when appropriate. Categorical variables will be summarized by frequencies and percentages.

Changes from baseline in dosimetric parameters and quality of life parameters will be assessed using a paired t-test or, if not normally distributed, the nonparametric Wilcoxon Signed-Rank test for continuous variables and Chi-Square and/or McNemar’s test for dichotomous variables.

Nominal p-values associated with statistical tests will be reported, but no significance level will be applied to the values. No adjustments to nominal p-values are planned since this is a hypothesis-generating study.

3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint (feasibility) will be Technical Success rate. Technical Success is defined as the administration and visualization (with TraceIT Visibility Score 2 or higher on post-TraceIT CT) of the TraceIT hydrogel between the head of pancreas and the duodenum. Technical Success rate is calculated as the proportion of subjects who are Technical Success in the intent-to-treat (ITT) population.

3.1.1 Hypotheses

This is an early feasibility study with an intent to collect information on the procedural characteristics and safety for TraceIT administration within the peri-duodenal space. Therefore, no formal hypothesis tests of primary or secondary effectiveness endpoints have been planned.

3.1.2 Sample Size

No formal hypothesis or sample size estimation has been established since this is an early feasibility study with an intent to collect information concerning the procedural characteristics and safety for TraceIT administration within the peri-duodenal space. Six (6) subjects should provide sufficient experience to allow for evaluation of procedural safety and to estimate the impact of space creation on duodenal radiation doses.

3.1.3 Statistical Methods

The proportion of TraceIT treated subjects in whom Technical Success has been achieved will be reported in ITT population, together with an exact (Clopper-Pearson) 95% confidence interval for the true proportion. This endpoint may be summarized separately also for the localized (resectable, BRPC and LAPC) subjects.

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. Due to the fact that subjects are undergoing therapy consistent with standard medical practices, it is anticipated that there will be minimal missing data. There will be no imputation of missing outcome data.

3.2 Secondary Effectiveness Endpoint

The secondary effectiveness endpoints of this study are the radiotherapy benefits evaluated by comparing treatment planning performed at the baseline and post TraceIT administration, which include:

- Ability to maintain safe duodenal dose constraints
- Percent/volume of GTV/PTV receiving prescription dose
- Overall duodenal dose/ dose distribution.

3.2.1 Statistical Methods

Radiotherapy Benefits will be assessed via comparison RT planning performed at baseline and post-TraceIT administration for MITT and PP population. For both scans, summary descriptive statistics will be presented by assessment (i.e., Pre- vs. Post-TraceIT Administration) for all target volume and dose constraint measurements. The GTV/PTV receiving prescription dose pre- and post-TraceIT will be reported in an additional table. For the post-TraceIT procedure data, the relative reduction from baseline in dose (V15, V20, V35, mean and maximum duodenal dose, etc.) to the duodenum will also be calculated and summarized.

For continuous radiotherapy benefit variables, the paired sample t-test will be used to test for a difference in means between treatment plans.

3.3 Exploratory Effectiveness Endpoint

The exploratory effectiveness endpoints are defined as:

- Incidence of resection
- Histology of duodenal tissues when resection is performed
- Incidence of acute (within 3 months) and late (>3 months) duodenal toxicity (for unresected subjects)
- Theoretical dose escalation from post-TraceIT treatment plan
- TraceIT persistence (at 6-months post-TraceIT in nonresected subjects)
- Change from baseline in EORTC QoL (QLQ-C30) and QLQ-PAN26
- Comparability of visualization of the fiducial marker and TraceIT hydrogel using a standardized visualization score
- Progression free and overall survival through follow-up

3.3.1 Statistical Methods

The proportion of resected subjects in the MITT or PP population, localized (resectable, BRPC or LAPC) subgroup may be calculated with an exact (Clopper-Pearson) 95% confidence interval for the true proportion, when appropriate.

The incidence of acute (within 3 months) and late (>3 months) duodenal toxicity for unresected subjects will be reported by CTCAE grade and timing.

Histology of duodenal tissue (Duodenum Damage Score) will be summarized for those subjects when resection is performed.

The summary of theoretical dose escalation from post-TraceIT treatment plan, and , migration and stability at 2-6 weeks post-TraceIT, TraceIT persistence at 6-months post-TraceIT in non-resected subjects will be presented in separated table. The pre-TraceIT and post-TraceIT duodenal space measured by site during index procedure and/or by independent assessors will be summarized separately. Average duodenal space will be

calculated if the measurements were taken from multiple observation points or duplication.

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. The pancreatic cancer module QLQ-PAN26 is intended for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation or palliative chemotherapy. Changes in Quality of Life Measures as assessed overall and subdomains (scales) of the EORTC-QLQ-C30 and QLQ-PAN26 will be evaluated.

The five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea & vomiting and pain), a global health status/QOL scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) from EORTC-QLQ-C30 will be summarized according EORTC QLQ-C30 Scoring Manual third edition.

The fifteen symptom items and two functional scales from QLQ-PAN26 will be analyzed according EORTC QLQ-PAN26 Scoring Manual 2.2.

Those analysis will be repeated by localized (resectable, BRPC and LAPC), as well as resected and unresected subgroup, if applicable. Scores will be compared to baseline using either a paired t-test or Wilcoxon Signed-Rank test when appropriate.

The result of comparability of visualization of the fiducial marker and TraceIT hydrogel will be summarized using a standardized visualization score for all subjects injected with TraceIT Tissue Spacer.

The following definitions will be used for Progression-Free Survival (PFS) and Overall Survival (OS) analysis:

- Progression-Free Survival (PFS): defined as the interval between the start of induction chemotherapy (prior to RT) to the earliest treatment failure (local, regional or distant progression) onset date or death (in months). Treatment failure events will be reported as SAE and adjudicated by CEC.
- Overall Survival (OS): defined as the interval between the start of induction chemotherapy (prior to RT) to death (in months).

3.4 Safety Endpoint

Any adverse event (AE) occurred Procedure through 18-month visit will be recorded and listed. All collected AEs will be recorded by body system and preferred term in accordance with NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (NCI, Oct 2009) for severity and/or MedDRA term.

The safety endpoint for this study is defined as "TraceIT administration procedure-related events which result in a delay in initiation of RT" as reviewed and adjudicated by a Clinical Events Committee.

The timing (month) of AE will be categorized as <=3 months, >3 to <=6 months, >6 to <=12 months,>12 to <=18 months, by its value calculated as:

(Date of AE started - Date of index procedure + 1) / (365.25/12) and rounded to 2 decimal places.

SADE is defined as a serious adverse event that is believed to have been caused by or is associated with the device. UADE is defined as any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the Investigational Plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. SADEs and UADEs will be investigated immediately once occurred and if the sponsor determines that unreasonable risk to subjects is possible, the study will be terminated.

To standardize the reporting, a Clinical Events Committee (CEC) was convened at the beginning of the study to provide:

- Continuous review and validation of all adverse events that occur over the course of the study and the subsequent classification of these adverse events as related to the device or procedure.
- Oversight for issues affecting general subject welfare, including recommendations on changes to the protocol or device and if appropriate recommendation concerning early study termination if new information is learned that would affect the risk/benefit analysis presented within this clinical investigational plan.

3.4.1 Statistical Methods

CEC adjudicated AEs will be summarized by term, by term and procedure/device relationship, and by terms and severity (CTCAE Grade). In addition to the general presentation of safety events, the following will be calculated and reported:

- The number and percentage of subjects who experienced TraceIT administration procedure-related events which result in a delay in initiation of RT
- The number and percentage of subjects with at least one duodenal adverse event presented by grade and timing; i.e., acute (within 3 months) and late (>3 months). A similar presentation will be provided for non-resected subjects only.

Additionally, the numbers and percentages will be calculated for subjects who have developed one or more following events: AEs, SAEs, UADE, SADE, procedure related

AEs, device related AEs, radiation therapy related AEs, duodenal related AEs by site and total.

Adverse event overall listing will include AE CTCAE term, AE CTCAE SOC , onset days since procedure and duration, AE attribution, CTCAE grade and adjudication term, SAE and classification, UADE, action taken, outcome and residual effects.

Single imputation will be implemented for partial start/end dates (missing month and/or day) of adverse events, or concomitant medications.

For the missing start date:

- Only the start day is missing: the 15th day of the month will be used if the resulted imputed date is after the index procedure date; otherwise the procedure date will be used.
- Both the start day and the start month are missing: the 15th day of January will be used if the resulted imputed date is after the index procedure date; otherwise the procedure date will be used.

For the missing end date:

- If the end day is missing, the 15th day of the month will be used if the resulted imputed date is after the corresponding start date; otherwise the last day of the month will be used.
- If end day and end month are both missing, the 15th day of December will be used if the resulted date is after the corresponding start date; otherwise the 31st day of December will be used.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

4.1.1 Intent-To-Treat Population (ITT)

All enrolled (consented) subjects for whom TraceIT administration is attempted. This will be the primary analysis population for evaluation of feasibility (i.e., technical success defined as the ability to place TraceIT and create space between the duodenum and HOP).

4.1.2 Modified Intent-To-Treat Population (MITT)

All subjects enrolled in the study and who are a Technical Success will be included in the Modified Intent-to-Treat population. This will be the primary analysis population for purposes of non-safety outcome data.

4.1.3 Per-Protocol Population (PP)

The Per Protocol (PP) Population is defined to be all subjects in the MITT population with no major protocol deviations that have the potential to affect the study outcomes.

Major protocol deviations will be defined by the clinical project manager.

4.1.4 No TraceIT Population

Subjects who were enrolled (consented) and for whom TraceIT administration was not technically successful (either hydrogel placement was abandoned due to clinical issues or no space created in the duodenal/pancreatic interface).

4.1.5 Safety Population (SAF)

The Safety Population is defined to be all subjects for whom TraceIT administration is attempted (whether or not administration was successful). For the purposes of this study, the Safety Population is the same as the ITT Population.

4.2 Control of Systematic Error/Bias

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection.

4.3 Number of Subjects per Investigative Site

About 6 people will be in this study at up to 4 clinics site in the United States. There is no limitation for number of subjects in each site.

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

5.1.1 Subject Disposition

The number and percentage of ITT, MITT, PP and SAF population will be summarized. Subjects who passed pre-screening will be consented for the study and will undergo a secondary screening. The number of subjects who consented, screening failed and early terminated prior index procedure (TraceIT administration isn't attempted) will be presented. The number and percentage of non-injection TraceIT subjects will be presented along with the reason they were not able to be injected. The number and percentage of treated subjects who do not complete the study will be presented, along with the reason for early termination/withdrawal. Subject accountability by investigative site and by study visit will also be presented.

5.1.2 Demographics and Baseline Characteristics

Subjects will be summarized with respect to baseline demographics and clinical characteristics (e.g., age, sex, tumor grade, resection status etc.) by ITT, MITT and PP population. These will be summarized by descriptive statistics including means, medians,

standard deviations and ranges (for quantitative variables) and percentages (for categorical variables).

5.1.3 Medical History

Medical history will be summarized by status (resolved and ongoing) for ITT, MITT and PP population. Tumor and therapy related medical history will be summarized in separated table.

The tumor anatomic stage will be calculated using the algorithm according Protocol REV.C Appendix A AJCC PANCREAS CANCER STAGING.

Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

5.1.4 Study Procedure

The index procedure will be summarized with number of fiducial markers placed, duration of EUS (time between EUS insertion and removal), duration of fiducial insertion (time between first and last fiducial insertion), duration of TraceIT needle (time between TraceIT needle insertion and removal), duration of TraceIT injection (time between TraceIT injection start and stop), the number of TraceIT injections, total volume of TraceIT used. Numbers and percentages of subjects given prophylactic antibiotics prior to procedure, whether TraceIT injection procedure successful, ease of access to injection site who experienced any access difficulties, any device malfunction, and feedback of device ease of use, ease of preparation will be presented.

A listing will include index procedure date, EUS insertion and removal time, first and last fiducial insertion time, fiducial placement success, type of fiducial, number of fiducial markers, TraceIT needle insertion and removal time, needle type, TraceIT injection start and stop time, FNA needle gauge usage and dilution factor, total volume of TraceIT, pre- and post-TraceIT space measurement, number of injections, device malfunction, access difficulties and description, prep ease, ease of use and any AEs during index procedure.

5.1.5 Concomitant Medication

Numbers and percentages of subjects in the ITT population with any medication changes to treat intestinal symptoms will be summarized by the timing of start administration.

The timing of concomitant medication will be categorized as prior index procedure date, from index procedure date up to 3 months post-procedure, after 3 months post-procedure. The month interval between index procedure and medication administration is calculated as:

(Date of medication started - Date of index procedure + 1) / (365.25/12) and rounded to 2 decimal places.

5.1.6 Physical Examination and Vital Signs

Physical examination findings will be summarized by visit in the ITT population using percentages. An additional table will summarize absolute and relative changes from baseline to each follow up visit in physical examination and vital signs.

5.1.7 Local Laboratory Tests

For the ITT Population, local laboratory blood test results of red blood cells (RBC), white blood cells(WBC), hemoglobin, platelet count, serum carbohydrate antigen CA-19-9, serum creatinine, total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase(AST) will be categorized as normal (N), out of normal ranges but not clinically significant (OR), and out of range and clinically significant (CS) at baseline, CA-19-9 will be summarized at Week 2-6 following completion of RT too.

5.2 Interim Analyses

There is no interim analysis planned for the study.

5.3 Subgroup Analyses

Data may be presented separately for localized (resectable, BRPC and LAPC) subjects as well as resected and unresected subjects, when appropriate.

5.4 Justification of Pooling

The study will be conducted at up to 4 investigational sites in the United States for six subjects. Poolability will not be tested for this feasibility study due to small sample size.

5.5 Multivariable Analyses

No multivariable analyses is planned for this six subject feasibility study.

5.6 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation.

7 PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

All statistical analyses and data manipulation will be performed using SAS 9.4 or higher for Windows or other validated statistical software.

7.2 Format of Output

SAS output delivery system supported RTF formats will be used. However, tables will be sent to clinical in a WORD or PDF format.

7.3 Rules and Definitions for calculated variables

Rules for programming will be documented accordingly in the SAS code or in the specific table or listing footnotes. This may include references to CRF pages, manipulation of variables, or other appropriate identifiers.