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

NCT03998566

27MAR2019

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THE TIPS PILOT STUDY

Investigational Protocol
AGX-17-001-US
REV. C

March 27, 2019

Sponsor: Augmenix Inc.
201 Burlington Road
Bedford, MA 01730 USA

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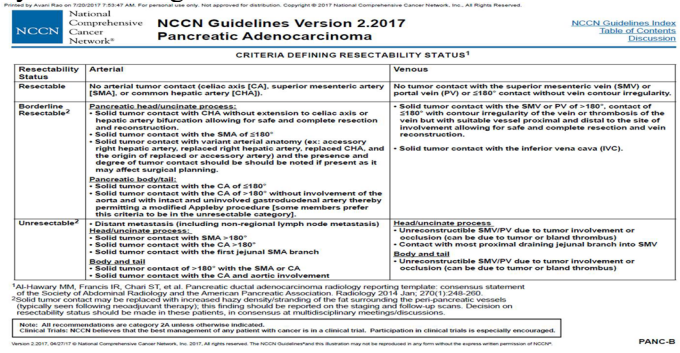
1 SUMMARY OF CHANGES

Protocol Revision	Protocol Section	Description of Change	Reason for Changes
REV A (October 10, 2017)	N/A	Original issue	Original issue
REV B (December 5, 2017)	Inclusion Criteria: Protocol Summary; Sec. 6.3.1	f. Serum creatinine: 1.5 times ULN *changed to* "f. Serum creatinine: < 1.5 times ULN"	Editorial Correction: Missing < symbol
	Clinical Events Committee (CEC): Protocol Summary	*Removed* "in each study arm"	Editorial Correction: Will only have 1 study arm
	Inclusion Criteria: Protocol Summary; Sec. 6.3.1	2. Biopsy-confirmed BRPC and LAPC in the head or neck of the pancreas that is able to be visualized via CT or other imaging modality (e.g., PET) with no evidence of distant metastasis (AJCC clinical stage IIA-III): a. Borderline resectable pancreatic carcinoma disease as defined by the NCCN guidelines as follows i. SMV and portal vein: Abutment, encasement, or occlusion of the short segment of vein, ii. Tumor abutment ≤ 180 degrees iii. Celiac Axis: Uninvolved celiac axis; short segment encasement or abutment of common hepatic that may be amenable to resection and reconstruction iv. No involvement of lymph nodes b. Locally advanced pancreatic carcinoma disease as defined: i. Major portal vein or superior mesenteric artery (SMA) thrombosis,	NCCN guidelines clarification based on TIPS investigators' input.

<table>
<tr>
<td></td>
<td></td>
<td>ii. Circumferential encasement of the SMA or
iii. Involvement of the aorta, celiac axis or proximal hepatic artery.

Changed to

2. Biopsy-confirmed BRPC or LAPC in the head or neck of the pancreas that is able to be visualized via CT or other imaging modality (e.g., PET) with no evidence of distant metastasis (AJCC clinical stage IIA-III) as defined by the NCCN guidelines:
 
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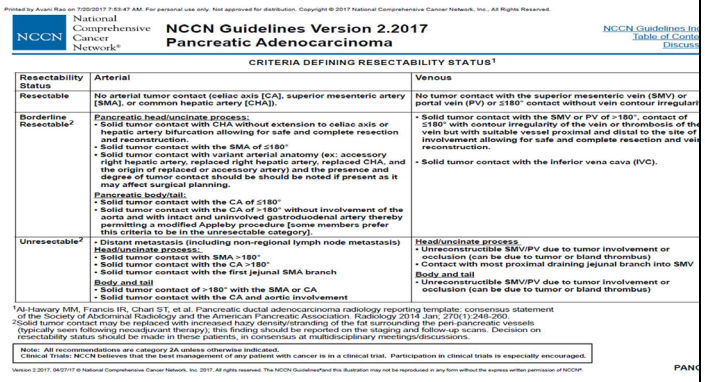
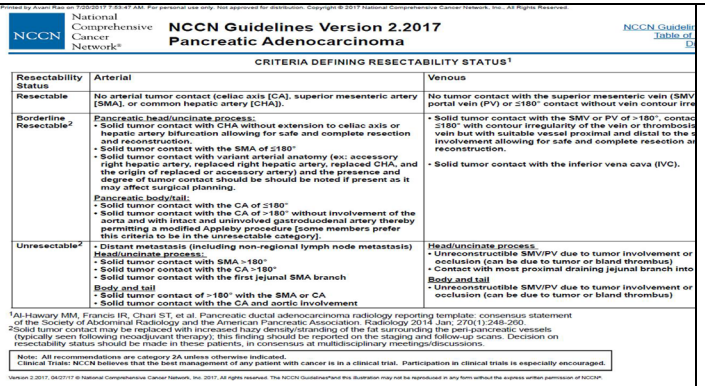
<td>Post-Injection RT Planning: Protocol Summary; Sec. 6.4.1 Table 2 and Figure 1; Sec. 6.4.8, ICF</td>
<td>5-10 days following Index Procedure changed to “less than 28 days following Index Procedure”</td>
<td>Window can be wider to accommodate patient convenience. RT is typically completed in 5 or 6 fractions and therefore longer duration between TraceIT administration and RT planning/initiation will not impact TraceIT performance (the</td>
</tr>
</table>

			hydrogel material is stable for 3 months).
	Selection and Training of Investigators: Sec. 6.2	Only radiation oncologists who meet the credentials … *changed to* "Only radiation oncologists and physicists who meet the credentials…"	Physicists may be sub-Investigators for this study
	RT Planning: Protocol Summary; Sec 6.4.6; Sec 7.6.3	*Changed* V33 *dose constraint measurement to* V35 *for* proximal duodenum, proximal stomach, small bowel and stomach.	Should match ongoing Alliance trial in same subject population
	Table of Contents	*Updated* "REFERENCES ……. ERROR! BOOKMARK NOT DEFINED." to "REFERENCES …….. 47"	Broken link in Table of Contents
Protocol Rev C (March 2019)	Study Title	EARLY FEASIBILITY STUDY FOR EVALUATION OF THE TRACEIT® TISSUE SPACER FOR CREATING SPACE BETWEEN THE DUODENUM AND PANCREAS IN PATIENTS WITH BORDERLINE RESECTABLE OR LOCALLY ADVANCED PANCREATIC CANCER UNDERGOING A COURSE OF SBRT Changed to 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	Clarification of resectable pancreatic cancer patient population and radiotherapy.

	Protocol Summary- Study Design	Multicenter prospective, single-arm early feasibility study. Six (6) subjects with either **borderline resectable or locally advanced pancreatic cancer** (defined per NCCN guidelines) having completed induction chemotherapy and for whom a course of **SBRT** is indicated will be enrolled Changed to Multicenter prospective, single-arm early feasibility study. 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 will be enrolled.	Clarification of resectable pancreatic cancer patient population and radiotherapy.
	Protocol Summary, Protocol	SBRT (Stereotactic body radiation therapy) Changed to RT (Radiotherapy)	Clarification of radiotherapy modalities

	Inclusion Criteria: Protocol Summary; Sec. 6.3.1	2. Biopsy-confirmed **BRPC and LAPC** in the head or neck of the pancreas that is able to be visualized via CT or other imaging modality (e.g., PET) with no evidence of distant metastasis (AJCC clinical stage IIA-III) as defined by the NCCN guidelines:  NCCN Guidelines Version 2.2017 Pancreatic Adenocarcinoma CRITERIA DEFINING RESECTABILITY STATUS[1] Resectability Status / Arterial / Venous Resectable: No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). / No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularit Borderline Resectable[2]: Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category]. / • Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vei reconstruction. • Solid tumor contact with the inferior vena cava (IVC). Unresectable[2]: • Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement / Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) [1]Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014 Jan; 270(1):248-260. [2]Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions. Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. Version 2.2017, 04/27/17 © National Comprehensive Cancer Network, Inc. 2017, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®. PANC *Changed to* 2. Biopsy-confirmed **localized pancreatic cancer** in the head or neck of the pancreas that is able to be visualized via CT or other imaging modality (e.g., PET) with no evidence of distant metastasis (AJCC clinical stage IIA-III) as defined by the NCCN guidelines:	Clarification of resectable pancreatic cancer patient population

		 NCCN Guidelines Version 2.2017 Pancreatic Adenocarcinoma CRITERIA DEFINING RESECTABILITY STATUS[1] Resectability Status / Arterial / Venous Resectable: No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). / No tumor contact with the superior mesenteric vein (SMV) portal vein (PV) or ≤180° contact without vein contour irre Borderline Resectable[2]: Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category]. / • Solid tumor contact with the SMV or PV of >180°, contac ≤180° with contour irregularity of the vein or thrombosis vein but with suitable vessel proximal and distal to the s involvement allowing for safe and complete resection a reconstruction. • Solid tumor contact with the inferior vena cava (IVC). Unresectable[2]: • Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement / Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) [1]Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014 Jan; 270(1):248-260 [2]Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions. Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. Version 2.2017, 04/27/17 © National Comprehensive Cancer Network, Inc. 2017, All rights reserved. The NCCN Guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®.	
	Inclusion Criteria: Protocol Summary; Sec. 6.3.1	3. Tumor is clearly delineable from duodenum **with at least 1 mm of space visible** and no invasion of the duodenum is seen at time of EUS performed for either diagnosis or fiducial placement. Changed to 3. Tumor is clearly delineable from duodenum and no invasion of the duodenum is seen at time of EUS performed for either diagnosis or fiducial placement.	Precise measurements are difficult with current visualization methods and an identifiable delineation is sufficient for enrollment.
	Inclusion Criteria: Protocol Summary; Sec. 6.3.1	**5.** Radiotherapy or chemoradiotherapy for treatment of the disease is indicated **with the intent for eventual surgical resection** Changed to 5. Radiotherapy or chemoradiotherapy for treatment of the disease is indicated	LAPC by nature cannot always be surgically resected

	Exclusion Criteria: Protocol Summary; Sec. 6.3.2	4. Presence of tumor invasion detected on EUS at time of biopsy Changed to 4. Presence of tumor invasion of **the duodenum detected** on EUS at time of biopsy	Clarification of location of tumor invasion
	Exclusion Criteria: Protocol Summary; Sec. 6.3.2	6. Active gastroduodenal ulcer or watery diarrhea Changed to 6. Active gastroduodenal ulcer or **uncontrolled** watery diarrhea	Clarified to uncontrollable watery diarrhea as many patients are on chemotherapy during screening which can cause watery diarrhea.
	Exclusion Criteria: Protocol Summary; Sec. 6.3.2	12. Pregnancy, breast-feeding, women of child-bearing age must use contraceptives. Changed to 12. Women who are pregnant or breast-feeding; women of child-bearing age must use contraceptives	Grammatical error
	Screening/Baseline: Protocol Summary	Subjects who appear to meet the eligibility criteria will be consented for the study and will undergo screening. Information to be collected **at this visit** includes: Changed to Subjects who appear to meet the eligibility criteria will be consented for the study and will undergo screening. Information to be collected **at screening and baseline** includes:	Clarification that the screening/baseline assessments can be done over several days and not at one visit.

	Protocol Summary: Week 2-6 Following Completion of RT (Restaging & Evaluation for Potential Resection at time of CT)	• CA-19-9 level Pancreaticoduodenectomy should be targeted to be performed Changed to • CA-19-9 level • Pancreaticoduodenectomy should be targeted to be performed	Typographical error
	Section 4	Adding: A recent study has shown that this outcome may be improved by adding a pre-operative neoadjuvant chemoradiotherapy for resectable patients.[4] Neoadjuvant therapy has the advantage of reducing the risk of developing metastatic disease in 15 to 35% of patients.[5]	Justification to include resectable pancreatic cancer patients
	Section 4.1.1	Adding: Pre-clinical and clinical investigational studies	Providing new information available for the device
	Table 1: TraceIT Tissue Spacer – Component Descriptions	Adding 3mL configuration option	Equivalent material in larger volume, allows for fewer dilution steps
	Section 5	Six (6) subjects with a biopsy confirmed **diagnosis of BRPC or LAPC (AJCC clinical stage IIA-III)** having completed a course of induction chemotherapy and indicated for **image-guided radiotherapy with SBRT** will be recruited… Changed to Six (6) subjects with biopsy confirmed **localized pancreatic cancer (AJCC clinical stage IA-III)** having completed a course of induction chemotherapy and	Clarification of radiotherapy modalities; removing reference to stereotactic RT to make protocol more consistent

		indicated for **image-guided radiotherapy** will be recruited…	
	Section 5	The study will be conducted at up to **3** investigational sites in the United States. Duration of participation for subjects is approximately **21** months. Changed to The study will be conducted at up to **4** investigational sites in the United States. Duration of participation for subjects is approximately **22** months.	Opening study to more sites due to lack of enrollment at current sites. Increasing the time for participation to account for longer fractionation schedule
	Section 6.2	All investigators that will use the investigational device will undergo training per the TraceIT Tissue Spacer Instructions for Use prior to initial use. Additionally, training for injections will be performed via a cadaver lab and/or the use of phantoms. Changed to All investigators that will use the investigational device will undergo training per the TraceIT Tissue Spacer Instructions for Use prior to initial use. Additionally, training for injections will be performed via **an animal lab**, a cadaver lab and/or the use of phantoms.	Adding additional appropriate method for Investigator training

	Section 6.4.1	The schematic of the trial is presented in **Table 2**, **Table 3**, and **Figure .** Changed to The schematic of the trial is presented in **Table 2**, **Table 3**, and **Figure 1.**	Typographical error
	Section 6.4.2	After the informed consent has been signed, each subject **will be entered on a screening/enrollment log, which will be submitted regularly to the Sponsor.** Once a **subject is consented,** a unique 5-digit subject identification number which includes the 2-digit site number plus a sequential 3-digit subject number starting at 001 (e.g., 01-001) will be assigned. Changed to **Each subject will be assigned a screening number and will be entered on a screening log, which will be submitted regularly to the Sponsor.** After the informed consent has been signed, a unique 5-digit subject identification number which includes the 2-digit site number plus a sequential 3-digit subject number starting at 001 (e.g., 01-001) will be assigned and **subject is screened for eligibility criteria and considered enrolled in the study if all eligibility criteria is met**.	Clarification of enrollment definition
	Section 6.4.2	A subject is considered enrolled in the study **at the time of the informed consent**. Changed to	Clarification of enrollment definition

		A subject is considered enrolled in the study **after screening has been completed and the subject meets eligibility criteria**.	
	Section 6.4.5.1	The subject is to be positioned in the **supine position** and an endoscopic ultrasound (EUS) will be used to identify the duodenum and HOP interface. Changed to The subject is to be positioned in the **left-lateral position** and an endoscopic ultrasound (EUS) will be used to identify the duodenum and HOP interface.	Standard of care for the fiducial procedure is performed in left-lateral position
	Section 6.4.6	The technique for delivering the external beam treatment **will employ stereotactic body radiation therapy (SBRT) techniques using daily image guidance**. Changed to The technique for delivering the external beam treatment **will be employed per institutional standard guidelines**.	Clarification of radiation therapy
	Section 6.4.14	6.4.14 Additional Follow-up at Month 3 (± 14 days) and Month 6 (± 14 days) **and** Post-Index Procedure Changed to 6.4.14 Additional Follow-up at Month 3 (± 14 days) and Month 6 (± 14 days) Post-Index Procedure	Typographical error
	Section 6.4.15	6.4.15 **Longer** Term Follow-Up Following the 6 month visit, subjects will be followed through to 18 months in accordance with standard of care	Updated to match study flow figure

		with at minimum clinical visits performed at Month 12 and Month 18 (± 28 days for each visit) Changed to 6.4.15 **Long** Term Follow-Up (Month 12 and Month 18 ± 28 days for each visit) The following assessments will be performed at the 12- and 18-Month Post-Index Procedure visit: • Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score. • Assessment of duodenal focused Adverse Events documented using NCI CTCAE • Other Adverse Events per NCI CTCAE • EORTC-QLQ-C30 and QLQ-PAN26 • Changes in concomitant medications used to treat intestinal symptoms	
	Section 7.4	Data may be presented separately for **BRPC and LAPC** subjects as well as resected and unresected subjects. Details will be provided in the statistical analysis plan Changed to Data may be presented separately for **localized (resectable, BRPC and LAPC)** subjects as well as resected and unresected subjects. Details will be provided in the statistical analysis plan	Inclusion of resectable pancreatic cancer patient population and external beam radiotherapy

	Section 7.5	The number of subjects signing the informed consent and the number of screening failures (consented but not treated subjects) and the number of secondary screening failures will be presented. Changed to The number of subjects signing the informed consent and the number of primary screening failures (consented but not treated subjects) and the number of secondary screening failures **(Duodenal invasion seen at time of index procedure)** will be presented.	Further clarification on primary and secondary screen failures
	Section 7.7	All adverse events occurring at the time of **TraceIT Tissue Spacer injection** or attempted injection and up through and including the **6 month** visit will be recorded and listed. **Thereafter, only information concerning duodenal toxicity or events deemed related to the TraceIT Tissue Spacer will be collected**. Changed to All adverse events occurring at the time of **initiation of fiducial marker placement** or attempted injection and up through and including the **18-month visit will be recorded and listed.**	Further clarification on collection of Adverse Events
	Section 9.1.1	All Adverse Events (AE) **and intervening illnesses** must be documented throughout the study. Changed to All Adverse Events (AE) must be documented throughout the study.	Removing redundancy

	Section 9.1.1	All adverse events, regardless of severity or relationship to investigational device, will be collected from the time of **TraceIT hydrogel injection** and through the 18-month visit. Changed to All adverse events, regardless of severity or relationship to investigational device, will be collected from the time of **initiation of fiducial marker** placement and through the 18-month visit.	Further clarification of protocol for consistency
	Section 9.1.2	The CEC will be charged with the following responsibilities: • 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. Changed to The CEC will be charged with the following responsibilities: • 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, procedure, **radiotherapy, or other**.	Further clarification of protocol for consistency
	Appendix C: Sample Informed Consent	You will receive **5 treatments every other day over a period of about 2 weeks**. Changed to	Clarification of radiation therapy

		You will receive **radiation therapy as per the institutional standard that will explained to you by your doctor**.	
	Appendix C: Sample Informed Consent	You will receive radiation treatment for about **2 weeks**. During this period, you will receive **5** treatments based on a schedule given to you by your doctor. Changed to You will receive radiation treatment for about **2 – 6 weeks**. During this period, you will receive **radiation treatments** based on a schedule given to you by your doctor.	Clarification of radiation therapy
	Appendix C: Sample Informed Consent	About 6 people will be in this study at up to **3** clinics in the United States. You will be in this study approximately **1 year and 9 months** beginning with your screening and continuing until your last study visit. Changed to About 6 people will be in this study at up to **4** clinics in the United States. You will be in this study approximately **1 year and 10 months** beginning with your screening and continuing until your last study visit.	Opening study to more sites due to lack of enrollment at current sites. Increasing the time for participation to account for follow-up schedule
	Appendix C: Sample Informed Consent	Adding to Risk section: The risks to an embryo, fetus and breastfeeding baby are not known at this time.	Updating risk section per ICH E6 R2 compliance
	Appendix C: Sample Informed Consent	Adding: Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study. _____ Yes, I want the study doctor to inform my primary care physician/specialist of my participation in this study.	Updating consent document per ICH E6 R2 compliance

		_____ No, I do not want the study doctor to inform my primary care physician/specialist of my participation in this study.	
	Appendix C: Sample Informed Consent	You will be given a copy of **this** consent document to keep. Changed to You will be given a copy of **signed** consent document to keep.	Updating ICF to clarify that subject will be given a copy of the signed consent document
	Appendix D	Investigator Agreement and Certification	Moved from Page 2 to Appendix for ease of use

2 PROTOCOL SUMMARY

Title:	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 a Course of Radiation Therapy: The TIPS Pilot Study
Device:	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.
Indication:	TraceIT Tissue Spacer is a radiopaque hydrogel material intended to temporarily position the duodenum away from the pancreas in subjects undergoing 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.
Study Objective:	To evaluate the feasibility, radiotherapy benefits, and safety when using TraceIT Tissue Spacer to create space between the pancreas and duodenum.
Study Design:	Multicenter prospective, single-arm early feasibility study. 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 will be enrolled. Enrolled subjects will undergo placement of intrapancreatic fiducial markers and peri-duodenal administration of TraceIT hydrogel within the same endoscopic ultrasound transduodenal procedure. The hydrogel will be distributed in small volumes (generally ~1 to 2 mL and up to a total of 20 mL) at several areas along the proximal portion of the duodenum in the areas closest to the head of the pancreas (HOP). RT simulation planning will be performed prior to and following TraceIT placement for evaluation and comparison of duodenal dose / dose distribution and to assess differences in RT dosing parameters. The pre- and post-TraceIT injection simulation planning will be performed using the identical technique and similar set-up, and with appropriate respiratory motion control (e.g., feedback-guided inspiratory breath-hold gating, end expiratory gating during free breathing or abdominal compression as appropriate).

	In accordance with standard medical practice, within 2-6 weeks after completion of therapy, subjects will be restaged to determine whether they may progress to surgery. If surgical resection is attempted and successful, pathological data will be recorded within the study eCRF. All subjects will be evaluated at minimum 3 and 6 months post-TraceIT administration. An MR will be performed at the 6 month visit to evaluate for TraceIT presence. Throughout the duration of the study, subjects will be clinically evaluated and assessed for duodenal adverse events using the grading of the NCI Common Terminology Criteria for Adverse Events (CTCAE v4). Quality of life data will be collected using the EORTC QLQ-PAN26 and QLQ-C30 questionnaires. Additional longer-term follow-up clinic visits will be performed in accordance with standard of care, at minimum, 12 and 18 months.
Safety Endpoints:	Subjects will be monitored for adverse events and radiotherapy (RT) toxicity (using CTCAE v4) and in particular for the safety endpoint 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.
Effectiveness Endpoints:	Effectiveness endpoints of interest for this study are as follows: • Feasibility: Feasibility will be defined to be Technical Success; i.e., the ability to place TraceIT and create space between the duodenum and HOP. • Radiotherapy Benefits: Will be assessed via comparison of pre- and post-TraceIT administration RT plans with consideration of the following: ability to maintain safe duodenal dose constraints, percent/volume of GTV/PTV receiving prescription dose and overall duodenal dose/ dose distribution. Additional data collection will include: • 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-treatment 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

Inclusion Criteria:

Subjects must meet all of the following criteria to be eligible for participation in the study:

1. Age ≥18 years old
2. Biopsy-confirmed localized pancreatic cancer in the head or neck of the pancreas that is able to be visualized via CT or other imaging modality (e.g., PET) with no evidence of distant metastasis (AJCC clinical stage IA-III) as defined by the NCCN guidelines:

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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Discussion

CRITERIA DEFINING RESECTABILITY STATUS[1]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[2]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

[1]Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014 Jan; 270(1):248-260.
[2]Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PANC-B

3. Tumor is clearly delineable from duodenum and no clear evidence of invasion of the duodenum is seen at time of EUS performed for either diagnosis or fiducial placement.
4. Subject is able to comply with motion management guidelines
5. Radiotherapy or chemoradiotherapy for treatment of the disease is indicated
6. In Investigator's opinion, medically fit to undergo endoscopy for fiducial marker implantation and TraceIT administration
7. Subjects Screening/Baseline laboratory testing must meet the following laboratory value criteria:
    a. White blood cell count: ≥ 3.0 x 10^9/L
    b. Absolute neutrophil count (ANC): ≥ 1.5 x 10^9/L
    c. Platelets: ≥ 100 x 10^9/L
    d. Total bilirubin: ≤ 2.0 times upper limit of normal (ULN)
    e. AST and ALT: ≤ 3.0 times institutional upper normal limit
    f. Serum creatinine: < 1.5 times ULN
    g. INR: < 1.5
    h. Serum pregnancy: Negative
    i. Hemoglobin: ≥ 8.0 g/dl
8. Zubrod Performance Status 0-2
9. Subject or authorized representative, has been informed of the nature of the study and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) of the respective clinical site
10. Life expectancy of at least 9 months

Exclusion Criteria	Subjects who meet any of the following criteria are not eligible for participation in the study: 1. Patients for whom radiotherapy is contraindicated 2. Previous thoracic or abdominal radiotherapy 3. Any GI abnormality that would interfere with the ability to access the injection site 4. Presence of tumor invasion of the duodenum detected on EUS at time of biopsy 5. Previous Whipple procedure or other resection of pancreatic tumor prior to screening 6. Active gastroduodenal ulcer or uncontrolled watery diarrhea 7. History of Chronic Renal Failure 8. Documented history of uncontrolled diabetes (i.e., symptomatic hyperglycemia that cannot be medically managed, fasting blood glucose level above 300 mg/dL, and/or frequent swings between hyperglycemia and hypoglycemia) 9. Currently enrolled in another investigational drug or device trial that clinically interferes with this study 10. Unable to comply with the study requirements or follow-up schedule 11. Any condition or comorbidity that the Investigator believes would interfere with the intent of the study or would make participation not in the best interest of the subject 12. Women who are pregnant or breast-feeding; women of child-bearing age must use contraceptives
Screening/Baseline: (within 45 days prior to planned TraceIT hydrogel injection)	Subjects who appear to meet the eligibility criteria will be consented for the study and will undergo screening. Information to be collected at screening and baseline includes: • Demographic information: date of birth, weight and height, race • Disease documentation: tumor location, initial resectability status, tumor staging, largest pre-treatment dimension of tumor (cm) • Medical/Surgical History/Current status: concomitant medical conditions, prior medical conditions, prior surgeries, prior therapies (e.g., induction chemotherapy) • Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score • Laboratory testing for hematology plus platelets, creatinine, AST/ALT and bilirubin and baseline serum carbohydrate antigen (CA) 19-9 • Pregnancy test for women of child-bearing potential. • EORTC-QLQ-C30 and QLQ-PAN26 • Assessment of baseline duodenal symptoms per NCI CTCAE • Baseline concomitant medications

<table>
<tr><td>Initial RT Planning & Documentation</td><td>Subjects who appear to meet the inclusion criteria and do not present with any of the exclusion criteria will undergo a CT for baseline RT Planning.

The initial <u>minimum target dose</u> will be 33 Gy in 5 fractions (or an equivalent biologically effective dose if >5 fractions is being delivered). CT simulation will be performed with immobilization.

Target dose constraints for OAR include:

<table>
<tr><th>Organs at Risk (OAR)</th><th>Dose Constraint*</th></tr>
<tr><td>Proximal duodenum, proximal stomach and small bowel</td><td>V15Gy<9cc, V20Gy<3 cc, and V35Gy<1cc
A duodenal maximum dose of ≤32 Gy should initially be attempted</td></tr>
<tr><td>Stomach</td><td>V12Gy<50%, V35Gy<1cc</td></tr>
<tr><td>Liver</td><td>V12Gy<50%</td></tr>
<tr><td>Combined Kidneys</td><td>V12Gy<75%;</td></tr>
<tr><td>Spinal Cord</td><td>V8Gy<1 cc</td></tr>
</table>
*or biologically equivalent dose constraints for >5 fractions

Radiographic tumor-vessel interface will be documented.

Other dosimetric data to be collected include: V5 (volume (cc) of the duodenum receiving 5 Gy or more), V10, V15, V20, V25, V30, V35, V40, duodenal mean/maximum doses, GTV/PTV minimum/mean/maximum doses as well as GTV/PTV volume, and total duodenal volume.</td></tr>
<tr><td>Index Procedure: Fiducial Placement/ TraceIT Hydrogel Injection</td><td>• Ability to access injection site and inject TraceIT material
• Average duodenal space measurements on CT measured at 3 points along the head of the pancreas
• TraceIT Injection Procedure Duration
• Ease of Device Use
• Device malfunctions
• Adverse Events per NCI CTCAE ver. 4.0</td></tr>
<tr><td>Follow-up for Non-Injection Subjects (30 days +7 days or until resolution/ stabilization of an adverse event if applicable)</td><td>A “Non-Injection” Subject is a subject who was intended to be treated with TraceIT, but in whom TraceIT was unable to be injected. No further image collection is required for these subjects.
• 30 Day Visit to include:
  o Physical Assessment: including sitting blood pressure, pulse, temperature, and Zubrod Performance Score
  o Assessment of Intestinal Adverse Events documented using CTCAE criteria
  o Other Adverse Events per NCI CTCAE
• Changes in concomitant medications used to treat intestinal symptoms</td></tr>
</table>

Post-injection RT Planning *(less than 28 days following Index Procedure)*	• Repeat CT Planning Imaging using the same number of beams and set-up as Pre-injection planning • Dosimetric data to be collected include: V5 (volume (cc) of the duodenum receiving 5 Gy or more), V10, V15, V20, V25, V30, V35, V40, duodenal mean/maximum doses, GTV/PTV minimum/mean/maximum doses as well as GTV/PTV volume, and total duodenal volume • Theoretical dose escalation (maximum dose to GTV while maintaining duodenal dose constraints)
RT Initiation	• RT must be initiated no later than (NLT) 28 days following TraceIT administration • RT should be initiated no sooner than (NST) 1 week from last chemotherapy dose
Final RT Fraction	• Physical Assessment (including vital signs, weight and Zubrod Performance score) • EORTC-QLQ-C30 and QLQ-PAN26 • Assessment of duodenal focused Adverse Events documented using NCI CTCAE • Other Adverse Events per NCI CTCAE • Changes in concomitant medications used to treat intestinal symptoms
Week 2-6 Following Completion of RT (Restaging & Evaluation for Potential Resection at time of CT)	• Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score • CT for restaging (also will evaluate TraceIT Persistence) • Assessment of duodenal focused Adverse Events documented using NCI CTCAE • Other Adverse Events per NCI CTCAE • Changes in concomitant medications used to treat intestinal symptoms • CA-19-9 level • Pancreaticoduodenectomy should be targeted to be performed within 8 weeks after the completion of RT if applicable. Restaging and determination of resectability will be performed in accordance with the standard institutional practices.
Resected Subjects (At time of resection)	• Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score • Assessment of duodenal focused Adverse Events documented using NCI CTCAE if available • Other Adverse Events per NCI CTCAE if available • Changes in concomitant medications used to treat intestinal symptoms

Resected Subjects (Histopathology record)	• Incidence of complete or partial response (Path PR and Path CR) • Pathologic duodenal damage score rated by a local board-certified gastrointestinal surgical pathologist using the methods outlined by Verma et al.,[1] where: o 1=no/minimal signs of mucosal damage: villi remain long and slender, epithelial cells have abundant eosinophilic cytoplasm with few mitotic figures, and the lamina propria have normal amounts of inflammatory cells including few or no neutrophils. o 2=moderate damage where villi are blunted or absent, epithelial cells have reactive/reparative, changes with basophilic cytoplasm, increase mitotic figures, and/or small erosions or focal ulcerations; the lamina propria show increased inflammation including eosinophils and neutrophils. o 3=severe damage with diffuse epithelial damage absent with or without extensive ulcerations and residual surviving epithelium displaying marked reactive/reparative changes; lamina propria replaced with granulation tissue and/or overlying fibrinoid inflammatory exudates with numerous neutrophils or marked damage.
Additional Follow-up at Month 3 (± 14 days) and Month 6 (± 14 days) Post-Index Procedure	• Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score • Unresected subjects only: MRI at Month 6 post-index procedure • Assessment of duodenal focused Adverse Events documented using NCI CTCAE • Other Adverse Events per NCI CTCAE • PAN26, EORTC-QLQ-C30 • Changes in concomitant medications used to treat intestinal symptoms • Post-surgical complications in resected subjects
Longer-Term Follow-up	Following the 6-month visit, subjects will be followed through to 18 months in accordance with standard of care with at minimum clinical visits performed at Month 12 and Month 18 (± 28 days for each visit).
Clinical Events Committee (CEC)	A CEC will be appointed by Augmenix. Members of the CEC will include physicians with a specialty in treating patients with pancreatic cancer including a radiation oncologist and a gastroenterologist. These physicians will be independent of the study Investigators and will be responsible for interim review and classification of adverse events observed and will review data related to the conduct and quality of the study. The CEC may make formal recommendations for protocol changes to mitigate risk of adverse events.

3 PRINCIPAL CONTACTS

Sponsor Contacts:

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4 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.[2] 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.[3]

The only curative treatment for pancreatic cancer is surgical resection, most commonly by pancreato-duodenectomy or distal pancreatectomy (for pancreatic tail tumors). Resectable patients have markedly improved 5-year overall survival (OS) of approximately 20%. A recent study has shown that this outcome may be improved by adding a pre-operative neoadjuvant chemoradiotherapy for resectable patients.[4] Neoadjuvant therapy has the advantage of reducing the risk of developing metastatic disease in 15 to 35% of patients.[5] By contrast unresectable disease is associated with dismal 5-year OS rates of <5%. However, since the signs and symptoms of pancreatic cancer are not usually clinically apparent until the advanced stages, it has been reported that, overall, less than 20 to 25% of pancreatic tumors are amenable to resection at the time of diagnosis. [6,7]

Among patients with pancreatic cancer, a subset present with borderline resectable pancreatic cancer (BRPC), for which neoadjuvant therapy has an established role in obtaining a margin negative (R0) surgical resection and thus improving long term survival.[8] Additionally, many patients present with locally advanced unresectable disease (LAPC) that with the proper neoadjuvant treatment could potentially be down-staged to resectable disease. In general, neoadjuvant treatment is becoming increasingly explored in hopes of improving the prognosis of pancreatic cancer by treating micrometastases, reducing tumor volume and increasing the likelihood of an R0 resection for both borderline resectable and locally advanced disease.[8]

Thus, current guidelines for the management of patients with borderline resectable and locally advanced disease include single- or multi-agent chemotherapy or chemoradiation (CRT) in sequence with chemotherapy.[7] Although results of studies comparing chemotherapy alone to CRT for patients with BR/LAPC have been mixed [10,11,12,13] in some series among patients with outright unresectable disease, 8% to 30% are converted to a resectable state following chemoradiotherapy. 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.[14]

The importance of local control or delaying local progression on improving morbidity and possibly mortality in patients with pancreatic cancer is supported by autopsy data demonstrating that 30% of patients die of locally destructive disease.[15] It follows then that in the cases of BR/LAPC, 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 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 radiosensitivity, 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.[16] 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.[17]

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. In a prospective randomized (2:1), controlled multicenter study evaluating 222 men with clinical stage T1 or T2 prostate cancer, SpaceOAR use was associated with significant rectal dosimetric benefits and reduced rectal toxicity severity as well as a decrease in the proportion of patients experiencing declines in bowel quality of life. [18,19] Thus 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 HOP may also provide a benefit in reducing incidental radiation to the duodenum due to intra and interfraction 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.

4.1 Report of Prior Investigations

The TraceIT Tissue Spacer, which consists primarily of water and polyethylene glycol (PEG) is formulated with constituents that have a long history of safe use in implantable medical devices. Additionally, the materials used in the manufacture of the TraceIT Tissue Spacer have a history of use as FDA approved and cleared degradable implants used adjacent to sensitive tissues (e.g. neurological tissues) and the hydrogel material is currently commercially available to be used for tissue marking similar to a fiducial marker. Results of biocompatibility testing demonstrate that TraceIT Tissue Spacer meets the requirements specified for a permanent implant (defined as a device that remains implanted for greater than 30 days) as delineated in ISO 10993: Biological Evaluation of Medical Devices. The TraceIT Tissue Spacer has been found to meet its performance specifications. Once injected into the body, TraceIT Tissue Spacer has been found to be non-toxic, compatible with surrounding tissues and degrades within 7 months. These results are to be expected, since the product components (primarily water and PEG) were chosen for biocompatibility. The results demonstrate TraceIT Tissue Spacer hydrogel safety in clinically relevant models.

4.1.1 Pre-Clinical and Clinical Investigations

Pancreas-duodenum spacing was studied in human cadavers[23] as a proof of concept study. Using the endoscopic ultrasound (EUS) approach, TraceIT Tissue Spacer was implanted in the pancreas-duodenum interface and adequate space was created. The TraceIT Tissue Spacer

created adequate space to demonstrate dosimetric advantages, including: limiting radiation dose to the duodenum, enhanced coverage of the theoretical tumor and a potential for dose escalation. In a similar porcine study, TraceIT Tissue Spacer was also successfully placed in the pancreas-duodenum interface using an EUS approach[24]. The hydrogel was clearly visible on computerized tomography (CT) and Cone-beam CT in all the animals that were successfully injected. A mild to moderate reactive inflammation isolated to the injection site was observed. Further, this porcine study showed that when TraceIT Tissue Spacer is injected directly into the pancreas, there was no evidence of pancreatitis or other adverse events. An equivalent injection was attempted into the duodenal wall to simulate improper injection. Though it was difficult to inject into the duodenal wall in the porcine model, when duodenal wall injection was successful, there was no evidence of local adverse events. Overall, the gel implants were tolerated well with no related adverse events. In a human clinical study, TraceIT hydrogel is being evaluated to access and mark the interface between the pancreas and duodenum using an EUS-guided approach in patients with pancreatic adenocarcinoma (ClinicalTrials.gov Identifier: NCT03307564). In this study, a small volume of hydrogel is injected to mark the interface. The visibility and safety of the hydrogel injection will be assessed.

4.2 Description of Investigational Device

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.

As shown in **Table 1**, the TraceIT Tissue Spacer consists of one prefilled glass syringe with endcap, one plastic receiving syringe and a luer-luer connector.

Table 1:TraceIT Tissue Spacer -Component Descriptions

Component	Description		Quantity
Prefilled glass syringe with endcap		A prefilled 1mL or 3mL glass syringe containing the radiopaque cross-linked hydrogel material with an endcap	1
Plastic receiving syringe		A plastic 1mL or 3mL receiving syringe used to receive and deliver the radiopaque cross-linked hydrogel material	1
Luer-Luer connector		Plastic component used to transfer the prefilled syringe material to the receiving syringe	1

4.3 Indication

The indication for use that will be utilized in this study is stated below.

TraceIT Tissue Spacer is a radiopaque hydrogel material intended to temporarily position the duodenum away from the pancreas in subjects undergoing 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.

5 STUDY SCOPE AND DURATION

This is a multicenter, prospective, non-randomized, single arm, open-label early feasibility study. Six (6) subjects with biopsy confirmed localized pancreatic cancer (AJCC clinical stage IA-III) having completed a course of induction chemotherapy and indicated for image-guided radiotherapy will be recruited for this study and followed for a minimum of 6 months after injection of the TraceIT hydrogel. **This visit serves as the end of the study for assessing device safety.** Subjects will also be required to return for long-term follow-up for up to 18 months.

Prior to enrollment, potential study candidates will undergo a thorough physical examination and documentation of medical/surgical history. A baseline Computed tomography (CT) simulation will be performed by Radiation Oncology department to generate a baseline RT plan. Subjects meeting the study eligibility criteria will undergo transduodenal injection of TraceIT Tissue Spacer under endoscopic ultrasound guidance performed by a participating endoscopist experienced with similar procedures. As part of the subjects' standard of care, a CT simulation scan will be acquired post TraceIT Tissue Spacer injection. A second radiation treatment plan will be generated using this CT simulation scan and the subject will begin RT for pancreatic cancer according to this post-injection plan. During the last fraction of RT, acute duodenal toxicity will be scored using CTCAE v4.0 criteria.

Following the course of RT, subjects will be required to return for follow-up evaluations 2-6 weeks after radiation therapy for a resectability assessment, followed by visits at 3, 6, 12 and 18 months.

The Sponsor will utilize a Clinical Events Committee (comprised of physicians experienced in treating pancreatic cancer) to provide ongoing review and adjudication of adverse events at an individual and aggregate level and to monitor emerging data with respect to device effectiveness. Any serious and/or unanticipated adverse events will be submitted for committee review within 48 hours of the Sponsor's receipt of notification of such events so that an evaluation of the risk/benefit assessment of the investigational treatment can be performed.

The study will be conducted at up to 4 investigational sites in the United States. Enrollment is anticipated to take approximately 3 months. Duration of participation for subjects is approximately 22 months.

6 PROTOCOL

6.1 Study Objectives

To evaluate the feasibility, radiotherapy benefits and safety when using TraceIT Tissue Spacer to create space between the pancreas and duodenum.

6.1.1 Safety Endpoints

Subjects will be monitored for adverse events and RT toxicity (using CTCAE v4) and in particular for the safety endpoint 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.

6.1.2 Effectiveness Endpoints

Effectiveness endpoints of interest for this study are as follows:

- Feasibility: Feasibility will be defined to be Technical Success; i.e., the ability to place TraceIT and create space between the duodenum and HOP.
- Radiotherapy Benefits: Will be assessed via comparison of pre- and post-TraceIT administration RT plans with consideration of the following: ability to maintain safe duodenal dose constraints, percent/volume of GTV/PTV receiving prescription dose and overall duodenal dose/dose distribution.

6.1.3 Additional Data Collection

Additional data collection will include but may not be limited to:

- Incidence of resection
- Progression free and overall survival
- Incidence of acute (within 3 months) and late (>3 months) duodenal toxicity (for nonresected subjects)
- Theoretical dose escalation from post-TraceIT treatment plan
- TraceIT persistence (at 6-months post-treatment 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

6.2 Selection and Training of Investigators

Only radiation oncologists and physicists who meet the credentials at their institution for planning and performing RT and endoscopists with prior experience with transduodenal procedures will be considered for participation as investigators in this study. All investigators that will use the investigational device will undergo training per the TraceIT Tissue Spacer Instructions for Use prior to initial use. Additionally, training for injections will be performed via an animal lab, a cadaver lab and/or the use of phantoms.

6.3 Subject Selection

6.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for participation in the study:

1. Age ≥18 years old
2. Biopsy-confirmed localized pancreatic cancer in the head or neck of the pancreas that is able to be visualized via CT or other imaging modality (e.g., PET) with no evidence of distant metastasis (AJCC clinical stage IA-III) as defined by the NCCN guidelines:

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Pancreatic Adenocarcinoma

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Discussion

CRITERIA DEFINING RESECTABILITY STATUS[1]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[2]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

[1]Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014 Jan; 270(1):248-260.
[2]Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PANC-B

3. Tumor is clearly delineable from duodenum and no clear evidence of invasion of the duodenum is seen at time of EUS performed for either diagnosis or fiducial placement.
4. Subject is able to comply with motion management guidelines.
5. Radiotherapy or chemoradiotherapy for treatment of the disease is indicated.
6. In Investigator's opinion, medically fit to undergo endoscopy for fiducial marker implantation and TraceIT administration.
7. Subjects Screening/Baseline laboratory testing must meet the following laboratory value criteria:
    a. White blood cell count: ≥ 3.0 x 10^9/L
    b. Absolute neutrophil count (ANC): ≥ 1.5 x 10^9/L
    c. Platelets: ≥ 100 x 10^9/L
    d. Total bilirubin: ≤ 2.0 times upper limit of normal (ULN)
    e. AST and ALT: ≤ 3.0 times institutional upper normal limit
    f. Serum creatinine: < 1.5 times ULN e
    g. INR: < 1.5
    h. Serum pregnancy: Negative
    i. Hemoglobin: ≥ 8.0 g/dl
8. Zubrod Performance Status 0-2
9. Subject or authorized representative, has been informed of the nature of the study and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) of the respective clinical site.
10. Life expectancy of at least 9 months

6.3.2 Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for participation in the study:

1. Patients for whom radiotherapy is contraindicated
2. Previous thoracic or abdominal radiotherapy

3. Any GI abnormality that would interfere with the ability to access the injection site
4. Presence of tumor invasion of the duodenum detected on EUS at time of biopsy
5. Previous Whipple procedure or other resection of pancreatic tumor prior to screening
6. Active gastroduodenal ulcer or uncontrolled watery diarrhea
7. History of Chronic Renal Failure.
8. Documented history of uncontrolled diabetes (i.e., symptomatic hyperglycemia that cannot be medically managed, fasting blood glucose level above 300 mg/dL, and/or frequent swings between hyperglycemia and hypoglycemia)
9. Currently enrolled in another investigational drug or device trial that clinically interferes with this study.
10. Unable to comply with the study requirements or follow-up schedule.
11. Any condition or comorbidity that the Investigator believes would interfere with the intent of the study or would make participation not in the best interest of the subject.
12. Women who are pregnant or breast-feeding; women of child-bearing age must use contraceptives

6.4 Study Procedures and Data Collection

6.4.1 Study Schematics

The schematic of the trial is presented in **Table 2**, **Table 3**, and **Figure 1**

Table 2: Study Protocol Synopsis for Subjects Injected with TraceIT Tissue Spacer

Procedure	Regulatory Phase: For Assessment of TraceIT Tissue Spacer Safety and Feasibility							
	Screening/ Baseline Assessment *(within 45 days prior to planned TraceIT hydrogel injection)*	**Initial RT Planning and Documentation**	**Index Procedure** *(Fiducial placement/TraceIT injection)*	**Post TraceIT injection RT Planning** *(less than 28 days after Index Procedure)*	**Final RT Fraction**	**Week 2-6 Following completion of RT** *(Restaging & Evaluation for Potential Resection)*	**Resected Subjects** *(at time of resection)*	**Additional Follow-up at 3M, 6M†, 12M and 18M Post Injection**
Demographic information [a]	✓							
Med./Surg. History/Current status[b]	✓							
Physical Exam[c]	✓				✓	✓	✓	✓
Laboratory Testing	✓[d]					✓		
Disease documentation[e]	✓							
Pregnancy test for women of child bearing age	✓							
EORTC-QLQ-C30, QLQ-PAN26	✓				✓			✓
CT Scan		✓		✓ **With visibility scoring**		✓		
MRI								✓ (Month 6, unresected subjects only)
Assessment duodenal symptoms (per NCI CTCAE)	✓		✓		✓	✓	✓	✓
Concomitant Meds	✓		✓		✓	✓	✓	✓
Adverse Events (per NCI CTCAE)			✓		✓	✓	✓	✓

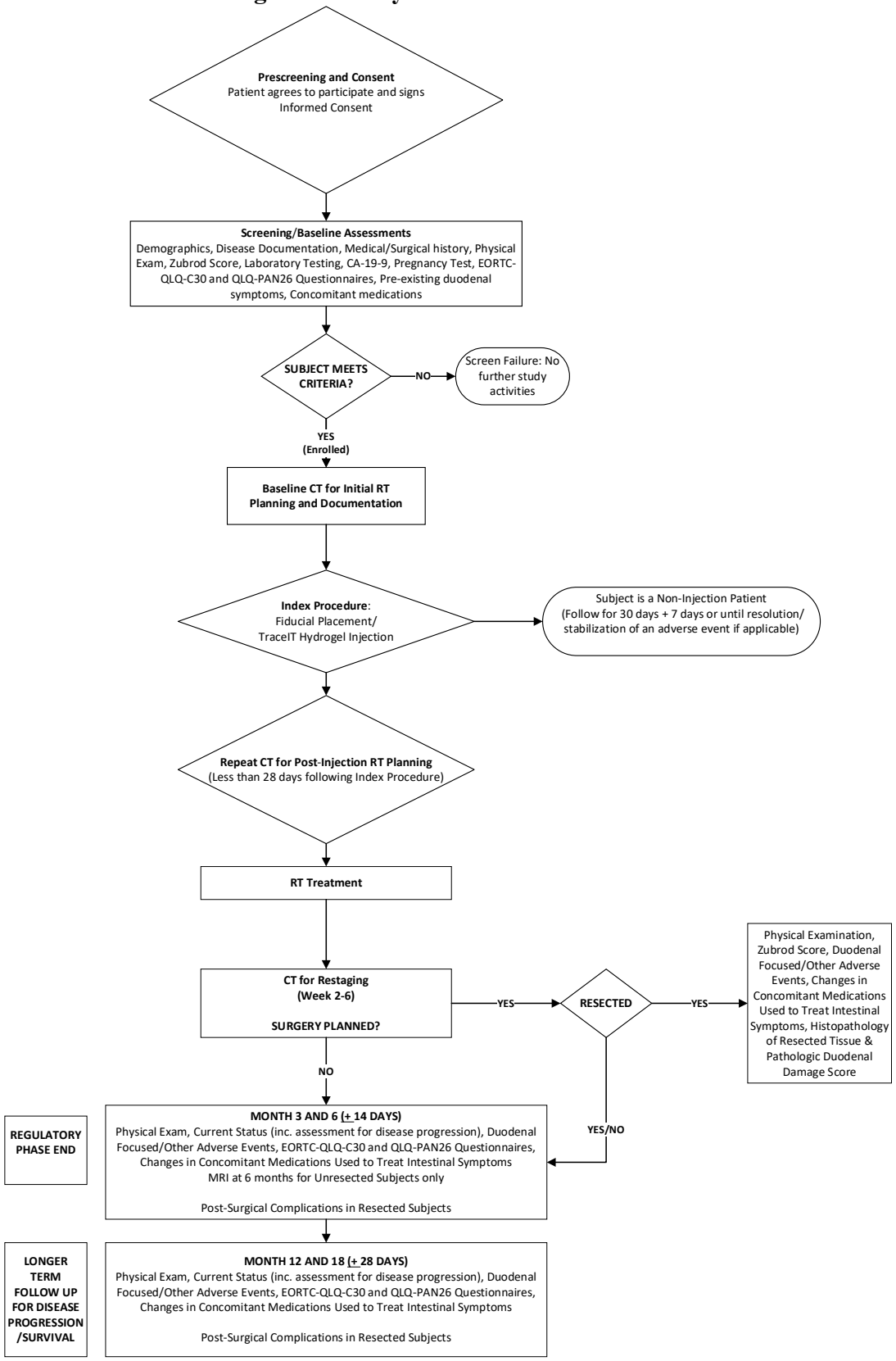
†End of regulatory phase
[a] Including date of birth, weight and height, race
[b] Concomitant medical conditions, prior medical conditions, prior surgeries, prior therapies (e.g., induction chemotherapy)
[c] Including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score
[d] Including hematology plus platelets, creatinine, AST/ALT and bilirubin and baseline serum carbohydrate antigen (CA) 19-9
[e] Including tumor location, initial resectability status, tumor staging, largest pre-treatment dimension of tumor (cm)

Table 3: Study Protocol Synopsis for Non-Injection Subjects

Procedure	Regulatory Phase: For Assessment of TraceIT Tissue Spacer Safety and Feasibility			
	Screening/ Baseline Assessment *(within 45 days prior to planned TraceIT hydrogel injection)*	**Initial RT Planning and Documentation**	**Index Procedure** *(Fiducial placement/TraceIT injection)*	**30 Days following Index Procedure** *(+7 days or until resolution/ stabilization of an adverse event if applicable)*
Demographic information [a]	✓			
Med./Surg. History/Current status[b]	✓			
Physical Exam[c]	✓			✓
Laboratory Testing	✓[d]			
Disease documentation[e]	✓			
Pregnancy test for women of child bearing age	✓			
PAN26, EORTC-QLQ-C30	✓			
CT Scan		✓		
MRI				
Assessment duodenal symptoms (per NCI CTCAE)	✓		✓	✓
Concomitant Meds	✓		✓	✓
Adverse Events (per NCI CTCAE)			✓	✓

[a] Including date of birth, weight and height, race
[b] Concomitant medical conditions, prior medical conditions, prior surgeries, prior therapies (e.g., induction chemotherapy)
[c] Including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score
[d] Including hematology plus platelets, creatinine, AST/ALT and bilirubin and baseline serum carbohydrate antigen (CA) 19-9
[e] Including tumor location, initial resectability status, tumor staging, largest pre-treatment dimension of tumor (cm)

Figure 1: Study Procedural Flow Chart



6.4.2 Subject Enrollment

Prior to enrollment in the study, subjects will be evaluated to determine eligibility. The subject's willingness and ability to meet the follow-up requirements will be determined. If the subject desires to participate in the study, written informed consent will be obtained prior to performance of any study-specific examinations (see Section 6.4.3). Each subject will be assigned a screening number and will be entered on a screening log, which will be submitted regularly to the Sponsor. After the informed consent has been signed, a unique 5-digit subject identification number which includes the 2-digit site number plus a sequential 3-digit subject number starting at 001 (e.g., 01-001) will be assigned and subject is screened for eligibility criteria and considered enrolled in the study if all eligibility criteria is met. No two subjects will have the same five-digit subject identification number. This subject identification number will identify the subject throughout the study and will be used for all source documents and CRFs. Subjects who meet the eligibility criteria and agree to participate will be scheduled for TraceIT Tissue Spacer injection and fiducial marker placement.

A subject is considered enrolled in the study after the subject meets eligibility criteria. Only subjects who undergo TraceIT Tissue spacer injection attempt (i.e., at the time the needle is inserted through the duodenum) will be included in the safety/effectiveness populations for analysis. All subjects enrolled in the study will be required to adhere to the follow-up schedule outlined in this protocol. Subjects withdrawing consent after treatment will not be required to undergo follow-up after withdrawal; however, these participants will still be considered part of the study cohort and included in the safety analysis.

6.4.3 Informed Consent

All subjects considered for enrollment in the study must complete an IRB approved informed consent PRIOR to any study-specific procedures being performed. The Investigator should adhere to GCP and to the ethical principles as delineated in 21 CFR Part 50. Failure to obtain a signed informed consent renders the subject ineligible for the study. Subjects must be willing to undergo transduodenal placement of fiducial markers and the TraceIT Tissue Spacer and must be willing to consent to study procedures and return for follow-up visits upon completion of RT.

6.4.4 **Screening/Baseline Assessments** (within 45 days prior to planned TraceIT hydrogel injection)

Subjects who appear to meet the eligibility criteria will be consented for the study and will undergo screening. Information to be collected at this visit includes:

- Demographic information: date of birth, weight and height, race
- Disease documentation: tumor location, initial resectability status, tumor staging, largest pre-treatment dimension of tumor (cm)
- Medical/Surgical History/Current status: concomitant medical conditions, prior medical conditions, prior surgeries, prior therapies (e.g., induction chemotherapy)
- Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score
- Laboratory testing for hematology plus platelets, creatinine, AST/ALT and bilirubin and baseline serum carbohydrate antigen (CA) 19-9
- Pregnancy test for women of child-bearing potential

- EORTC-QLQ-C30 and QLQ-PAN26
- Assessment of baseline duodenal symptoms per NCI CTCAE
- Baseline concomitant medications

6.4.5 Fiducial Placement and TraceIT Tissue Spacer Injection

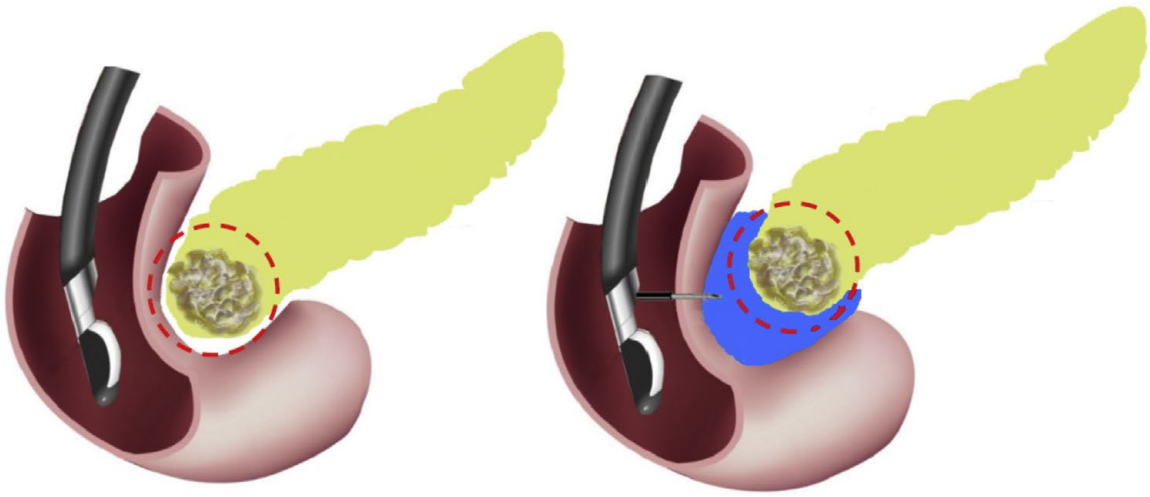
6.4.5.1 Injection

The TraceIT Tissue Spacer is to be injected between the pancreas and the duodenum by the participating study physician using a transduodenal approach and with endoscopic ultrasound (EUS) guidance as depicted in **Figure** 2.

An EUS assessment of the space between the pancreas and the duodenum before and after injection is to be performed. The following information will be collected:

- Ability to access injection site and inject TraceIT material
- Average duodenal space measurements on CT measured at 3 points along the head of the pancreas
- TraceIT Injection Procedure Duration
- Ease of Device Use
- Device malfunctions
- Adverse Events per NCI CTCAE ver. 4.0

Figure 2: TraceIT Tissue Spacer Injection into Periduodenal Space using Endoscopic Ultrasound Guidance (Rao et al, used with permission)



The subject is to be positioned in the left-lateral position and an endoscopic ultrasound (EUS) will be used to identify the duodenum and HOP interface.

Under EUS guidance, the 19 or 22G fine needle aspiration (FNA) needle will be guided through the EUS scope and into the potential space between the duodenum and pancreas. The TraceIT Tissue Spacer will be prepared per the supplied IFU. Once the needle has been confirmed to be in

the proper position, the TraceIT hydrogel will be injected in 1mL increments. This process will then be repeated as the needle is repositioned around the target region, injecting TraceIT hydrogel at each location to a total volume of up to 20 mL hydrogel (40 mL of diluted TraceIT hydrogel in a 1:1 ratio).

- Note: If the needle is inserted through the duodenum, but the TraceIT Tissue Spacer is not injected, the subject will be followed for 30 days and included in the safety analysis. No further imaging is required for these "non-injection" subjects.

Following injection of the TraceIT hydrogel, the needle is to be removed, EUS images are to be acquired and measurements obtained as described above.

The lot number of the TraceIT Tissue Spacer device(s) used, the number and timing of applications is to be recorded on the TraceIT Tissue Spacer Injection CRF.

The subject should be assessed for adverse events during the follow-up period following the TraceIT Tissue Spacer injection.

6.4.5.2 Post-Injection CT Scan Acquisition

Following the TraceIT hydrogel injection, each subject is to undergo a repeat planning simulation scan to obtain a second RT radiation computer treatment plan with the TraceIT Tissue Spacer *in situ*.

The first and second RT treatment plans (pre- and post-TraceIT Tissue Spacer injection) will be compared to evaluate the displacing properties of the TraceIT Tissue Spacer.

6.4.6 RT Planning and Radiation Treatment

The technique for delivering the external beam treatment will be employed per institutional standard guidelines. Identical treatment planning studies will be performed both before (pre-TraceIT) and after (post-TraceIT) hydrogel injection in each subject. The technique and setup for these two simulation studies should be nearly identical particularly with respect to patient immobilization and respiratory motion management (i.e., active breath-hold method, forced shallow breathing with abdominal compression or real-time tracking and/or gating) and beam arrangement and angle. Planning set-up/parameters for the pre- and Post-injection RT planning will be documented within the CRF.

The initial **minimum target dose** will be 33 Gy in 5 fractions (6.6 Gy per fraction) or an equivalent biologically effective dose if >5 fractions is being delivered. The goal should be that at that the V33Gy for the PTV be at least 95%. CT simulation will be performed with immobilization when possible.

Normal tissue contours will be performed in accordance with the Upper Abdominal Normal Organ Contouring Guidelines recommended by the 2013 RTOG Consensus Panel.

Target dose constraints for OAR include:

Organs at Risk (OAR)	Dose Constraint*
Proximal duodenum, proximal stomach and small bowel	V15Gy<9cc, V20Gy<3 cc, and V35Gy<1cc A duodenal maximum dose of ≤32 Gy should initially be attempted
Stomach	V12Gy<50% and V35Gy<1cc
Liver	V12Gy<50%
Combined Kidneys	V12Gy<75%;
Spinal Cord	V8Gy<1 cc

*or biologically equivalent dose constraints for >5 fractions

Target coverage, doses to OAR, dose conformity, mean and maximum proximal duodenal dose and dose volume histograms will be documented pre- and post-TraceIT Injection.

6.4.7 Follow-up for Non-Injection Subjects (30 days +7 days or until resolution/stabilization of an adverse event if applicable)

A "Non-Injection" Subject is a subject who was intended to be treated with TraceIT, but in whom TraceIT was unable to be injected. No further image collection is required for these subjects.

- 30 Day Visit to include:
  - Physical assessment: including sitting blood pressure, pulse, temperature and Zubrod Performance Score
  - Assessment of Intestinal Adverse Events documented using CTCAE criteria
  - Other Adverse Events per NCI CTCAE
  - Changes in concomitant medications used to treat intestinal symptoms

6.4.8 Post-injection RT Planning *(less than 28 days following Index Procedure)*

The following assessments will be performed during the post-injection RT planning:

- Repeat CT Planning Imaging using the same number of beams and set-up as Pre-injection planning
- Dosimetric data to be collected include: V5 (volume (cc) of the duodenum receiving 5 Gy or more), V10, V15, V20, V25, V30, V35, V40, duodenal mean/maximum doses, GTV/PTV minimum/mean/maximum doses as well as GTV/PTV volume, and total duodenal volume.
- Theoretical dose escalation (maximum dose to GTV while maintaining duodenal dose constraints)
- TraceIT Hydrogel and Fiducial Visibility Scoring: Visibility of the TraceIT hydrogel and the fiducial markers will be scored as follows: 1 – not visualized; 2 – faint or trace visibility (shadow or haze); 3 – visibility but indistinct borders (definable entity, not just haze); 4 – partially distinct border, partial haze; and 5 – clearly visualized, unequivocal.

6.4.9 RT Initiation

RT must be initiated NLT 28 days following TraceIT administration. RT should be initiated NST 1 week from last chemotherapy dose. At the initiation of each fraction, the appearance of the TraceIT hydrogel with respect to presence and material distribution should be compared to RT planning CT.

6.4.10 Final RT Fraction

The following assessments are to be performed at the final RT fraction:

- Physical Assessment (including vital signs, weight and Zubrod performance score)
- EORTC-QLQ-C30 and QLQ-PAN26
- Assessment of duodenal focused Adverse Events documented using NCI CTCAE
- Other Adverse Events per NCI CTCAE
- Changes in concomitant medications used to treat intestinal symptoms

6.4.11 Week 2-6 Following Completion of RT (Restaging & Evaluation for Potential Resection)

The following assessments are to be performed at week 2-6 following completion of RT (Restaging and Evaluation for Potential Resection). These assessments can be performed at the time the subject returns for the restaging CT:

- Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score.
- CT for restaging (also will evaluate TraceIT Persistence)
- Assessment of duodenal focused Adverse Events documented using NCI CTCAE
- Other Adverse Events per NCI CTCAE
- Changes in concomitant medications used to treat intestinal symptoms
- CA-19-9 level
- Pancreaticoduodenectomy should be targeted to be performed within 8 weeks after the completion of RT if applicable.

Restaging and determination of resectability will be performed in accordance with the standard institutional practices.

CT's will be reviewed by a radiologist and any radiological findings suggestive of duodenal injury shall be documented and graded when possible. Duodenal perforation would be suspected if there is a retroperitoneal collection of extraluminal gas or a lack of continuity of the duodenal wall. Duodenal erosion/ulceration is suspected with edema or hematoma of the duodenal wall, intramural gas accumulations, and focal duodenal wall thickening (>4 mm) as findings of small bowel injury.

6.4.12 Resected Subjects (at time of resection)

The following assessments are to be performed at time of resection:

- Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score.
- Assessment of duodenal focused Adverse Events documented using NCI CTCAE if available
- Other Adverse Events per NCI CTCAE if available
- Changes in concomitant medications used to treat intestinal symptoms

6.4.13 Resected Subjects (Histopathology record)

The following assessments are to be performed at time of histopathology:

- Incidence of complete or partial response (Path PR and Path CR)
- Pathologic duodenal damage score rated by a local board-certified gastrointestinal surgical pathologist using the methods outlined by Verma et al.,[1] where:
    - 1=no/minimal signs of mucosal damage: villi remain long and slender, epithelial cells have abundant eosinophilic cytoplasm with few mitotic figures, and the lamina propria have normal amounts of inflammatory cells including few or no neutrophils.
    - 2=moderate damage where villi are blunted or absent, epithelial cells have reactive/reparative, changes with basophilic cytoplasm, increase mitotic figures, and/or small erosions or focal ulcerations; the lamina propria show increased inflammation including eosinophils and neutrophils.
    - 3=severe damage with diffuse epithelial damage absent with or without extensive ulcerations and residual surviving epithelium displaying marked reactive/reparative changes; lamina propria replaced with granulation tissue and/or overlying fibrinoid inflammatory exudates with numerous neutrophils or marked damage.

6.4.14 Additional Follow-up at Month 3 (± 14 days) and Month 6 (± 14 days) Post-Index Procedure

The following assessments will be performed at the 3 and 6 Month Post-Index Procedure visit:

- Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score.
- Unresected subjects only: MRI at Month 6 post-index procedure
- Assessment of duodenal focused Adverse Events documented using NCI CTCAE
- Other Adverse Events per NCI CTCAE
- EORTC-QLQ-C30 and QLQ-PAN26
- Changes in concomitant medications used to treat intestinal symptoms
- Post-surgical complications in resected subjects

6.4.15 Long Term Follow-Up (Month 12 ± 28 days and Month 18 ± 28 days)

The following assessments will be performed at the 12- and 18-Month Post-Index Procedure visit:

- Physical Examination: including sitting blood pressure, pulse, temperature, weight, anticoagulation status, Zubrod Performance Score.
- Assessment of duodenal focused Adverse Events documented using NCI CTCAE
- Other Adverse Events per NCI CTCAE
- EORTC-QLQ-C30 and QLQ-PAN26
- Changes in concomitant medications used to treat intestinal symptoms

6.5 Subject Withdrawal

For any subject who withdraws their consent following enrollment, the reason(s) for withdrawal will be documented on the appropriate CRF. In the event that a study subject does not finish their course of RT, the subject should be followed through 6 months from the date of the TraceIT hydrogel injection, whichever occurs sooner. For these subjects, participation will be concluded at that time and the subject will not participate in the longer-term toxicity assessment phase. Every attempt will be made to contact subjects who are non-compliant or lost to follow-up, and such attempts will be documented in the subject's study record.

Subjects may be replaced at the discretion of the Sponsor.

7 STATISTICAL ANALYSIS

7.1 Sample Size Determination

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.

7.2 General

The statistical analysis of the data obtained from this study will be performed using SAS® Version 9.3 or higher.

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. 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 assigned to the values. No adjustments to nominal p-values are planned since this is a hypothesis-generating study.

A detailed statistical analysis plan will be developed and finalized prior to database lock.

7.3 Analysis Populations

7.3.1 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).

7.3.2 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.

7.3.3 Per Protocol Population

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.

7.3.4 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).

7.3.5 Safety Population

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.

7.4 Subgroup Analyses

Data may be presented separately for localized (resectable, BRPC and LAPC) subjects as well as resected and unresected subjects. Details will be provided in the statistical analysis plan.

7.5 Subject Disposition

The number and percentage of enrolled (ITT Population), MITT, PP and Safety Populations will be summarized. The number of subjects signing the informed consent and the number of primary screening failures (consented but not treated subjects) and the number of secondary screening failures (Duodenal invasion seen at time of index procedure) 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.

7.6 Planned Analyses

7.6.1 Baseline Characteristics

Subjects will be summarized with respect to baseline demographics and clinical characteristics (e.g., age, sex, tumor grade, etc.). These will be summarized by descriptive statistics including means, medians, standard deviations and ranges (for quantitative variables) and percentages (for categorical variables).

7.6.2 Technical Success, TraceIT Injection and Device Use

Summary statistics will be presented for characteristics of TraceIT injection using descriptive statistics or counts and percentages, as appropriate. In addition, the proportion of TraceIT treated subjects in whom Technical Success has been achieved will be reported, together with an exact (Clopper-Pearson) 95% confidence interval for the true proportion. Technical Success is defined as the administration and visualization (on post-injection CT) of the TraceIT hydrogel between the head of pancreas and the duodenum.

Ease of device use and preparation, and whether any device malfunctions occurred will be summarized by counts and percentages. Details of device malfunctions will be presented in a listing.

7.6.3 Radiotherapy Benefits

Treatment planning will be performed as a component of the Baseline Assessment and repeated following TraceIT administration. 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. 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 variables, the paired sample t-test will be used to test for a difference in means between treatment plans.

7.6.4 Change in Baseline in Quality of Life Measures

Changes in Quality of Life Measures as assessed overall and subdomains of the EORTC-QLQ-C30 and QLQ-PAN26 will be evaluated. Raw scores and change from baseline scores will be calculated for all domains. Scores will be compared to baseline using either a paired t-test or Wilcoxon Signed-Rank test.

7.6.5 Other Outcome Measures

All other measures as identified in Section 6.1.3 not described above will be evaluated in accordance with the general statistical methods previously identified. The following definitions will be used for PFS and OS:

- Progression-Free Survival (PFS): defined as the interval between the start of induction chemotherapy (prior to RT) to treatment failure (local, regional or distant progression) or death (in months).
- Overall Survival (OS): defined as the interval between the start of induction chemotherapy (prior to RT) to death (in months).

7.7 Safety Analysis

Incidence of adverse events will be summarized 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 incidence of adverse events will be summarized by term, by term and procedure/device relationship, and by term and severity. All adverse events occurring at the time of initiation of fiducial marker placement or attempted injection and up through and including the 18 month visit will be recorded and listed. In addition to the general presentation of safety events, the following will be calculated and reported:

- The number and percentage of subjects who experience 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 (>3months). A similar presentation will be provided for non-resected subjects only.

7.8 Incomplete/Missing data

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 data.

8 RISK/BENEFIT ANALYSIS

8.1 Risk/ Benefit Analysis

Radiation therapy is a common component of treatment for pancreatic cancer. However, due to the pancreas' anatomic proximity to the duodenum, duodenal radiation injury is a risk of radiotherapy. 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[17]. Since the risk of developing duodenal complications increases exponentially as greater volumes are irradiated, it is understandable that clinicians are seeking technologies that can reduce duodenal radiation dose to minimize the risk of duodenal injury associated with radiation therapy and maximize the tumor coverage.

Based upon the results of the preclinical investigations and validated through clinical use, PEG-based hydrogels have been shown to be safe in multiple tissue types including sensitive neurological and intra-abdominal tissues. The transduodenal injection procedure used for administration of the TraceIT hydrogel is commonly performed by endoscopists for the performance of pancreatic biopsies and the delivery of fiducial markers. Moreover, Augmenix in conjunction with researchers at John Hopkins Medical Center has performed a cadaver study demonstrating that creation of space between the duodenum and pancreas can substantially reduce the level of duodenal radiation exposure while maintaining or in some cases even improving PTV coverage, having a positive impact for both the reduction in duodenal toxicity and maximizing effects of RT on the tumor. Conversely, there is no information in the preclinical data to suggest that the hydrogel material or the methods used for administration present the potential for significant harm when used as intended.

Therefore, TraceIT hydrogel when used to displace the duodenum from the pancreas may provide a substantial clinical benefit as a duodenal-sparing technology that allows for a reduction in duodenal radiation dose and improvement in PTV coverage in patients undergoing radiotherapy for pancreatic cancer. It is acknowledged, however, that as with any medical procedure and implanted material there are risks associated with the use and administration of the TraceIT hydrogel. Based on the clinical knowledge for the device's application and preclinical study outcomes, potential risks associated with the hydrogel have been identified (outlined below). Risks have been mitigated to the extent possible, providing a favorable risk/benefit profile for the TraceIT Tissue Spacer.

8.2 Risks of Study Procedures and Investigational Material

The associated risks and potential benefits of the procedure and the device are provided below.

Risks associated with radiation therapy of the pancreas

The following risks are associated with radiation therapy of the pancreas:

- Pancreatitis
- Duodenal hemorrhage
- Duodenal stricture
- Duodenitis
- Bleeding
- Obstructive jaundice
- Diarrhea
- Nausea/vomiting
- Epigastric/abdominal pain
- Mucositis

Risks associated with transduodenal placement of fiducial markers:

- Bleeding
- Pain
- Pancreatitis
- Infection
- Nerve damage
- Anesthetic related complications
- Fiducial implant misplacement or migration
- Foreign body reaction
- Tumor seeding

Specific Potential Risks associated with the study treatments

Potential complications that may be associated with the use of TraceIT Tissue Spacer include, but are not limited to:

- Pain associated with TraceIT Tissue Spacer injection
- Pain or discomfort associated with TraceIT hydrogel
- Needle penetration of pancreas during injection
- Injection of TraceIT Tissue Spacer into pancreas, duodenal wall or other organs
- Local inflammatory reactions
- Infection
- IV injection of air/material
- Duodenal stricture
- Duodenal mucosal damage, ulcers or necrosis
- Bleeding
- Delay in initiation of RT or surgery

- Potential to exacerbate local progression due to protection of undiagnosed/microscopic duodenal invasion
- Potential for hydrogel migration

The TraceIT Tissue Spacer is completely synthetic and therefore allergic reactions are not anticipated.

8.3 Potential Benefits to the Subject

Potential benefits associated with the use of the TraceIT Tissue Spacer include reduced radiation exposure to the duodenum during the radiotherapy procedure. This has the potential to reduce both acute and chronic complications associated with radiation exposure to the duodenum as stated above as well as an improvement to the PTV coverage.

8.4 Minimization of Risks

The risks associated with the TraceIT Tissue Spacer have been minimized by formulating the hydrogel with constituents that have a long history of safe use in implantable medical devices. The study sponsor conducted Biocompatibility testing per GLP regulation and in accordance with ISO 10993 – Biological Evaluation of Medical Devices. Tests were selected and performed according to the type of device, intended use, and degree and duration of tissue contact. The response to TraceIT Tissue Spacer Implants was evaluated in healthy tissues including subcutaneous and intramuscular implant locations. All biocompatibility testing results are consistent with a biocompatible material.

Preclinical studies were also done to evaluate the response to TraceIT Tissue Spacer adjacent to the duodenum and pancreas—the intended human implant site. No adverse histologic change or safety concerns were noted.

Based upon the results of the preclinical investigations and validated through clinical use, PEG-based hydrogels have been shown to be safe in multiple tissue types including sensitive neurological and intra-abdominal tissues. The transduodenal injection procedure used for administration of the TraceIT hydrogel is commonly performed by endoscopists for the performance of pancreatic biopsies and the delivery of fiducial markers. TraceIT hydrogel is FDA cleared and has been used commercially for marking purposes in multiple organs including the esophagus[20], bladder[21] and cervix[22]. Studies evaluating application of TraceIT in these organs reported that the hydrogel remained dimensionally stable throughout the RT course, without migrating through the tissue. These organs, admittedly, have many different properties than the interface between the pancreas and duodenum, but TraceIT hydrogel has so far been stable, even in highly mobile organs such as the bladder and esophagus.

Appropriate therapeutic intervention following standard medical practices will be used in the event of medical complications. This study will be monitored to ensure the identification, documentation and analysis of all adverse events, compliance with the protocol, the terms of the participating IRB to protect the safety and rights of all subjects, and applicable local regulations. In addition, risks will be minimized through selection of investigators who are Endoscopists and Radiation Oncologists skilled

in the performance of periduodenal injections and/or radiation therapy and via ongoing review of both safety and performance data by a Clinical Events Committee.

9 ADVERSE EVENTS

9.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a subject that is of new onset or has become worse including consequences of medical therapy resulting from a potential study-related delay in radiation treatment

Adverse events are to be recorded from initiation of fiducial marker placement through the 18 month visit.

Adverse Device Effect (ADE): An adverse event that is believed to have been caused by or is associated with the device.

Serious Adverse Event (SAE): An adverse event that:

a. Led to death
b. Resulted in a life-threatening illness or injury
c. Resulted in a permanent impairment of a body structure or a body function
d. Resulted in in-patient hospitalization or prolongation of existing hospitalization
e. Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

The investigator will report serious events to the Sponsor and to his/her IRB per the institution's requirements and as specified in section 8.1.1.

Serious Adverse Device Effect (SADE): A serious adverse event that is believed to have been caused by or is associated with the device.

Unanticipated Adverse Device Effect (UADE): 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.

Event Severity: Event severity will be graded in accordance with the guidelines provided in the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 (NCI, Oct. 2009). For those events that do not have a term identified in the CTCAE, events should be identified using the following criteria:

> **Mild:** Event causes a low level of inconvenience or discomfort, does not interfere with subject's usual activities, and is usually transient; treatment not ordinarily needed for relief of symptoms.

Moderate: Event causes moderate level of inconvenience or discomfort, may interfere with subject's usual activities; new treatment or change in treatment for symptoms may be needed.

Severe/Serious: Event causes severe discomfort and considerable interference with subject's usual activity and requires treatment and/or hospitalization.

9.1.1 Recording and Reporting of Adverse Events

All study staff are responsible for ensuring that complete safety information has been recorded on the CRF and in source documents. All Adverse Events (AE) must be documented throughout the study. Medical assessments must be performed during each scheduled study visit and serve as the primary basis for identifying AEs. Although spontaneous or elicited medical complaints will likely constitute the majority of AEs, any non-scheduled visit to a healthcare provider or the initiation of a new medication should trigger additional questioning as to the occurrence of an AE.

All adverse events, regardless of severity or relationship to investigational device, will be collected from the time of initiation of fiducial marker placement and through the 18-month visit. Subjects who experience an adverse event related to TraceIT hydrogel will be followed until the adverse event has resolved or until the subject has stabilized and follow-up care has been transferred to the subject's primary care physician.

Any changes in a subject's condition noted prior to the procedure should be adequately assessed and included in the medical history for the subject.

Any event precipitating an intestinal acute CTCAE score of grade 2 or more must be documented as an adverse event.

To the extent possible, the event to be recorded and reported is the event **diagnosis** as opposed to event **symptoms**. Please refer to the following examples:

- Fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as an infection only.
- Pain on urination in the presence of a clinically diagnosed urinary tract infection is to be reported as a urinary tract infection only.

Reporting Serious Adverse Events

All serious adverse events and serious adverse device effects shall be reported to the Sponsor or their representative (by fax or by phone) within 24 hours of the time the investigator learns of the event. A written report detailing the event and signed by the investigator shall be submitted to the Sponsor within 5 working days. The investigator shall notify the reviewing IRB of all serious adverse events occurring in the study according to the IRB's requirements.

Device failures or problems not associated with adverse events will be documented separately on the appropriate case report form. The product should be retained for evaluation.

Investigator reporting responsibilities are summarized in **Table 4**.

Table 4. Investigator Reporting

Report	Submit To:	Description/Time Constraints	Regulatory Reference
Device Malfunction	Augmenix, Inc.	Notify within 24 hours (or next business day)	N/A
Serious Adverse Event	Augmenix, Inc.	Notify within 24 hours (or next business day) Written report within 5 working days	N/A
	IRB	Per IRB requirements	N/A
Unanticipated Adverse Device Effect	Augmenix, Inc.	Notify within 24 hours (or next business day) Written report within 5 working days	21 CFR 812.150(a)(1)
	IRB	Within 10 working days	21 CFR 812.150(a)(1)
Subject Death During Investigation	Augmenix, Inc.	Notify within 24 hours (or next business day) Written report within 5 working days	N/A
	IRB	Per IRB requirements	N/A
Subject Withdrawal	Augmenix, Inc.	Within 5 working days	N/A
	IRB	Per IRB requirements	N/A
Withdrawal of IRB Approval	Augmenix, Inc.	Within 5 working days	21 CFR 812.150(a)(2)
Annual Progress Report*	Augmenix, Inc.	Submitted annually	21 CFR 812.150(a)(3)
	IRB		
Deviations from Investigational Plan**	Augmenix, Inc.	Within 5 working days	21 CFR 812.150(a)(4)
	IRB		
Informed Consent Not Obtained	Augmenix, Inc.	Within 5 working days	21 CFR 812.150(a)(5)
	IRB	Per IRB Requirements	
Final Study Report	Augmenix, Inc.	Within 3 months after completion or termination of the study.	21 CFR 812.150(a)(6)
	IRB		

*Note: Continuance review provided to the IRB will fulfill the requirements for an annual report to the Sponsor

**Please refer to 21 CFR 812.150(a)(4) for the conditions under which this notification applies.

9.1.2 Clinical Events Committee

The Sponsor will utilize a Clinical Events Committee (CEC) to provide ongoing review and adjudication of adverse events and review of emerging device performance data. Members of the CEC will include physicians with a specialty in treating subjects with pancreatic cancer including a radiation oncologist and a gastroenterologist. The CEC will be charged with the following responsibilities:

- 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, procedure, radiotherapy or other.
- Provide 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.

The Sponsor will meet with the CEC on a regular and ongoing basis. All serious and/or unanticipated adverse effects will be reviewed with the CEC within 48 hours of Sponsor receiving such notification.

9.2 Device Malfunctions

All device malfunctions of TraceIT Tissue Spacer will be documented on the appropriate CRF. The investigational device will be retained and the malfunction reported to Augmenix within 24 hours. Augmenix will advise whether the investigational device(s) should be returned to the Sponsor for analysis according to the instructions provided in the study materials. The incidence of device malfunctions will be included in the final analysis.

10 GENERAL INFORMATION

10.1 Termination of Study

Augmenix, Inc., reserves the right to discontinue the study at any stage, with suitable written notice to the Investigators and regulatory authorities as appropriate. Similarly, Investigators may withdraw from the study subject to providing written notification to Augmenix, Inc., within 30 days of their intent to withdraw. However, Augmenix, Inc., and Investigators will be bound by their obligation to complete the follow-up of subjects already enrolled into the trial. The subjects must be followed according to the clinical protocol and information obtained during subject follow-up shall be reported to Augmenix, Inc., on follow-up CRFs.

Any serious and/or unexpected adverse device effects will be investigated immediately and if the Sponsor determines that unreasonable risk to subjects is possible, the study will be terminated, and all regulating authorities and participating Investigators will be notified.

10.2 Monitoring Procedures

The Investigator and the investigating center will permit authorized clinical research personnel, auditors and clinical monitors from Augmenix, Inc. and/or designee(s) employed by Augmenix, Inc., the IRB and regulatory agencies to review subject medical records, source documents, completed CRFs, IRB decisions, and Investigator and clinical site records at regular intervals throughout the study. Subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. In instances where data protection regulations and/or hospital policies prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor.

The monitor (or designate) will conduct pre-investigational and interim visits to all investigative sites and will ensure that the study protocol is thoroughly understood by all Investigators and appropriate supporting staff. If the monitor discovers that an Investigator is not complying with the signed Investigator Agreement, the investigational plan, applicable GCP requirements, or any conditions of approval imposed by the reviewing IRB or regulatory authorities, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, device shipments to the Investigator may be discontinued and the

Investigator's participation in the investigation terminated. The monitor (or designate) shall also require such an Investigator to return to Sponsor any unused devices.

10.3 Modifications to the Protocol

If any significant changes to the protocol are made during the course of the study, the Sponsor will do so in the form of a protocol amendment which must be approved by the FDA and the IRB prior to implementation of the changes by the Investigator. A significant change is one that affects the safety of the subjects, the scope of the investigation, or the scientific quality of the study. Changes to the protocol that do not affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study will also be made by the Sponsor in the form of a protocol amendment. Implementation of these changes cannot be made until the amendment is reviewed and approved by the IRB.

10.4 Protocol Violations / Deviations

The Investigator will not deviate from the protocol. In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate. However, all such procedures must have written documentation and be promptly reported to the Sponsor and IRB (as appropriate).

10.5 Financial Disclosure

In accordance with 21 CFR Part 54 and 21 CFR Part 812.110(d), before the start of the study, the Investigator will disclose to the Sponsor any proprietary or financial interests he/she might hold in the investigational product or the Sponsor companies as outlined in the financial disclosure form provided by the Sponsor. The Investigator must update this information in case of significant changes during the study or within 1 year of its completion.

Similar information will be provided by each co-investigator to whom the Investigator delegates significant study related responsibilities.

10.6 Record Retention

The Investigator will maintain the records of the investigation including all correspondence, the study protocol with any/all amendments, all correspondence with and approval from the IRB, the budget agreement, the Investigator agreement, investigational device accountability records, individual subject records, and signed informed consent forms in the Investigator Binder. These Documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements.

The files may be discarded only upon notification from Augmenix, Inc. To avoid error, the Investigator should contact Augmenix, Inc. before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, in accordance

with the Investigator Agreement, Augmenix, Inc. should be contacted if the site's Investigator plans to leave the Investigational Site so that appropriate arrangements can be made to replace him/her.

11 REFERENCES

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12 APPENDICES

12.1 APPENDIX A – AJCC PANCREAS CANCER STAGING AND ZUBROD PERFORMANCE SCORE SCALE

AJCC PANCREAS CANCER STAGING*

Primary Tumor (T)

Tx primary tumor cannot be assessed

T0 no evidence of primary tumor

Tis carcinoma in situ1**

T1 tumor limited to the pancreas, 2cm or less in greatest dimension

T2 tumor limited to the pancreas, more than 2cm in greatest dimension

T3 tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

T4 tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

NX regional lymph nodes cannot be assessed

N0 no regional lymph node metastasis

N1 regional lymph node metastasis

Distant Metastasis (M)

M0 no distant metastasis

M1 distant metastasis

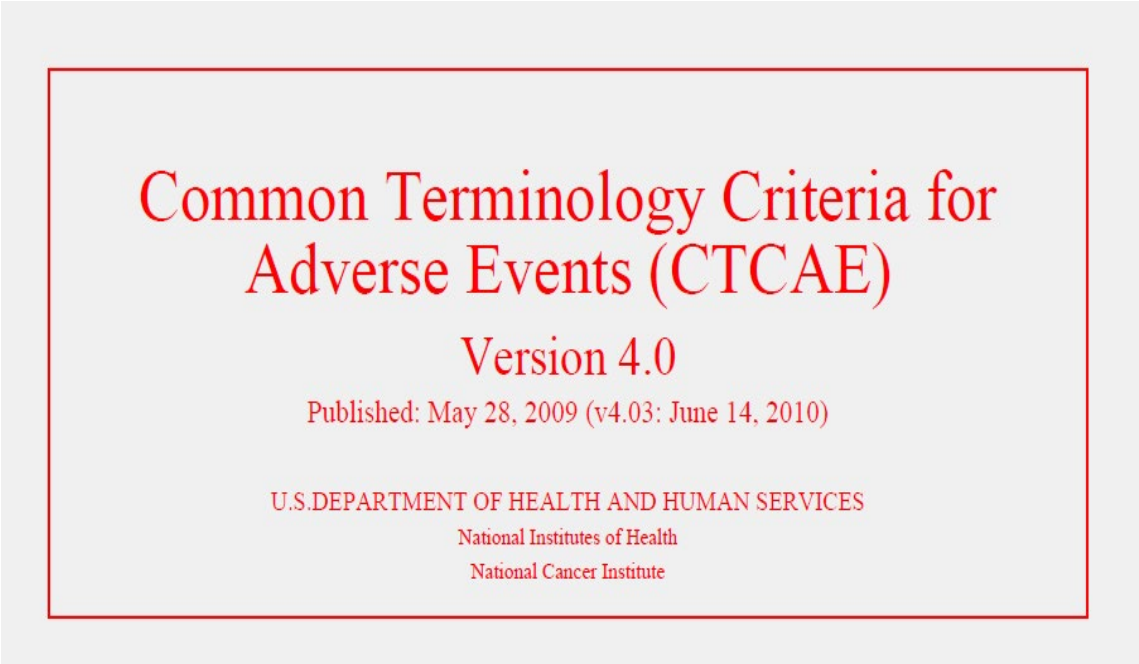
Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Notes
*Endocrine AND exocrine tumors are now staged by a single pancreatic staging system
**Also includes the “PanInIII” Classification

ZUBROD PERFORMANCE SCORE

Score	Criteria
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX B – COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)



APPENDIX C. SAMPLE INFORMED CONSENT FORM

NOTE: This is a SAMPLE consent form provided at study start. Subsequent updates may be made to the study template.

AN AGREEMENT TO BE IN A RESEARCH STUDY

INFORMED CONSENT DOCUMENT

This consent form may contain words that you do not understand. Ask the study doctor or study staff to explain any words that you do not clearly understand.

Sponsor: Augmenix, Inc.
City, State and Country: Bedford, MA, USA

Protocol Number and Title: AGX-17-001-US

Study Doctor: <<Investigator>>

Address of Study Site(s): <<Study_Site>>
<<Address>>
<<City_State_Zip>>

Telephone number: <<XXX-XXX-XXXX>>

Introduction

You are being asked to be part of a medical research study. Before you decide to join, you should read this document. This is called an informed consent document; it explains what will happen during the study. Please ask as many questions as needed so that you can decide whether you want to be in the study.

You have the right to know what will happen during this study, as well as the possible side effects and benefits of this study. This document has important information to help you decide if you want to be a part of this study. Signing the last page of this document will mean that you agree to participate.

During the study, you will be told of any important new findings about the study device. You can use this information to decide about continuing in the study.

Summary

To summarize, consent is being sought for your participation in an early feasibility study. An early feasibility study is a research study of an innovative use of a medical device in a small number of patients to gain initial insights to the basic safety and device functionality. Participation in an early feasibility study means that you will be one of the first patients to receive treatment with the TraceIT Tissue Spacer, the device being evaluated in this research.

Specifically, the purpose of this research is to evaluate the feasibility and safety of an experimental device called the TraceIT Tissue Spacer. The TraceIT Tissue Spacer is an absorbable implant that will be injected between a portion of your small intestine (called the duodenum) and your pancreas to create space between the two organs. The expected duration of this study is 22 months beginning with screening and continuing until the last follow up visit. The procedures to be performed are traditional fiducial marker placement and the experimental TraceIT injection. Radiation therapy will take place with follow up visits at a few different time points. The reasonably foreseeable risks or discomforts include risks associated with radiation therapy of the pancreas, the transduodenal placement of fiducial markers and the TraceIT material, and the risks associated with the experimental TraceIT device. There may be unforeseeable risks associated with participation in an early feasibility study due to limitations in available data and experience with the device. Possible benefits are that this research may help to improve radiation coverage of pancreatic tumors. Appropriate courses of treatment may include standard radiation therapy without any type of spacer device. Further discussion on each of these discussion points can be found in the appropriate sections of the informed consent document.

Purpose of the study

It has been explained to you that you have pancreatic cancer and you have chosen to undergo Radiation Therapy (RT) with fiducial markers, a common therapy used to treat people with pancreatic cancer. Radiation therapy targets high-energy rays or particles in order to kill the cancer cells. RT is a type of radiation therapy where an x-ray of your pancreas is taken in the treatment room just before radiation. The fiducial markers, tiny gold seeds placed within the pancreas, show up on this x-ray and will help your doctor see your pancreas before delivering radiation. This is important because your pancreas can move every day. This x-ray will be used to more accurately target the cancer at each treatment.

Before your first RT treatment, a radiation oncologist will create a treatment plan that will focus the radiation on your pancreas and minimize the amount of radiation that will hit healthy organs in the area around the pancreas. You will receive radiation therapy as per the institutional standard that will explained to you by your doctor. During this time, organs that are close to the pancreas, such as the duodenum, will be exposed to some radiation. Radiation exposure to the duodenum can cause symptoms such as duodenal bleeding, duodenal stricture, duodenitis, bleeding, obstructive jaundice, and diarrhea. One possible way to reduce the amount of radiation to the duodenum is to place a “spacer” between the pancreas and the duodenum. Placement of the spacer may reduce duodenal problems by moving the duodenum away from the radiation target site (the pancreas) during your radiation treatment.

The purpose of this research is to evaluate the feasibility and safety of an experimental device called the TraceIT Tissue Spacer. The TraceIT Tissue Spacer was developed to provide a space between the pancreas and the duodenum during radiation therapy. The TraceIT Tissue Spacer is a soft, gel-like material that is made mostly of water. The gel also contains iodine so your doctor can see it on an x-ray. The gel is injected into the space between the pancreas and duodenum using an endoscopic needle. The gel will be naturally absorbed by the body in approximately 7 months. This study will evaluate whether the space created by the TraceIT Tissue Spacer can help improve the treatment of your pancreatic tumor. The material that the TraceIT Tissue Spacer gel is made from has been used in other medical implants such as a spacer between the prostate and rectum for radiation therapy.

What will happen during the study

If you choose to participate in this study, the Study Doctor will gather information about you to decide if you meet the requirements of the study. This is called "screening."

Screening does not guarantee entry into the study. Entry into the study will depend upon the results of your tests, study guidelines, and the opinion of the Study Doctor. Even if you pass the screening tests, there is a chance that you will not be invited to participate. There may be other reasons why you cannot participate in the study. The Study Doctor and/or the study staff will discuss this with you.

During the screening process for this study you will:

- Provide a complete medical/surgical history
- Undergo a physical exam and have your blood pressure, pulse, and temperature taken
- Be asked if you are taking any medications to thin your blood
- Be asked about your gastrointestinal symptoms
- Have about 1-2 tablespoons of blood collected for laboratory testing
- Have a sample of urine collected for analysis
- Have a radiation treatment planning session. Prior to this planning session you will undergo a CT scan. This scan takes about one hour
- Complete the EORTC-QLQ-C30 and QLQ-PAN26 quality of life questionnaires. These questionnaires ask you to record your opinion about how you are feeling

It is very important that you provide a complete and honest medical history. Giving false, incomplete, or misleading information about your medical history could have serious health consequences.

Procedure

Prior to this procedure, your doctor will give you medicine to put you to sleep. Your doctor will discuss this medication plan with you. A sponsor representative or designee may attend your procedure.

Screening for this study will be performed approximately 45 days prior to the injection of TraceIT. During the screening visit your medical and prior surgical history will be obtained, a physical exam will be performed and you will be asked about your disease symptoms. Approximately 1 tablespoon of blood will be collected for laboratory testing.

A control radiation treatment planning session will be done before the TraceIT injection. The planning session involves a CT scan that may take about one hour.

Experimental TraceIT Tissue Spacer Injection Procedure

The spacer will be injected between the pancreas and the duodenum using a transduodenal approach. Under endoscopic ultrasound guidance (EUS), a 19 or 22G fine needle will be guided through the EUS scope into the potential space between the duodenum and the pancreas. Once the needle has been confirmed to be in the proper position and fiducial markers have been placed,

the TraceIT hydrogel will be injected. Following the injection, the needle will be removed, EUS images will be acquired and measurements will be obtained.

As part of your standard radiation treatment, a second treatment planning session will be done less than 28 days after the TraceIT has been injected. This planning session will be used to get images of your pancreas and duodenum to help plan the radiation fields and to measure the distance between the pancreas and duodenum. The planning session involves a CT and will take about one hour.

If the TraceIT Tissue Spacer cannot be injected, a second planning simulation scan will not be done. You will be asked to return for a follow-up clinic visit approximately 30 days after the procedure. A physical assessment will be performed to measure your blood pressure and temperature and a Study Doctor will ask you about how you feel.

Once the TraceIT Tissue Spacer is placed, it cannot be removed but it will be resorbed in approximately 7 months.

RT Therapy

Within 4 weeks of the procedure, your planned radiation therapy will start. You will receive radiation treatment for about 2 – 6 weeks. During this period, you will receive radiation treatments based on a schedule given to you by your doctor. While you are receiving radiation treatment, your doctor may ask you questions about how you are feeling and any duodenal symptoms you may be having.

You should know that the radiation treatment course you receive in this study is not experimental as it would be the same even if you were not participating in this study.

Study Visits After RT Therapy

After completion of radiation therapy, you will be asked to return for five follow-up visits. The timing of these visits is 2-6 weeks following your radiation therapy, then 3, 6, 12, and 18 months from the date of your initial procedure.

Consistent with standard medical practice, at the 2-6 week follow-up visit a physical assessment will be performed to measure your blood pressure, pulse and temperature. You will be asked about how you are feeling and any duodenal symptoms you may be having. You will be asked if you are taking any medications to treat pain or duodenal symptoms. In addition, you will have a CT scan so you can be evaluated for the potential to undergo a surgical procedure called the "Whipple" procedure, a common procedure used to remove tumors in the pancreas. In a standard Whipple procedure, the surgeon removes the head of the pancreas, the gallbladder and part of the duodenum. If you are eligible for this surgery, the study doctor will provide you with more information concerning the procedure.

At each follow-up visit a physical assessment will be performed to measure your blood pressure, pulse, and temperature. You will be asked about how you are feeling and any duodenal symptoms you may be having. You will be asked if you are taking any medications to treat pain or duodenal symptoms. You will also be asked if you are taking any medications to thin your blood. The

EORTC-QLQ-C30 and QLQ-PAN26 questionnaires will be given to you to complete. At the 6 month visit you will have an MRI.

Length of the study and number of volunteers expected to participate

About 6 people will be in this study at up to 4 clinics in the United States. All 6 people will be treated with the TraceIT gel. You will be in this study approximately 1 year and 10 months beginning with your screening and continuing until your last study visit. There is a possibility that you may be asked to return for additional follow up.

Side effects and other risks

One of the reasons for this study is to learn more about the possible side effects of TraceIT Tissue Spacer. It is important you keep the study staff informed about any possible side effects you may be experiencing.

The following risks are associated with radiation therapy of the pancreas:

- Pancreatitis (inflammation of the pancreas)
- Duodenal bleeding
- Duodenal stricture (narrowing of the duodenum)
- Duodenitis (inflammation of the duodenum)
- Bleeding
- Obstructive jaundice (blockage of bile to the intestines)
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Mucositis (inflammation of the lining of the digestive tract)

The following risks are associated with transduodenal placement of fiducial markers:

- Bleeding
- Pain
- Pancreatitis
- Infection
- Nerve damage
- Anesthetic related complications
- Fiducial implant misplacement or migration
- Foreign body reaction
- Tumor seeding; e.g., tumor cells are transferred to other tissues near the fiducial marker insertion site.

If you are treated with the TraceIT gel these are your additional risks, however, since this study represents the first use of the TraceIT gel in patients for tissue spacing there is no information to fully predict the frequency or severity of these risks:

- Pain associated with TraceIT Tissue Spacer injection

- Pain or discomfort associated with TraceIT hydrogel
- Needle penetration of pancreas during injection
- Injection of TraceIT Tissue Spacer into pancreas, duodenal wall or other organs
- Local inflammatory reactions
- Infection
- IV injection of air/material
- Duodenal stricture
- Damage to the tissues of the duodenum including ulcers or necrosis (tissue death)
- Bleeding
- Delay in initiation of RT or surgery
- Potential to protect undiagnosed/microscopic duodenal cancer cells from radiation

The TraceIT Tissue Spacer is completely synthetic and therefore allergic reactions are not anticipated.

Although the above risks are possible, the TraceIT gel has been tested in studies in animals and was determined to be safe.

Risks of Radiation Exposure:

Participation in this research study may involve exposure to radiation from the additional research CT scan performed for the purposes of the study. The amount of radiation exposure that you will receive from the extra CT scan is about 1 rem (a unit of radiation exposure) to your abdomen, with minimum exposure of other areas of your body. This amount of radiation is approximately one thousand times less than the amount of radiation you will be receiving as part of your cancer therapy. Therefore, the risk associated with the additional amount of radiation exposure that you will receive from taking part in this study is felt to be very low.

Unforeseeable risks

The administration of the study device may involve risks to you that are presently unforeseen and unknown. Rare or unknown side effects could possibly occur, some of which could be life-threatening.

Minimizing Risk

During your participation in this study you will be closely monitored for any potential complications so that your study doctor can provide treatment as soon as possible. If for some reason the TraceIT gel cannot be successfully placed between the duodenum and pancreas this will not affect your ability to undergo radiation therapy.

The risks to an embryo, fetus and breastfeeding baby are not known at this time.

Possible benefits of the study

Taking part in this study may or may not provide any help to you since the actual benefits of the TraceIT Tissue Spacer are not known. A possible benefit of the TraceIT Tissue Spacer is that it may help to improve the radiation coverage of your tumor. Future patients with pancreatic cancer may also benefit from the information obtained during this study.

Compensation

There will be no additional cost to you because you are participating in the study. Tests that are not part of your standard medical care, but are required as part of your participation in this study (for example, the extra MRI and CT scan), will be paid for by the study sponsor.

Alternatives to participating

There are other treatments available if you decide not to be in the study. Treatments may include standard external beam radiation therapy (EBRT) therapy without any type of spacer device. The Study Doctor can discuss these options and decide what treatment is best for you.

Confidentiality

If you participate in this study, the Sponsor and their delegates will look at and copy your study medical records. In addition, study medical records will be given to the Sponsor, the Institutional Review Board (IRB), the U.S. Food and Drug Administration, and other regulatory agencies. If study results are published, your name will not be used. Any information regarding your participation in this study that identifies you by name will not be released to any other party without your written consent. It is likely that the results of this study will be published in one or more medical journals or presented at medical meetings. Any such publication will not identify you by name.

Photo/Video Release

You give the Sponsor the right to use, copy, and give out the video or pictures from the video taken of your ultrasound. We will make every effort to hide your identity.

Your pictures/videos will only be used for training, advertising or in scientific conferences, journals or magazines. Your pictures/videos may also be edited or used as part of a larger presentation, along with other pictures or videotapes. The Sponsor may give other people or companies permission to use your pictures/videos.

In case of an injury related to this research study

Treatment will be offered if you have an injury or problem as a result of being in this study. If you have any problems directly from the use of the TraceIT Tissue Spacer, Augmenix, Inc. will pay for the reasonable costs of medical treatment that are not covered by your health insurance or other provider. No other forms of payments are available.

If you have any payment or medical questions or if you think you have had a study related injury, you may contact Doctor _____ at _____.

Legal Rights

You do not lose any legal rights by signing this consent document. The above statement, "In Case of an Injury Related to This Research Study," does not stop you from getting legal help in case of negligence.

Whom to contact

You may contact the Study Doctor at _____:

- for answers to questions about this research study
- to report a research related injury or
- for information about study procedures

If you are unsuccessful in your attempt to contact the Study Doctor or study staff, please contact the local IRB at _____. Please do so directly and immediately by calling _____.

You may contact _____ if you would like to speak with someone unrelated to the research and/or have "questions, concerns, or complaints" regarding the research study.

The IRB has approved this study and this consent document. An IRB is a group of scientific and non-scientific people who review and approve or reject research. This group is also required by regulatory authorities to do periodic review of ongoing research studies. Questions about your rights as a participant may be addressed to:

[Hospital contact and phone number]

Leaving the study

Your decision to be in this study is up to you. You have the right to leave this study at any time. If you do not want to be in the study, there will be no penalty to you, and you won't lose any benefits that you are entitled to.

However, if you wish to leave this study, please call the Study Doctor or study staff right away at the telephone number listed on page one of this informed consent document to schedule study exit procedures.

Your part in this study may be stopped at any time without you being asked. The following people can stop your participation:

- the Study Doctor
- the IRB
- The United States Food and Drug Administration (FDA)
- the Sponsor

If you do not follow the study procedures, you may be taken out of the study.

Authorization to use and disclose health information (HIPAA)

Your personal health information is protected by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). During your participation in this research study, the Study Doctor and study staff will collect and create personal health information about you and record it on forms. This section provides information about how these medical records and health information will be used and disclosed in this clinical research study. If you volunteer to take part in this research study, you have the right to know that others may know your identity. Study information may identify you in the following ways:

- Name
- Other details about you

This study includes a number of businesses and government agencies. They may use your health information and share it with others. We want you to know who may use this information and how they may use it.

We also want to tell you about your rights before you agree to take part in the study.

Who may use and give out information about you?

The Study Doctor and study staff will have information about your health that tells your identity. They may give this information to others during and after the study.

Who may see this information?

The study sponsor also may see your health information and know your identity. "Sponsor" includes any people or companies working for or with the sponsor or owned by the sponsor. They all have the right to see information about you during the study.

The following people, agencies, or businesses may get information that identifies who you are:
- The Sponsor and its representatives
- Doctors and healthcare professionals taking part in this study
- U.S. Food and Drug Administration (FDA)
- U.S. Department of Health and Human Services (DHHS)
- Government agencies in other countries
- Government agencies that must receive reports about certain diseases
- The Institutional Review Board (IRB)

What information may be used and shared?

If you decide to be in this study, medical information that identifies you and relates to your information will be created. This may include the following types of medical information:

- Information obtained from the procedures used to find out whether you are eligible to take part in this study. This may include information that you may release to us, including information about your health history.
- All information about you which is collected or created during the study for research purposes. It also includes your personal health information that is related to this study and that is maintained in your medical records at this institution and at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, how you respond to study activities or procedures, laboratory and other test results, medical images, and information from study visits, phone calls, questionnaires, and physical examinations.

Why will this information be used and/or shared?

Information about you and your health, that might identify you, may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition,

people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. The information may also be used to meet the reporting requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by the Institutional Review Board.

What if you decide not to give permission to use and give out your health information?

By signing this informed consent document, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in the research study.

May you review or copy the information obtained from you or created about you?

You have the right to review and copy your health information. However, if you decide to be in this study and sign the consent document, you will not be allowed to look at or copy your information until after the research is completed.

May you withdraw or revoke (cancel) your permission?

This permission does not stop automatically.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the Study Doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information that might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is your health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

Informed consent statement

It is important that you read and understand several general principles, which apply to all who take part in this study:

- Your participation in the study is entirely voluntary.
- Personal benefits to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others.

- You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled.
- You will be told about any new information discovered during the course of this study that may affect your willingness to continue participating in the study.

Informed consent agreement

I understand that I am being asked to participate in a research study to evaluate the use of the TraceIT Tissue Spacer. After reading and understanding the information in this Informed Consent document, and after having received answers to any additional questions or concerns I had, I freely and voluntarily agree to participate in this study and to comply with the study requirements.

I understand that my personal physician may be informed that I am participating in this research study or have stated my disagreement to such notification and agree to the use of relevant personal data for the purpose of this clinical study. Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study.

_____ Yes, I want the study doctor to inform my primary care physician/specialist of my participation in this study.
_____ No, I do not want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Person Explaining Consent Document Date

_____
Printed Name of Person Explaining Consent Document

You will be given a copy of signed consent document to keep.

APPENDIX D. INVESTIGATOR AGREEMENT AND CERTIFICATION

THE TIPS PILOT STUDY

I hereby agree to participate in the clinical investigation of the **TraceIT Tissue Spacer** sponsored by Augmenix Inc. (hereinafter "Study Sponsor"). I agree to conduct this investigation in accordance with the agreement, the investigational plan, 21 CFR Part 812, other applicable FDA regulations and conditions of approval imposed by the reviewing IRB or FDA. I agree to supervise all use of the investigational device and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study. The rights, safety, and well-being of clinical investigation subjects shall be protected consistent with the ethical principles laid down in 21 CFR Part 50. This shall be understood, observed, and applied at every step of the investigation.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee employed by Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor. I am also aware that I may be inspected by a representative of the Food and Drug Administration (FDA) and other regulatory authorities/agencies to verify compliance with applicable requirements related to clinical research on human subjects. I am aware that my contact for all matters related to this investigation is Augmenix at (781) 895-3235.

I am aware that Study Sponsor reserves the right to discontinue this investigation at any time. In the event that I decide to discontinue my participation as an Investigator in this study, I will notify Study Sponsor 30 days prior of my intent to discontinue. I understand that I am obligated to complete the follow up of the subjects already participating in the investigation.

Any data generated as a result of this investigation will be the exclusive property of Study Sponsor who retains all rights of publication. I understand that Study Sponsor encourages me to pursue independent publications related to my experience with this investigational device with the understanding that Study Sponsor reserves the right of prior review and approval of these publications.

I agree to provide to the Sponsor a current curriculum vitae along with the curriculum vitae of those physicians at this institution who will be using this investigational device or participating in this study as sub-Investigators under my supervision. These CVs include the extent and type of our relevant experience with pertinent dates and locations. I certify that I have not been involved in an investigation that was terminated for noncompliance at the insistence of Study Sponsor, this institution's IRB, or FDA.

I understand that this investigation, protocol, and trial results are confidential and I agree not to disclose any such information to any person other than a representative of Study Sponsor or a regulatory authority (IRB/FDA/Office of Human Research Protections-OHRP) without the prior written consent of Study Sponsor.

I will provide financial information, as indicated in U.S. Code of Federal Regulations: 21 CFR Part 812.43(c)(5) and 21 CFR Part 54

Accepted by:

Principal Investigator Signature	Date	Printed name
Co-Investigator Signature	Date	Printed name
Co-Investigator Signature	Date	Printed name
Co-Investigator Signature	Date	Printed name
Co-Investigator Signature	Date	Printed name
Co-Investigator Signature	Date	Printed name