Evaluation of therapeutic efficacy and safety of concurrent FOLFIRINOX plus high intensity focused ultrasound (ALPIUS 900) for locally advanced/borderline resectable pancreatic cancer: A prospective single-center, single-arm, investigator-initiated, open-labeled, exploratory clinical trial

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Summary of Clinical Trial Protocol

Title	**Evaluation of therapeutic efficacy and safety of concurrent FOLFIRINOX plus high intensity focused ultrasound (ALPIUS 900) for locally advanced/borderline resectable pancreatic cancer: A prospective single-center, single-arm, investigator-initiated, open-labeled, exploratory clinical trial**
Purpose	Through a number of preclinical studies and our recent preliminary clinical study corresponding to phase 1 (Korean FDA approval number No. 584), we demonstrated that high-intensity focused ultrasound (HIFU) increases the effectiveness of chemotherapy, shows significantly longer survival periods, and has safety and potential effectiveness. This clinical study, which corresponds to phase 2, is a prospective, single-center, single-arm, investigator-initiated, open-label, exploratory clinical trial to be conducted to verify the therapeutic effect of high-intensity focused ultrasonography (HIFU) and anti-cancer drugs (FOLFIRINOX) in patients with locally advanced pancreatic cancer (LAPC)/ borderline resectable pancreatic cancer (BRPC).
Institute	Seoul National University Hospital/Prof. Jae Young Lee (Radiology)
Medical Device Manager	Seoul National University Hospital /technician Dong Hyuk Park (Radiology)
Sponsor	FUS foundation
Monitor	Synex Consulting Ltd. (CEO, Young Kim) 10F Asia Tower, 430, Nonhyeon-ro, Gangnam-gu, Seoul 06223, Korea Monitor personnel : Hyun-Ji Kim, CRA
Subject	Patients diagnosed with locally advanced/borderline resectable pancreatic cancer through biopsy and CT/MRI imaging and planned to undergo anti-cancer treatment using FOLFIRINOX
Subject number	30 + 30 subjects that can be assessed
Clinical Trial Device	'ALPIUS 900' (Subject 14-3227, Manufacturer: Alpine Medical System Co., Ltd.) U.S.-guided High Intensity Focused Ultrasound Unit

Trial Design	In patients diagnosed with LAPC/BRPC and planned chemotherapy using FOLFIRINOX, HIFU/FOLFIRINOX combined treatment is performed on patients who agree to this study. The combined treatment group is treated in parallel with FOLFIRINOX and HIFU for the first four cycles and then CT is taken for reaction evaluation immediately, 2 months, and 4 months after the four cycle treatment. For the response assessment, the response rate using RECIST ver. 1.1 and operable rate are evaluated, and compared with the results of already established FOLFIRINOX single treatment in our institute. Time-to-progress and overall survival are calculated.
Trial Method	1. Patients diagnosed with pancreatic cancer through biopsy and diagnosed with LAPC/BRPC through computed tomography (CT) or magnetic resonance imaging (MRI) are referred to this clinical trial. When the referred patients are voluntarily signed a written consent form after hearing sufficient explanations related to this study, they will be registered for this clinical trial if all criteria for selection/exception are met. 2. A management log will be prepared for all subjects who have signed a clinical trial agreement and are registered in the study. These management logs are used to assign sequential subject numbers to subjects registered in clinical trials, and subject numbers are assigned 'screening numbers' and 'registration numbers'. 3. The subjects will visit on the scheduled date to receive chemotherapy and HIFU combined therapy, and will be treated in accordance with the following treatment procedures and protocols. **<Visit 1 to Visit 4: Combined Treatment, Cycle 1, Cycle 2, Cycle 3, Cycle 4 ± 14 Days>** The subjects will receive combined treatments with anticancer drugs (FOLFIRINOX) and HIFU (ALPIUS 900) over four cycles over eight weeks. Afterwards, CT for reaction evaluation is taken immediately after 4 cycles (i.e., 2 months after the onset of combined treatment). CT is taken at intervals of two months up to 6 months after the onset of combined treatment. At the end of each combined treatment, the patient will be observed about adverse events including anticancer drug adverse events and skin change and can be back home or hospitalized for one to two days after collecting blood for blood tests according to doctor's opinion. • **Schedule and procedures for combined treatment**

Perform a total of four treatments every two weeks for eight weeks.

Combined treatment procedure

① Subjects are hospitalized and given anti-cancer drugs for about 50 hours in accordance with the standard protocol for anti-cancer treatment.

☞ If the medication is canceled or postponed due to the condition of the subject, the HIFU procedure will be canceled or postponed.

② After the start of chemotherapy, receive HIFU treatment within 48 hours (30 minutes to 1 hour) and go up to the inpatient ward to monitor for 1 to 2 hours.

☞ If adverse events caused by anticancer drugs have not been recovered within 24 hours of administration or adverse events have not been fully recovered from previous HIFU procedures, the HIFU procedure may be canceled or postponed under the judgment of the investigator.

③ When combined treatment (anti-cancer drug administration) is completed, the subject shall be hospitalized for one to two days or return home depending on the physical condition of the subject.

■ Treatment protocol

- Anti-cancer drug administration (one time regimen)

No.	**FOLFIRINOX** regimen	**Daily administration dose** (route)	**Administration schedule**
1	Oxaliplatin	**85 mg/m^2 (Intravenous, IV)**	It is administered at the following schedule every two weeks. • Day 1 : Oxaliplatin, Irinotecan, Leocovorin, 5-FU (IV-push), 5-FU (IV infusion) • Day 2-3 : 5-FU (IV infusion)
2	Irinotecan	**180 mg/m^2 (Intravenous, IV)**	
3	Leucovorin(Folic acid)	**400 mg/m^2**	

		(Intravenous, IV)	
4	5-FU	**400 mg/m^2 (IV push)**	
5	5-FU	**2400 mg/m^2 (Intravenous, IV)**	

The administration of anticancer drugs (FOLFIRINOX therapy) is applied equally to each treatment group and according to the institution's standard procedure..

<Table 1> Dose and schedule of FOLFIRINOX therapy

** The FOLFIRINOX dose and administration cycle (interval) can be adjusted by the researcher's judgment depending on the condition and progress of the subject.*

e.g. 20% reduction by drug, Oxaliplatin 85mg/m^2 -> 60mg/m^2, Irinotecan 180mg/m^2->150mg/m^2->120mg/m^2

** Anti-cancer drugs used in clinical trials are licensed medicines and are used within the scope of permission.*

- **HIFU treatment (one-time treatment)**

The HIFU procedure is in accordance with the HIFU parameter (Table 2), and the details of the pre-procedure, procedure, and post-procedure care of the subjects are in accordance with the manufacturer's ALPIUS 900 User Manual (see Supplemental material).

<Table 2> HIFU parameter

Acoustic Intensity	**Duty cycle**	**Exposure time**	**PRF**
2.0 kW/cm^2	1%	3 sec/point	10 Hz

4. Immediately, 2 months, and 4 months after completion of the 4th cycle combined treatment, the subjects visit the hospital to conduct the efficacy

	and safety assessment. The DLT or ADE assessment will be evaluated on each planned visit. 5. Treatment after the end of combined treatment of HIFU/Anticancer drug Subsequent treatment of patients who have completed HIFU/anti-cancer combined treatment in the first 4 cycles is determined and performed according to findings of CT performed after 4 cycles of combined treatment, overall physical condition of patients, and standard care guidelines. The implementation of surgery, continuation of FOLFIRINOX chemotherapy, conversion to other anticancer drugs, and further radiation therapy can be considered as possible treatments. This assessment is conducted after 8 and 12 cycles of treatment if the treatment continues for FOLFIRINOX chemotherapy, and further treatment policies are determined in accordance with the standard care guidelines. If surgery is performed after 8 or 12 cycles, additional cancer or radiotherapy may be performed after surgery according to surgery and pathological findings, and it is required to be determined in accordance with the standard care guidelines.
Clinical trial period	24 months from the date of approval of clinical planning by the FDA
Inclusion Criteria	All of the following selection criteria must be met before they can be registered for this clinical trial. 1. Adults over 19–85 2. Persons with a Karnofsky Performance Scale (KPS) of 70 percent or more; 3. A person diagnosed as a tubular adenocarcinoma through biopsy. 4. A person diagnosed with LAPC/BRPC by computed tomography (CT) or magnetic resonance imaging (MRI) 5. A person willing to voluntarily agree to a clinical trial and comply with the test plan
Exclusion Criteria	The following exclusion criteria may not be registered in clinical trials. 1. The presence of a cystic lesion within pancreatic cancer to be treated with HIFU or at the pancreas adjacent to the pancreatic cancer. 2. The presence of a wide range of scar or surgical clips observed in the passage through the ultrasonic beam. 3. In case proper ultrasound images for HIFU procedures are not shown

	4. A person who cannot lie down in a comfortable position. 5. A person who has difficulty communicating 6. A person who has experience in toxic or hypersensitive reactions to FOLFIRINOX anticancer drugs. 7. A person pregnant or breastfeeding 8. Pancreatic cancer patients who have previously been anti-cancer treatment 9. If severe side effects such as aortic rupture, duodenum perforation, gastrointestinal damage or intestinal necrosis are expected due to HIFU procedures. 10. Other cases where participation in this clinical trial is judged inappropriate by the investigator (specific reasons should be recorded in the case report form)
Efficacy Validation Variables	● Tumor response on CT taken 2 months, 4 months and 6 months after the start of combined treatment ● Percentage of subjects who were subject to surgical resection 4 months and 6 months after the start of combined treatment ● Time-to-Progression ● Survival time
Safety Validation Variables	All adverse events that occurred to the subject during the clinical trial period
Methods and criteria for efficacy assessment	The tumor response and the percentage of subjects that were subject to surgical resection are the primary efficacy variable and the rest are the secondary efficacy variables. 1. Tumor response on CT taken 2 months, 4 months and 6 months after the start of combined treatment Based on the findings of CT taken at screening and 2 months, 4 months, or 6 months after the start of combined treatment, the tumor response is assessed as the complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to Response Evaluation Criteria In Solid Tumors(RECIST, Ver. 1.1) below

Table> Solid tumor response indicators by Response Evaluation Criteria In Solid Tumors (RECIST, Ver. 1.1)

구분		내용
CR	Complete Response	In case all lesions and pathological lymph nodes are completely lost
PR	Partial Response	The sum of the lesion diameters is reduced by more than 30% from the pre-treatment (Baseline)
SD	Stable Disease	PR or PD is not applicable either
PD	Progressive Disease	If the sum of the lesion diameters measured during the clinical trial is increased by more than 20% from the sum of the lesion diameters at the time of the smallest and the difference in values is at least 5 mm or a new lesion is observed.

Reference) Watanabe H, Okada M, Kaji Y, Satouchi M, Sato Y, Yamabe Y, Onaya H, Endo M, Sone M, Arai Y.New response evaluation criteria in solid tumours-revised RECIST guideline (version 1.1) Gan To Kagaku Ryoho. 2009 Dec; 36(13):2495-501.

2. Percentage of subjects who were subject to surgical resection 4 months or 6 months after the start of combined treatment

When surgery is determined according to AJCC (American Joint Committee on Cancer, 8 edition) guidelines based on computed tomography (CT) images taken 4 months or 6 months after the start of the combined treatment, the percentage of subjects who were able to be operated on compared to the total number of registered subjects is calculated.

3. Time-to-Progression

The time taken from the date of diagnosis of pancreatic cancer or from the start date of combined treatment of pancreatic cancer until the date of first documented progression, assessed up to 24 months. Judging by RECIST ver. 1.1

	4. Survival time The time taken from the date of diagnosis of pancreatic cancer or the start date of combined treatment of pancreatic cancer until the date of death from any cause, assessed up to 24 months.
Methods and criteria for safety assessment	The safety assessment is observed for all adverse events that occurred from the time of the start of the first cycle of chemotherapy and HIFU combined treatment to the end of the clinical trial as follows: All undesirable medical findings that are newly observed during clinical trial are classified as an adverse event. Side effects predicted according to the definitions and criteria described in the section "14. Evaluation Criteria, Evaluation Methods, and Reporting Methods for Safety including Side Effects" are also classified as adverse events. The degree of adverse events caused by medical devices is graded according to the NCI-CTCAE (Version 4.03) criteria, and the use of terms in medical coding is based on MedDRA's "Preferred Term" and "System organ class". However, in case of an adverse events that do not have any applicable items, write 'Other' of the appropriate 'Categories' and record the details and select the appropriate grade from grade 1-5 (see 14.3.1 Severity Degree Assessment Section).
Observation item	<Schedule for Clinical Trial>
anticipated adverse events	■ Expected adverse events due to HIFU treatment 1. Skin burns, bleeding, or infections in the treatment area; 2. Subcutaneous fat sclerosis 3. Abdominal pain 4. Pancreatitis 5. Tumor hemorrhage 6. Peritonitis 7. Jaundice 8. Vascular injury (aortic rupture) 9. Pancreatoduodenal injury and perforation. 10. Gastric injury and perforation

	11. Bowel necrosis ■ Expected adverse events due to anticancer drugs 1. Thrombocytopenia 2. Neutropenia 3. leukopenia 4. Anemia 5. Lymphopenia 6. Febrile neutropenia 7. Hair loss 8. Peripheral sensory neuropathy 9. Lacking appetite 10. Rash 11. Nausea 12. Dullness 13. Fatigue 14. Diarrhea 15. Alanine aminotransferase (ALT) increase 16. Hyponatremia

Clinical Trial Progress Schedule

	Screening	Period of combined treatment and follow-up observation						
Visits		V1 (Cycle1**)	V2 (Cycle2)	V3 (Cycle3)	V4 (Cycle4)	V5	V6	V7
Days elapsed	≤ -4W	Day1	Day15	Day29	Day43	After four-cycle treatment (Month 2)	Two months after four-cycle treatment (Month 4)	Four months after four-cycle treatment (Month 6)
Visit window		-*	± 14 days	± 14 days	± 14 days	± 14 days	±28 days	±28 days
Observation Form	Visiting	hospitalization	hospitalization	hospitalization	hospitalization	outpatient/ hospitalization	outpatient /hospitalization	outpatient /hospitalization
Consent acquisition	√							
Inclusion/Exclusion Criteria	√							
Demographic Survey[1)]	√							
Pregnancy Test[2)]	√							
Vital Signs[3)]	√	√	√	√	√	√		
Physical Examination[4)]	√							
Medical History[5)]	√							
Ultrasound[6)]	√							
KPS evaluation[7)]	√					√		
CT Imaging[8)]	√					√†	√†	√†
Blood Test[9)]	√	√	√	√	√	√	√	√

CA-19-9[10]		√					√	√	√
NRS Pain Assessment[11]		√					√	√	√
Survival rate[12]							√	√	√
Combined treatment	Anticancer drug medication[13]		√	√	√	√			
	HIFU treatment[14]		√	√	√	√			
Adverse events/Serious adverse event[15]			√	√	√	√	√	√	√
Concurrent medication and treatment[16]			√	√	√	√	√	√	√
Immune analysis			√	√	√		√		

* Based on the first date of chemotherapy

** Cycle: Anti-cancer drug administration interval according to FOLFIRINOX standard treatment protocol, FOLFIRINOX is administered every two weeks, so it becomes a cycle of two weeks. The first anti-cancer drug administration cycle will be one cycle and the next two weeks later.

Visit 5: Visit for CT scanning and other examinations immediately after completion of 4 cycles of cancer.

Visit 6: Visit for CT scanning and other examinations 2 months after Visit 5. Subject's visit is terminated with Visit 5 if surgery is performed based on the findings of CT performed on Visit 5.

Visit 7: Visit for CT scanning and other examinations 4 months after Visit 5. Subject's visit is terminated with Visit 6 if surgery is performed based on the findings of CT performed on Visit 6.

† CT scan: CT for response assessment is usually performed during an outpatient visit before the next chemotherapy treatment, but if he/she is a local resident or there are any special circumstances, CT is performed during hospitalization for the next chemotherapy treatment.

< Terminology >

① ADE: Adverse Device Effect

② AE: Adverse Event

③ CRC: Clinical Research Coordinator

④ DVT: Deep Vein Thrombosis

⑤ FAS: Full Analysis Set

⑥ HIFU: High Intensity Focused Ultrasound

⑦ IRB: Institutional Review Board

⑧ KGCP: Korea Good Clinical Practice

⑨ MRgHIFU: Magnetic Resonance Imaging-Guided High Intensity Focused Ultrasound

⑩ MRI: Magnetic Resonance Imaging

⑪ PP: Per-Protocol

⑫ SAE: Serious Adverse Event

⑬ SSS: Symptom Severity Score

⑭ USgHIFU: Ultrasound-Guided High Intensity Focused Ultrasound

⑮ VAS: Visual Analogue Scale

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1. Title of Clinical Trial

Evaluation of therapeutic efficacy and safety of concurrent FOLFIRINOX plus high intensity focused ultrasound (ALPIUS 900) for locally advanced/borderline resectable pancreatic cancer: A prospective single-center, single-arm, investigator-initiated, open-labeled, exploratory clinical trial

2. Name and Location of the Institution conducting Clinical Trial

■ Seoul National University Hospital

Daehak-ro 101, Jongro-gu, Seoul (110-744) Tel: 02-2072-2114

3. Name and Title of Principal Investigator, Sub-investigator, and Co-investigator

■ Seoul National University Hospital or Seoul National University College of Medicine.

Role	Name & Title	Affiliation	Tel.
PI	Jae Young Lee, Prof.	Radiology	822-2072-3073
Co-Investigator	Sang-Hyup Lee, Prof.	Gastroenterology	822-2072-4892
Co-Investigator	Jin-Young Jang, Prof.	Surgery	822-2072-2194
Co-Investigator	Hong Beom Kim, Assistant Prof.	Surgery	822-2072-1272
Co-Investigator	Dong Ho, Lee, Associate Prof.	Radiology	822-2072-0348
Co-Investigator	In Rae Cho, Assistant Prof.	Gastroenterology	822-2072-2199
Co-Investigator	Hang Rae Kim, Prof.	Cell Immunology	8210-8920-3607
CRC	Soo Yeon Kang, Nurse	Radiology	822-2072-3073

Technician	Dong Hyuk Park, Radiation Tech.	Radiology	822-2072-3073
CRC	Seong Ho Choi, Nurse	Surgery	822-2072-2194
CRC	Hyun Ji Lee, Nurse	Gastroenterology	822-2072-4892

4. Name and Title of Clinical Trial Medical Device Manager.

■ Seoul National University Hospital

Role	Name and Title	Affiliation	Tel.
Medical device manager	Dong Hyuk Park, Radiation tech.	Radiology	822-2072-7354

5. Name and Title of Clinical Trial Monitor

Role	Name and Title	Affiliation	Tel.
Clinical trial monitoring	Hyun-ji Kim, CRA	Synex Consulting Ltd.	822-2284-9400

6. Goal and Background of Clinical Trial

6.1. Goal

This clinical trial is a prospective, single-institute, single-arm, investigator-initiated, open-labelled, exploratory one for evaluating the efficacy and safety of drug-delivery-enhancing effects of the combined treatment of HIFU (ALPIUS 900) and anti-cancer drugs (FOLFIRINOX) in patients with locally advanced pancreatic cancer/borderline resectable pancreatic cancer.

In addition, we would like to compare the therapeutic effect of HIFU/anti-cancer drug combined treatment with the current standard treatment method through the matching method in the histological cohort that underwent the current standard treatment, FOLFIRINOX chemotherapy.

6.2 Background

Malignant pancreatic exocrine tumors refer to ductal adenocarcinoma, mucinous cystic adenocarcinoma, intraductal papillary mucinous carcinoma, acinar cell carcinoma, pancreatoblastoma, and solid pseudo-papillary carcinoma, among which ductal adenocarcinoma accounts for 80 to 90 percent of pancreatic cancer [1]. Pancreatic cancer is the eighth of all cancers in terms of incidence, at 2.3 percent, but the fifth cause of death from cancer. More than 5,000 people in the country die from pancreatic cancer and more than 200,000 people worldwide are dying from pancreatic cancer each year.

Pancreatic cancer is a pathological feature that does not have clear boundaries with surrounding pancreas, and because of its abundance of fibrous tissue and low vascular distribution, it is firm by touching and its color is light yellow or gray [1; 2]. Pancreatic cancer tissues characteristically form extensive stroma around cancer cells, showing characteristics such as desmoplasia. It is prone to invade peripancreatic tissue or organs, and lymph node invasion occurs before vascular invasion usually by invading fat tissue, nerve tissue, and lymphatic system around the pancreas first. 55 to 65% occur in pancreatic head or uncinated process; 15 to 35% in body and tail; and 10 to 20% in entire pancreas as a diffuse tumor.

The diagnostic method can be largely divided into imaging, histopathology and laparoscopic examination [3]. The most frequently used imaging modality for the diagnosis and staging is multi-detector CT, which can be reconstructed with three-dimensional images. Magnetic resonance imaging is also used frequently, and it is helpful if the diagnosis or margin of pancreatic cancer is unclear in CT, but it is not superior to abdominal CT when evaluating surgical resection. Recently, endoscopic ultrasound has been used more and more, and they have the advantage of being able to obtain tissues through a fine needle aspiration. PET CT may be required. In the case of pancreatic cancer which can be surgically resected, preoperative biopsy is not necessary. Histologic examination is needed for chemotherapy, and even when they are not typical for pancreatic cancer, it is also needed. The tissue can be obtained through percutaneous and endoscopic approaches. Laparoscopic examination is conducted when it is necessary to detect liver or peritoneal metastases to avoid unnecessary surgery.

The prognosis of pancreatic cancer is still very poor, with a five-year survival rate of less than 10 percent in total patients, despite considerable advances in surgery and medical technology and radiation treatment. The 5-year survival rate is 8.7 percent in our country and 5 percent worldwide. The reason for the low survival rate is that when pancreatic cancer was discovered, the proportion of patients who are surgically treated is only 10 to 20 percent worldwide. Pancreatic cancer has a worse prognosis than any other cancer, with a five-year survival rate of only about 10-20 percent even after a radical resection.

For pancreatic cancer patients, the only curable method is surgical resection. However, surgical resection can be performed in only 20% of patients with pancreatic cancer at the time of discovery due to the absence of screening tests for early detection. There are chemotherapy and radiation

treatments for patients with advanced pancreatic cancer that can be operated and borderline resectable pancreatic cancer that are not sure whether it can be operated. In a study comparing chemo-radiotherapy with chemotherapy alone, conflicting results are published according to the research institute, requiring further study.

What is practically necessary to determine the treatment policy is the evaluation of resectability. Pancreatic cancer is divided into metastatic pancreatic cancer and localized pancreatic cancer, and localized advanced pancreatic cancer is divided into resectable pancreatic cancer, borderline resectable pancreatic cancer and locally advanced pancreatic cancer. In addition to distant metastasis, the most important cause to make surgical resection of pancreatic cancer impossible is vital vessel invasion, such as superior mesenteric artery or celiac artery invasion by tumors. In the case of locally advanced pancreatic cancer (LAPC), FOLFIRINOX regimen (combination of 5-FU, Oxaliplatin, Irinotecan, Folinic acid) is regarded as a standard treatment based on its excellent results over convention chemotherapy [4-6].

In addition, the concept of borderline resectable pancreatic cancer (BRPC), a disease in which the determination of surgical resectability is ambiguous, has recently been widely accepted. Vascular invasion criteria defining borderline resectable pancreatic cancer most commonly use NCCN 2018 version. Recent studies have shown that neoadjuvant chemotherapy using FOLFIRINOX regimen before surgery has a better prognosis than direct surgical resection in BRPC, and gradually, it is recommended to implement neosdjuvant chemotherapy for BRPC patients. [7-9] There is still controversy over the addition of radiotherapy to neoadjuvant chemotherapy.

In a recent clinical study of 117 borderline resectable pancreatic or local advanced pancreatic cancers published in Korea, the overall survival time of patients treated with prior FOLFIRINOX was 19 months, and surgery was possible in about a quarter, and the average survival period of patients who underwent surgery was 28.6 months, which led to the conclusion that neoadjuvant chemotherapy of FOLFIRINOX was helpful in the outcome[10].

High Intensity Focused Ultrasound (HIFU) is an extracorporeal non-invasive medical device that uses high-intensity focused ultrasound to ablate local tissues or nerves in the body without damaging surrounding organs and tissues, and is mainly applied to the treatment of benign and malignant tumors such as uterine fibroid, benign prostate hypertrophy, and prostate cancer. The HIFU can be divided into a continuous HIFU that continuously gives ultrasonic waves and a pulsed HIFU that gives pulsed wave with a frequency. Early studies on the treatment of pancreatic cancer mostly used continuous HIFU to generate heat in tumors or used pulsed HIFU using long duty cycle pulse. However, such HIFU treatment using high heat can cause heat damage to the surrounding organs or tissues. There are many physicians who feel at risk of applying it to the pancreas with complex surrounding vital organs. Actually, severe complications caused by this type of HIFU have been reported.

The HIFU study on the treatment of pancreatic cancer was published in Spain, Germany, and other countries as well as in China, and used heat-producing continuous HIFU.[11-14]. Pancreatic cancer treatment by pulsed HIFU has recently begun to be reported [15-17]. The operating principle of the pulsed HIFU is almost identical to that of the continuous HIFU, but the difference is that ultrasonic waves are given in pulse form. In the case of pulsed HIFU, not only intensity but also pulse repetition frequency (PRF) and duty cycle can be adjusted to create various phenomena.

Recently, research on anti-cancer drugs using a special condition of pulsed HIFU using relatively low duty cycle, which only transforms cell barriers without heat generation of tumor tissue, has been actively reported.[7; 18; 19]. HIFU and anti-cancer drug combined therapy can minimize side effects of anti-cancer drugs and increase the efficacy of anti-cancer drugs against cancer cell apoptosis by making anti-cancer drugs act in a more specific and targeted way to the pancreatic cancer cells. Relevant reports have shown that HIFU disrupts the cell membrane of targeted cancer cells by sonoporation to help drugs get into cancer cells. Figure 1 below shows the main mechanism of action in which HIFU transiently disrupts the cell membrane and consequently induces apoptosis of cancer cells.

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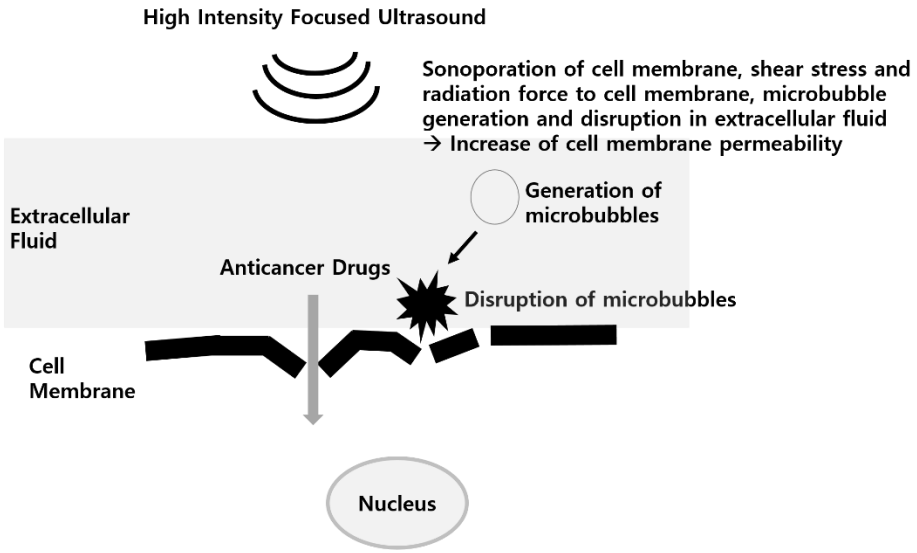

Fig. 1. Mode of Action of HIFU in combination with anticancer drugs. Ultrasound causes changes in pressure in the propagation medium. Microbubbles are generated in extracellular fluid and cells by negative pressure of ultrasound. The microbubble expansion and contraction occur due to pressure changes, and eventually the microbubbles collapse due to liquid microstreaming or Jetting. The force generated by the high pressure jet and shear stress by liquid streaming are sufficient to damage or increase permeability of the surface of surrounding cell membrane. It results in anticancer drug to easily penetrate cells.

We have conducted various preclinical study treatment to prove the combined effect of HIFU and anti-cancer drugs on pancreatic cancer for 10 years and reported the results in SCI papers [16; 19-21], and recently conducted a preclinical study to evaluate the combined treatment effect of HIFU and anti-cancer drugs under HIFU conditions where its mechanical effect is exaggerated [19]. The effect of tumor suppression was higher when the mechanical effect was increased by adjusting the duty cycle and intensity, proving that the effect of anti-cancer drugs on tumor cells could increase when tumors are irradiated with stronger intensity at a shorter duration rather than with lower intensity at a longer duration under the same energy conditions, and reported that significant tumor growth suppression and complete remission of 30% were found when the above conditions were repeated at intervals of one week like clinical regimen (Fig. 2).

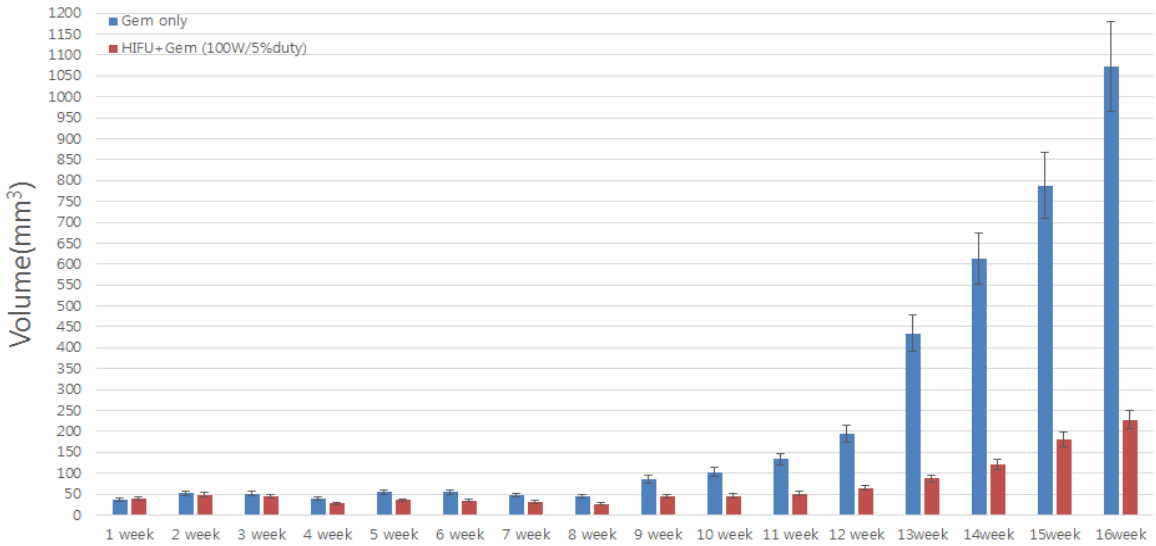

Fig. 2. Change in tumor size during the four-cycle treatment (one cycle = three-week treatment + one-week monitoring) in two groups (gemcitabine only group vs. combined treatment group of gemcitabine and HIFU (using mechanical effect-dominant condition). The combined treatment group (red color) shows significant inhibition of tumor growth, compared to gemcitabine only group (blue color).

Therefore, our preclinical studies can be summarized as follows: all our studies continued to show the following facts: the concurrent use of HIFU and anti-cancer drugs increases apoptosis rates of pancreatic cancer cells and decreases the growth of pancreatic cancer tissues. In addition, using mechanical effect-dominant HIFU condition is more beneficial to enhance tumor growth suppression.

Last year, we performed a pilot clinical trial to investigate the safety and initial efficacy of combined treatment of HIFU (parameter: 1.5 kW/cm^2 to 2.5 kW/cm^2, duty cycle of 2%) and chemotherapy in nine patients with unresectable pancreatic cancer, using ALPIUS 900 unit (US-guided HIFU system, Alpinion Medical System), which is clinically being used in our institute to treat uterine myoma and uterine adenomyosis. A total of nine patients was treated safely without aggravating the side effects

of chemotherapy. In particular, the intermediate intensity group (2.0kW/cm^2) showed statistically significant extension of the survival period (median survival > 28 months, $p<0.01$). All patients in intermediate intensity group are still survived. This results were presented at the RSNA 2019. Given the safety and potential effectiveness identified in the pilot clinical studies and the theoretical advantages that HIFU/anti-cancer combined therapy has, we can believe that HIFU and anti-cancer drug combined treatment could lead to improvement of tumor response in LAPC/BRPC patients, and furthermore, would help improve the prognosis of pancreatic cancer patients. **Therefore, this clinical trial was planned to evaluate the therapeutic effect of combined treatment of HIFU and anti-cancer drug in LAPC/BRPC patients with a study design having a higher power of proof.**

7. Overview of Clinical Trial Medical Device

7.1 Name of Medical Device, Item Classification, and Prior Permission

-Name of Medical Device: 'ALPIUS 900' (Subject 14-3227, Manufacturer: Alpine Medical System Co., Ltd.)

- Item Classification: U.S.-guided High Intensity Focused Ultrasonic Surgical Unit Degree 3, A35100.02, a device for treating cancer or others using ultrasound integrated with high intensity.

- - Pre-authorization: Non-invasive treatment of uterine myoma and adenomyosis not less than 3cm but less than 12cm non-invasively using ultrasound-guided high intensity focused ultrasound

7.2 Composition

No.		Name
1		Operating monitor
2		Steel Handle/Wheel
3		Emergency Button
4		Imaging Monitor
5		Positioning Arm
6		Treatment Head

7.3 Specification

1) Treatment Transducer

(1) Number of Transducer elements: 256

(2) Diameter: 135mm

(3) Frequency: 1 MHz

(4) Power: < 600W

(5) Adjustable insonation range for treatment: Lateral ± 13 mm, Axial ± 25 mm

(6) Focal distance: Variable with beam steering

(7) Diameter of focus: -6 dB length: according to beam steering 1.6 mm ± 20%

(8) Length of focus: -6 dB length: according to beam steering 11 mm ± 20%

(9) Sonication Energy: 800J/point

(10) Reflection/cavitation monitoring: Passive Cavitation Monitoring

2) Pre-scan Transducer

(1) Acoustic Power: 173.2 mW/cm2

(2) Applied frequency: 1~6 MHz

(3) Application Plane Size: 66*16mm

(4) Scanning depth: 300 mm

(5) Vertical Resolution: 1.7 mm (@65mm), 1.1 mm(@ 105mm)

(6) Horizontal resolution: 3.4 mm (@65mm), 4.2mm(@105mm)

(7) FOV: 60 도

※ A previous approved product (Approval No. 10-1247) is used for ultrasonic imaging devices.

3) Supply power

(1) Input power: 200-230 VAC, 50/60Hz

(2) Power consumption: 3.5 KVA

4) OCM workstation minimum specification

(1) CPU: Intel Core i7 > 3.40G

(2) Standard Desktop PC

(3) 3xPCI

(4) Memory: > 1MB Cash

(5) Hard disk capacity: > 100GB

(6) HP CD-RW (IDE) 8x or higher

(7) Audio (Built in PCI)

(8) 2xFast Ethernet adaptor

(9) 1Xapg GE Graphics Adaptor

(10) 21.5 inch Color LCD monitor

5) Imaging module Control Computer Minimum Specification (CPC)

(1) Intel core 2 duo > 2.26G

(2) Power Supply System: 350W

(3) HDD capacity: > 40GB

(4) 1x Fast Ethernet PCI adaptor

(5) 18.5 inch color LCD monitor

(6) OS: Microsoft Windows XP

(7) Input power: 220 VAC, 50/60Hz

6) Water Circulation Module

(1) Degassing method: Gas separation membrane type. standard flow rate: 1L/min

(2) Vacuum meter: > Max 60 (-700mmHG)

(3) Power: single phase 220 VAC, 60Hz

(4) Power Consumption: 300W

7) Software

Number	Name	version
1	ALPIUS 900	1.0
2	Armstrong ALPIUS 900	3.5

7.4 How to use

The procedures for the use of clinical trial device are as follows, and the detailed instructions of the manufacturer (attached Form) shall be followed.

- Prerequisites for medical device use
  - Checking the power supply and turning it on/off
  - Connecting and disconnecting imaging transducers

- Confirm activating and deactivating imaging transducers

■ How to use and operate

1. Pre-treatment Patient Preparation Procedure
   - Fasting from 4 hours before the procedure
   - Keep skin clean
   - Shaving (mechanical chemical shaving) depending on skin condition
   - Anesthetic or sedative administered according to the patient's prescription
   - Posture : Supine position
   - Measurement of vital signs (blood pressure, pulse rate, respiration rate, oxygen saturation)

2. HIFU Procedure
   - After checking patient's readiness for treatment, scan the treatment area. Clinicians treat patient in accordance with a pre-established treatment plan.
   - The clinicians check tumor response in real-time during treatment through ultrasound and, if necessary, immobilizes the subject.

3. Post-treatment procedure
Subjects who have completed the procedure can return to the inpatient ward and observe 1 to 2 hours after the end of the chemotherapy, and may return home or stay in the hospital for 1 to 2 days, depending on the opinion of the medical faculties.

4. Precautions for Use
<Refer to Annex> ALPIUS 900 User Manual

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7.5 Technical Features and Performance

The clinical trial medical device has a transducer that produces high-intensity focused ultrasound, its supporting structures and hardware and software to monitor treatment. Its electrical characteristics are 220VAC, 60Hz, and 3.5kVA, and its protection type and degree is Class 1 and BF type. The medical device for this clinical trial consists of imaging display monitor, operational display monitor, positioning arm, treatment head, handle, treatment head membrane, body and mobile wheel (see 9.5.1 Overview of clinical trial medical device). Various ultrasound examinations are possible and even deep-seated tumors can be visualized using imaging control panels, and the treatment head has imaging probes for real-time imaging, membrane in contact with the human body, and temperature sensor that measures the temperature of cooling water. The operational display monitor shows all the information and real-time treatment scenes as well as the images acquired (see attached item license).

7.6 Purpose of Use

In this clinical trial, ALPIUS 900 (U.S.-guided HIFU System) will be used to enhance drug delivery of anticancer drug by applying focused ultrasound beam with relatively low Duty cycle pulse that can induce deformation of the cell barrier of tumor tissue without heat generation to pancreatic cancer.

7.7 Target Diseases and Indications

Locally advanced/ borderline resectable pancreatic cancer is targeted in patients who have not received any other treatment with histological diagnosis of pancreatic adenocarcinoma.

8. Inclusion Criteria, Exclusion criteria, and Target Population Number and its Reasoning

8.1 Inclusion and Exclusion Criteria

8.1.1 Inclusion Criteria

All of the following selection criteria must be met before they can be registered for this clinical trial.

1. Adults over 19–85
2. Persons with a Karnofsky Performance Scale (KPS) of 70 percent or more;
3. A person diagnosed as a tubular adenocarcinoma through biopsy.
4. A person diagnosed with LAPC/BRPC by computed tomography (CT) or magnetic resonance imaging (MRI)

   - Diagnosis results based on CT or MRI taken at the hospital where pancreatic cancer was first diagnosed or being treated are recognized as valid. However, only the results obtained within 4 weeks from the screening date are accepted.

   - LAPC/BRPC is determined by investigators based on the American Point Committee on Cancer (AJCC) guidelines (see table below).

T staging	
T1	Tumor diameter < 2cm
T2	2cm ≤ tumor diameter ≤ 4cm
T3	Tumor diameter > 4cm

T4	Invasion of the celiac trunk, the superior mesenteric artery, and proper hepatic artery, regardless of tumor size.

N staging	
N0	No LN metastasis
N1	Regional LN metastasis 1~3
N2	Regional LN metastasis 4 or more

M staging	
M0	No distant metastasis
M1	Distant metastasis

- Cases with distant metastasis are excluded; LAPC indicates T4NxM0; and BRPC indicates when T4 is not clear with NxM0.

5. A person willing to voluntarily agree to a clinical trial and comply with the test plan

8.1.2 Exclusion Criteria

The following exclusion criteria may not be registered in clinical trials.

1. The presence of a cystic lesion within pancreatic cancer to be treated with HIFU or at the pancreas adjacent to the pancreatic cancer.

2. The presence of a wide range of scar or surgical clips observed in the passage through the ultrasonic beam.

3. In case proper ultrasound images for HIFU procedures are not shown

4. A person who cannot lie down in a comfortable position.

5. A person who has difficulty communicating

6. A person who has experience in toxic or hypersensitive reactions to FOLFIRINOX anticancer drugs.

7. A person pregnant or breastfeeding

8. Pancreatic cancer patients who have previously been anti-cancer treatment

9. If severe side effects such as aortic rupture, duodenum perforation, gastrointestinal damage or intestinal necrosis are expected due to HIFU procedures.

10. Other cases where participation in this clinical trial is judged inappropriate by the investigator (specific reasons should be recorded in the case report form)

8.2 Estimation of Target Population Number and its Reasoning

Number of subjects: 60 total

To date, there has been no prior study on how effective the combined treatment of HIFU and chemotherapy is in pancreatic cancer patients, so there is no evidence study on the number of subjects needed for this study. Studies using FOLFIRINOX, which have been published so far, have mostly recruited 30-40 patients, and a recently published randomized clinical trial of FOLFIRINOX study included 50 patients with BRPC. **A total of 60 patients**, including LAPC and BRPC, are expected to be needed in consideration of these previous prior studies and considering a 15% dropout rate in this study.

9. Clinical Trial Period

After obtaining approval of the clinical trial plan from the FDA in our country and IRB, it is expected that it will take at least 24 months, including 12 months of subject registration (from the date of first subject registration to the date of last subject registration) 6 months of treatment and follow-up observation, and about 6 months for data processing, statistical analysis, and report preparation after clinical trial is completed.

10. Clinical Trial Method

10.1 Research Design

Prospective, single-center, single-arm, investigator-initiated, open-labeled, exploratory clinical trial

10.2 Clinical Trial Procedure

Patients diagnosed with pancreatic cancer through biopsy and diagnosed with LAPC/BRPC through computed tomography (CT) or magnetic resonance imaging (MRI) are referred to this clinical trial. Patients who voluntarily sign a written consent form after hearing sufficient explanations related to this study will be registered for this clinical trial if all criteria for selection/exception are met.

10.2.1 Subject Numbering

A management log will be prepared for all subjects who have signed a clinical trial agreement and are registered in the study. These management logs are used to assign sequential subject numbers

to subjects registered in clinical trials, and subject numbers are assigned 'screening numbers' and 'registration numbers'.

The screening number is assigned according to the following methods, including the "S" of the screening and two digits in the order of the subjects.
- Screening : S
- Two digits according to the screened order
  Example > Identification code of the first screened subject: S – 01

The registration number is assigned according to the following methods, including the "R" of the registration and two digits in the order of the subjects.
- Registration: R
- Two digits according to the registered order
  Example > Identification code of the first registered subject: R – 01

10.2.2 Screening

Patients diagnosed with pancreatic cancer through biopsy and diagnosed with LAPC/BRPC through computed tomography (CT) or magnetic resonance imaging (MRI) are referred to this clinical trial by surgeon or internal physician. Patients who voluntarily sign a written consent form after hearing sufficient explanations related to this study are registered for this clinical trial and undergo following evaluation if all criteria for selection/exception are met.

- Demographic Survey
- Pregnancy test
- Vital signs
- Physical examination
- Past medical history
- Ultrasound exam
- KPS Evaluation
- CT scan
- Blood test
- CA19-9
- NRS Pain Assessment

Following items are observed and recorded on ultrasound and CT exams.

<Ultrasound examination>

- The presence of abdominal wall scarring
- The presence of surgical clip

- The presence of proper acoustic window for HIFU treatment

< CT examination>

- Nature of tumor: Cystic or Solid
- Location of tumor in the pancreas: Head, Body, Tail
- Number of tumor
- TNM stage
- The presence and location of distant metastasis.
- Whether or not metastasized and the organization that metastasized

10.2.3 Visit 1~ Visit 4

The subjects will receive combined four-cycle treatments of anticancer drugs (FOLFIRINOX) and HIFU (ALPIUS 900) at intervals of two weeks over eight weeks. The CT for tumor response evaluation is then taken immediately after the fourth cycle (i.e., 2 months after start of combined treatment). Regardless of whether the FOLFIRINOX treatment persists or not, CT is taken at intervals of two months up to 6 months after start of combined treatment.

At the end of each combined treatment, an adverse reaction or skin change is observed. After blood collection for blood tests, the subjects may return home or be hospitalized for one to two days according to medical faculties opinion.

1. At each visit for combined treatment (Cycles 1, 2, 3, 4), the following items are recorded and evaluated:

    - Vital signs
    - Blood test
    - Adverse events / serious adverse events
    - Confirmation of concurrent medication and treatment

2. Detailed combined treatment schedules and procedures and combined treatment protocols are as follows.

    A. Schedule and procedures for combined treatment

    - Perform a total of four repeated treatments every two weeks for eight weeks.
    - Subjects are hospitalized and given anti-cancer drugs for about 50 hours in accordance with the standard protocol for FOLFIRINOX.

☞ If the medication is canceled or postponed due to the condition of the subject, the HIFU procedure will also be canceled or postponed.

- After the start of chemotherapy, receive HIFU treatment within 48 hours (30 minutes to 1 hour) and go up to the inpatient ward after completion of HIFU treatment for post-treatment monitoring for 1 to 2 hours.

  ☞ If adverse events caused by anticancer drugs have not been recovered within 24 hours of administration or adverse events by HIFU treatment have not been fully recovered, the HIFU procedure may be canceled or postponed under the judgment of investigators.

- When anticancer drug administration of combined treatment is completed, the subjects shall be hospitalized for one to two days or returned home depending on the physical condition of the subject.

B. Combined Treatment Protocol

- **Anti-cancer drug administration (one cycle dose) :** The administration of anticancer drugs (FOLFIRINOX regimen) is applied equally to each enrolled patient according to the institution's standard protocol.

<Table 1> Dose and schedule of FOLFIRINOX therapy

No.	**FOLFIRINOX** regimen	**Daily administration dose** (route)	**Administration schedule**
1	Oxaliplatin	**85 mg/m^2 (Intravenous, IV)**	It is administered at the following schedule every two weeks.
2	Irinotecan	**180 mg/m^2 (Intravenous, IV)**	

3	Leucovorin(Folic acid)	**400 mg/m^2** **(Intravenous, IV)**	• Day 1 : Oxaliplatin, Irinotecan, Leocovorin, 5-FU (IV-push), 5-FU (IV infusion) • Day 2-3 : 5-FU (IV infusion)
4	5-FU	**400 mg/m^2** **(IV push)**	
5	5-FU	**2400 mg/m^2** **(Intravenous, IV)**	

** The FOLFIRINOX dose and administration cycle (interval) can be adjusted by the researcher's judgment depending on the condition and progress of the subject.*

e.g. 20% reduction by drug, Oxaliplatin 85mg/m^2 -> 60mg/m^2, Irinotecan 180mg/m^2->150mg/m^2->120mg/m^2

** Anti-cancer drugs used in clinical trials are licensed medicines and are used within the scope of permission.*

- **HIFU procedure**

The details of the pre-procedure, procedure, and post-procedure care of the subjects are in accordance with the manufacturer's ALPIUS 900 User Manual (see Supplemental material).

< Pre-treatment Preparation>

1) Preparation of subjects

Depending on the condition of the skin, the subject will be shaving (using shaving cream) on the skin to which HIFU will be applied within three days prior to the treatment, and no cream should be used after shaving. To reduce side effects by gases or food in the gastrointestinal tract, fasting is required from midnight the day before the procedure (NPO 4 hours prior to HIFU treatment).

2) Pancreatic cancer treatment area plan

The volume ratio of pancreatic cancer to be treated will be determined by the investigator (typically, the treatment area is planned with a safety margin of 0.5 cm from the margin of pancreatic cancer). Based on the ultrasound image findings of pancreatic cancer, only pancreatic cancer tissues that can be identified in the ultrasound images will be considered for treatment.

<HIFU procedure>

The operator shall perform the HIFU procedure according to the pre-established procedure plan. HIFU parameter that is used in this trial is seen in Table 2 based on the result of our pilot clinical trial. After the entire planned procedure is completed, keep the entire treatment record in the patient record.

<Table 2> HIFU parameter

Acoustic Intensity	Duty cycle	Exposure time	PRF
2.0 kW/cm^2	1%	3 sec/point	10 Hz

During the procedure, observe and record the following items:

- vital signs such as body temperature, blood pressure (a retractor/a relaxation device), pulse rate, respiration rate, and oxygen saturation.
- Treatment time
- HIFU insonation time
- HIFU insonation energy

<Post-HIFU Treatment Process>

After the HIFU procedure is completed, the subjects will observe one to two hours of abnormal cases, including skin changes, in the inpatient ward and will be given residual anticancer drugs.

10.2.4 Visit 5~ Visit 7

After completion of 4th cycle combined treatment (2M), 2 months after completion of the combined treatment, 4 months after completion of the combined treatment (4M), the subjects visit to our hospital and the following items are recorded and evaluated. The clinical trial will be ended for a subject after all assessment are completed if there are no adverse event to need to be followed for the subject. The following items are recorded and evaluated during follow-up period.

- Vital signs
- KPS evaluation (only conducted at Visit 5)

- CT scan.
- Blood test
- CA19-9 values
- NRS Pain Assessment
- Evaluation of survival rate
- Adverse event cases / Serious adverse event cases
- Checking concurrent medication and treatment

10.3 Prohibition and Permission in Concomitant Medication or Therapy

Drugs or alternative treatments that may affect the results of the clinical trial are prohibited. All medications already taken due to underlying diseases are recorded in the screening. Only medications added after the start of clinical trial are recorded in case report form. If they receive prohibited drugs or alternative treatments during the clinical trial period, they will be eliminated from the study and the reasons for the elimination are recorded.

However, if a prohibited drug is required in a one-time manner, it can be used within the extent that it does not affect the outcome of the clinical trial according to the investigator's judgment, and the details are recorded in the column of the concomitant medications in the case report form.

Based on the investigator's judgment, painkillers and local anesthetics can be administered in accordance with the institution's standard procedures, taking into account the subjects' condition.

- Prohibited medication/therapy

Anti-cancer drugs and radiotherapy other than FOLFIRINOX are prohibited during the combined treatment period.

- Allowed medication/treatment

Analgesics to be commonly used for conservative symptom management of cancer patients (Codeine, Diamorphine, Fentanyl, Hydrocodone, Meperidine, Methadone, Morphine, Oxycodone, Propoxyphene, Supethanil, Tramadol), G-CSF, Dexamethasone, antiemetics (Ondansetron, Aprepitant etc), Gabapentin, tricyclic antidepressant, etc. are not prohibited. Anti-cancer drugs are administered until the tumor's progression is confirmed in accordance with the standard treatment procedure of FOLFIRINOX, or until it is no longer possible to administer to the patient due to drug side effects.

10.4 Therapy after ending combined HIFU/chemotherapy treatment

Subsequent treatment of patients who have completed the first 4 cycle HIFU/FOLFIRINOX combined treatment is determined and performed in accordance with the CT findings, the overall condition of the patient, and the standard care guidelines. The implementation of surgery, continuation of FOLFIRINOX chemotherapy, conversion to other anticancer drugs, and further radiation therapy can be considered as possible treatments. This assessment is conducted after 8 or 12 cycles of treatment if the treatment continues for FOLFIRINOX chemotherapy, and will be determined later in accordance with the standard care guidelines. If surgery is performed after 8 or 12 cycles, additional (Adjuvant) chemotherapy may be performed according to surgical and pathological findings and should be determined in accordance with the standard care guidelines.

11. Observation Items, Clinical Examination Items, and Observational Inspection Methods

	Screening	Period of combined treatment and follow-up observation						
Visits		V1 (Cycle1**)	V2 (Cycle2)	V3 (Cycle3)	V4 (Cycle4)	V5	V6	V7
Days elapsed	≤ -4W	Day1	Day15	Day29	Day43	After four-cycle treatment (Month 2)	Two months after four-cycle treatment (Month 4)	Four months after four-cycle treatment (Month 6)
Visit window		-*	± 14 days	± 14 days	± 14 days	± 14 days	±28 days	±28 days
Observation Form	Visiting	hospitalization	hospitalization	hospitalization	hospitalization	outpatient/ hospitalization	outpatient /hospitalization	outpatient /hospitalization
Consent acquisition	√							
Inclusion/Exclusion Criteria	√							
Demographic Survey[1)]	√							

Pregnancy Test[2)]		√						
Vital Signs[3)]		√	√	√	√	√	√	
Physical Examination[4)]		√						
Medical History[5)]		√						
Ultrasound[6)]		√						
KPS evaluation[7)]		√				√		
CT Imaging[8)]		√				√†	√†	√†
Blood Test[9)]		√	√	√	√	√	√	√
CA-19-9[10)]		√				√	√	√
NRS Pain Assessment[(11)]		√				√	√	√
Survival rate[12)]						√	√	√
Combined treatment	Anticancer drug medication[13)]		√	√	√	√			
	HIFU treatment[14)]		√	√	√	√			
Adverse events/Serious adverse event[15)]			√	√	√	√	√	√	√
Concurrent medication and treatment[16)]			√	√	√	√	√	√	√
Immune analysis [17)]			√	√	√		√		

* Based on the first date of chemotherapy

** Cycle: Anti-cancer drug administration interval according to FOLFIRINOX standard treatment protocol, FOLFIRINOX is administered every two weeks, so it becomes a cycle of two weeks. The first anti-cancer drug administration cycle will be one cycle and the next two weeks later.

Visit 5: Visit for CT scanning and other examinations immediately after completion of 4 cycles of cancer.

Visit 6: Visit for CT scanning and other examinations 2 months after Visit 5. Subject's visit is terminated with Visit 5 if surgery is performed based on the findings of CT performed on Visit 5.

Visit 7: Visit for CT scanning and other examinations 4 months after Visit 5. Subject's visit is terminated with Visit 6 if surgery is performed based on the findings of CT performed on Visit 6.

† CT scan: CT for response assessment is usually performed during an outpatient visit before the next chemotherapy treatment, but if he/she is a local resident or there are any special circumstances, CT is performed during hospitalization for the next chemotherapy treatment.

1. Demographic Survey

date of birth, gender, height, weight record

2. Pregnancy test

In the case of fertile women, urine hCG test is performed prior to the procedure to confirm pregnancy, and those who have been confirmed pregnant are excluded from this clinical trial.

3. Vital signs

Body temperature, blood pressure, pulse rate, respiration rate, and oxygen saturation

4. Physical examination

examination of appearance, skin, head and neck, thoracic cage/lung, heart, abdomen, genitourinary system, extremities, musculoskeletal system, nervous system, lymph nodes, and other organs

[5] Past medical history

Medical history within the past one year

[6] Ultrasound examination

For subject screening, the presence or absence of abdominal scarring and surgical clips in the passage through which the ultrasonic beam passes are checked. It is also checked if adequate acoustic window for HIFU procedure is secured.

[7] KPS Evaluation

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disable; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

The Karnofsky Performance Status (KPS) is evaluated, and those with a KPS index of less than 70% during screening are excluded from the subjects subject to this clinical trial.

[8.] CT exam

To evaluate the size change and tumor response of pancreatic cancer by the combined treatment, the size of pancreatic cancer tissue is measured by computed tomography (CT) before and after treatment. It is measured with the longest length in the axial image of CT with the largest pancreatic tumor visible. It is also determined whether or not metastasis is present.

[9.] Blood test

Specific test items for blood test are as follows.

Purpose	items
Complete Blood Count	Hemoglobin, Hematocrit, Red blood cell count, White blood cell count with differential, Platelet count
Renal function	Blood urea nitrogen(BUN), Creatinine
Liver function	serum Aspartate aminotransferase(AST), Alanine aminotransferase(ALT), Albumin, Bilirubin
Pancreatic function	Amylase, Lipase

[10.] CA19-9

Measure serum CA19-9 levels to observe significant changes after HIFU treatment.

[11] NRS pain assessment

For the evaluation of pancreatic cancer-related pain, a survey using a numerical rating scale (NRS, 0-10 points) is performed.

[12.] Survival rate

The duration of the subject's life from the diagnosis date of pancreatic cancer or from the combined treatment date to the date of death is tracked and observed for the evaluation of survival rate.

[13-14] Anti-cancer Drug Administration & HIFU Treatment

The subjects registered in this clinical trial are treated with anticancer drugs on the scheduled date of treatment and receive HIFU procedures in accordance with ALPILUS 900 User Manual within 24 hours of administration. A total of four combined treatments are performed for eight weeks.

[15.] Adverse events/Serious Adverse Events

Evaluate in accordance with the criteria defined in chapter 14 of the clinical trial proposal and record them in the case report form.

[16] Concomitant medication and treatment

Drugs and treatment activities that may affect the results of this clinical trial are prohibited, and all medications already taken due to underlying diseases are recorded during screening, and only additional medications and treatment activities are recorded in the case report form

[17] Immune analysis

Perform phenotypic analysis of leukocytes with flow cytometry analysis of blood samples just before HIFU-chemo treatment at each visit to prove if any immune reaction occurs during the treatment by the help of an immunology professor in our college (Kim HR, 20 years' experience in cell immunology). All remaining blood samples for immune analysis will be stored in deep freezer.

* Phenotypic analysis of leukocytes

	Set1	Set2	Set3

	viable dye	viable dye	viable dye
	CD45	CD45	CD45
1	CD19	CD4	CD4
2	CD27	CD8	CD8
3	IgD	CCR7	CD25
4	CD38	CD45RA	PD-1
5	CD24	IL-7Rα	FoxP3
6	CD14	PD-1	Ki-67
7	CD16	Tim3	GzmB
8	CD56	Lag3	T-bet
9	TCRγδ	CD38	Tcf1
10	TCRαβ	CTLA-4	Tox

Set1: B-cell subsets (naive, memory, regulatory B cells, and plasma/plasambalst), monocyte-subset (classical, intermediate, and inflammatory monocytes), $CD56^{bright}$t NK (regulatory), $CD56^{dim}$ NK cells, αβ T cells, γδ T cells

Set2: Effector/memory T-cell subsets (CD4 and CD8 T-cell subsets), exhausted/activated phenotype of T cells (immune checkpoint molecules: PD-1, Tim-3, Lag3, CD38, CTLA-4).

Set3: regulatory T cells (FoxP3), proliferating T cells (PD-1, Ki-67+), effector molecule expression (granzyme B), and effector/memory/exhausted subsets by transcriptional factors (T-bet, Tcf1, and Tox)

12. Expected Adverse Events

12.1 Expected Adverse Events by HIFU

① Skin burns, bleeding, or infections in the treatment area;

② Subcutaneous fat sclerosis

③ Abdominal pain

④ Pancreatitis

⑤ Tumor hemorrhage

⑥ Peritonitis

⑦ Jaundice

⑧ Vascular injury (aortic rupture)

⑨ Pancreatoduodenal injury and perforation.

⑩ Gastric injury and perforation

⑪ Bowel necrosis

12.2 Expected Adverse Events by Anticancer Drugs

① Thrombocytopenia

② Neutropenia

③ leukopenia

④ Anemia

⑤ Lymphopenia

⑥ Febrile neutropenia

⑦ Hair loss

⑧ Peripheral sensory neuropathy

⑨ Lacking appetite

⑩ Rash

⑪ Nausea

⑫ Dullness

⑬ Fatigue

⑭ Diarrhea

⑮ Alanine aminotransferase (ALT) increase

16 Hyponatremia

13. Clinical Trial Suspension and Termination Criteria

13.1 Suspension Criteria

① If it is deemed that the conditions observed during the clinical trial are unreasonable to continue the clinical trial, the clinical trial PI may suspend the clinical trial, and shall immediately notify the IRB of this fact and submit a detailed statement of reasons for early termination and suspension.

② Clinical trials may also be suspended in the event of a life-threatening adverse event/ adverse device effects or for the treatment of an adverse event occurring.

13.2 Termination Criteria

① When the subject or legal representative requests discontinuance of participation in clinical trials;

② When surgery, medication, or medical devices that may affect safety and validity are used in combination

③ When it is impossible to continue participating in a clinical trial due to a serious adverse event.

④ When the measurement method is not performed properly

⑤ When the subject fails to comply with the instructions of investigator or fails to comply with the conditions given in the consent form, which affects the evaluation of the validity of the study

⑥ When clinical trial personnel determine that there is a problem with the progression of clinical trial

13.3 Suspension Process

① In case that the clinical trial is suspended, record and store the reason for the suspension and data related to the clinical trial conducted before the suspension, and submit a statement of reasons to the IRB.

② If the clinical trial is suspended, appropriate measures and follow-up monitoring shall be taken.

③ Suspended subjects are excluded from the validity assessment.

13.4 Termination Process

① 1 In the case of termination from a clinical trial, the reason for the termination and data related to the clinical trial conducted before termination shall be recorded and stored, and a statement of reasons shall be submitted to the IRB.

② Date collected until the subjects are dropped out are included in safety analysis and excluded from the validity assessment.

14. Efficacy and Safety: Evaluation Criteria, Evaluation Methods and Reporting Methods

14.1 Efficacy Evaluation..

14.1.1 Efficacy Variables

<Primary endpoints>

1) Tumor response on CT after 2 months, 4 months and 6 months after the start of combined treatment

2) Percentage of subjects who were subject to surgical resection 4 months and 6 months after the start of combined treatment

<Secondary endpoints>

1) Time-to-Progression

2) Survival time

14.1.2 Evaluation Criteria and Methods

Efficacy variables were based on clinical studies to investigate the effectiveness of the FOLFIRINOX neoadjuvant chemotherapy. [23-27]. These efficacy variables are commonly used in clinical trials for conventional anticancer drugs, and the same variables are used in this study because HIFU is an auxiliary equipment used to enhance the efficacy of chemotherapy. **Tumor response** is to evaluate tumor reaction by anticancer drugs by size and is the primary and most widely used evaluation method for evaluating tumor reactions. **The percentage of subjects that were subject to surgical resection** is a measure that must be addressed in view of the curative effects of pancreatic cancer patients by FOLFIRINOX. Both LAPC and BRPC are tumors that are either impossible or seemingly impossible to surgical resection, and when the invasions of vital vessel become smaller or eliminated by the effects of anticancer drugs, they can be treated by surgical resection, which can produce a better outcome. Although many patients are reported to be able to be operated on after the completion of the eight-cycle FOLFIRINOX chemotherapy, or four months after the start of chemotherapy [23], the percentage of subjects who are subject to surgical resection after the 12-cycle treatment (or 6 months after start of the combined treatment) was also evaluated in this study, as surgery is often performed between one and two months after the last anti-cancer treatment, or six months after the start of chemotherapy. Both **tumor progression and overall survival rate** are essential measures used to see prognosis in chemotherapy. [24-27]. The success criteria of clinical efficacy are statistically significantly higher than the historical cohort.

1) Tumor response on CT taken 2 months, 4 months and 6 months after the start of combined treatment

Based on CT findings taken 2 months, 4 months, and 6 months after the start of combined treatment (each cycle is 14 days), 2-month, 4-month, and 6-month tumor responses are evaluated with complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria In Solid Tumors (RECIST, Ver 1.1)

Table> Response Evaluation Criteria In Solid Tumors (RECIST, Ver. 1.1)

Classification		Criteria
CR	Complete Response	Disappearance of all lesions and pathologic lymph nodes
PR	Partial Response	≥ 30% decrease in the sum of longest diameters of targeted lesions
SD	Stable Disease	Neither PR nor PD
PD	Progressive Disease	≥ 20% increase in the sum of longest diameters and ≥ 5 mm absolute increase in the sum of longest diameters or new lesions

Reference) Watanabe H, Okada M, Kaji Y, Satouchi M, Sato Y, Yamabe Y, Onaya H, Endo M, Sone M, Arai Y.New response evaluation criteria in solid tumours-revised RECIST guideline (version 1.1)Gan To Kagaku Ryoho. 2009 Dec; 36(13):2495-501.

2) Percentage of subjects who were subject to surgical resection 4 months or 6 months after the start of combined treatment

When surgery is determined according to AJCC(American Joint Committee on Cancer, 8 edition) guidelines based on computed tomography (CT) images taken at 8th and 12th cycles (4M, 6M) after the onset of the combined treatment, the percentage of subjects who were able to be operated on compared to the total number of registered subjects is calculated.

3) Time-to-Progression

The time taken from the date of diagnosis of pancreatic cancer or from the start date of combined treatment of pancreatic cancer until the date of first documented progression, assessed up to 24 months. Judging by RECIST ver. 1.1

4) Survival time

The time taken from the date of diagnosis of pancreatic cancer or the start date of combined treatment of pancreatic cancer until the date of death from any cause, assessed up to 24 months

14.2. Safety Evaluation

14.2.1 Safety Variables

All adverse events that occurred to the subject during the clinical trial period.

14.2.2 Evaluation Criteria and Methods

The safety assessment is observed for all adverse events that occurred from the start of the first cycle of chemotherapy and HIFU combined therapy to the end of the clinical trial as follows:

All undesirable medical findings that are newly observed during clinical trial are classified as an adverse event. Side effects predicted according to the definitions and criteria described in the section "14. Evaluation Criteria, Evaluation Methods, and Reporting Methods for Safety including Side Effects" are also classified as adverse events. The degree of adverse events caused by medical devices is graded according to the NCI-CTCAE (Version 4.03) criteria, and the use of terms in medical coding is based on MedDRA's "Preferred Term" and "System organ class". However, in case of an adverse events that do not have any applicable items, write 'Other' of the appropriate 'Categories' and record the details and select the appropriate grade from grade 1-5 (see 14.3.1 Severity Degree Assessment Section).

14.3. Data Collection and Statistical Analysis

All data measured and recorded in this study will be summarized according to the definition of the appropriate analysis group as defined in 14.3. Summary statistics are based on average ± standard deviation for continuous data and frequency (percentage) for categorical data.

14.3.1. Definition of Analysis Group

[Efficacy Analysis Group]

The demographic information is analyzed for the FAS analysis group, and the efficacy analysis is conducted for the FAS and PP analysis groups respectively.

- Full Analysis Set (FAS): It is the main analysis group of the efficacy assessment of this study and is defined as all subjects who, after agreeing to participate in the study, are treated with the device for clinical trials and have more than one effective assessment data.

- Per Protocol Analysis Set (PP): It is defined as all subjects who after agreeing to participate in the study, are treated with the device for clinical trial and have finished the clinical trial in accordance with the study plan without significant research plan violations until the end of the study. Any concomitant medication or alternative treatment that affects efficacy during the clinical trial period is excluded from the PP analysis group.

☞ Significant research contract violations:

① In case of violation of inclusion and exclusion criteria

② In case of taking a prohibited medication or a prohibited medical treatment that affects the efficacy evaluation during the clinical trial period.

[Safety Analysis Group]

The safety assessment is performed in the SAS analysis group.

- Safety Analysis Set (SAS): After agreeing to participate in the study, SAS is defined as all subjects who have received at least one combined treatment.

[Processing of missing data (missing value)]

If missing values occur in the efficacy variables, they are excluded from the analysis.

14.3.2 Statistical analysis methods

[General analysis]

For demographic information, continuous data are summarized in descriptive statistics (numbers, means, standard deviations, median, minimum and maximum), while categorical data are presented with frequency and fraction. This study is an exploratory study and therefore does not necessarily require a statistical hypothesis validation. However, if a statistical validation is possible or necessary, but both tests are carried out at a significant level of 5% unless they are specifically stated where statistical tests are possible or necessary. unless specifically stated, a two-sided test shall be carried out at a significant level of 5%. All statistical analyses are conducted using the MedCalc (ver 19.4.1) statistical program. Regarding covariate variables related to chemotherapy, since patients with past-medical history of previous anticancer treatment for pancreatic cancer are excluded by exclusion criteria, and FOLFIRINOX regimen are fixed variables, previous anticancer medication, drug type, medication interval, and medication method are all controlled. Therefore, the covariates related to chemotherapy will proceed in a controlled state, but if there are other uncontrolled variables, they will be corrected by using 1) multivariate regression, 2) propensity score matching, or 3) inverse probability of treatment weighting.

[Analysis of Efficacy Variables]

Primary endpoints

1) Tumor response after 4th, 8th, and 12th cycles (2M, 4M, 6M)

- The tumor response measured at each time point is presented with the number and percentage of subjects for each tumor response category (CR, PR, SD, PD).

2) The percentage of operated subjects to total subjects after 8 or 12 cycles (4M, 6M)

- The number and percentage of subjects who are subject to operation at each time point shall be presented.

Secondary endpoints

3) Time for tumor progression and overall survival rate are estimated using the Kaplan-Meier method.

4) After the initial analysis, for comparison with a standard FOLFIRINOX treatment, the control group is established by performing matching with clinical trial group, using the following variables in the histological cohort treated with LAPC/BRPC in our institute

- Location of pancreatic cancer tumors (head-uncinate/neck-body/tail), size of tumors, presence and degree of vascular invasions (SMA, Celiac Axis, common hepatic artery, SMV, MPV), age, sex, CA19-9 at the time of diagnosis

5) In the control group, tumor response after 4th, 8th, and 12th cycles (2M, 4M, 6M) ia evaluated and compared with test group using the chi-square test.

6) the percentage of patients who were able to be operated on after 8 or 12 cycles (4M, 6M) is calculated from the control group and compared with test group using the chi-square test.

7) Time for tumor progression and survival rate are estimated in the control group and compared with the test group using log-rank test.

- Consideration of potential covariates: For major covariates related to chemotherapy, a stratification analysis is conducted for each evaluation variable to evaluate its effects.

[Analysis of Safety Variables]

All adverse events that occurred during the clinical trial period are classified into 'System Organ Class' of MedDRA (ver 18.0) and 'Preferred Term' and presented as the number of subjects, proportion (%) and number of cases for each degree.

15. Evaluation Criteria, Methods and Reporting of Adverse Events

15.1 Definition of Adverse Events

① "**Adverse Event (AE)**": Any untoward medical occurrence, unintended disease or injury or ant untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device

② "**Adverse Device Effect (ADE)**": All harmful and unintended reactions caused by medical devices for clinical trials, which cannot exclude causality with medical devices for clinical trials.

③ "**Unexpected Adverse Device Effect**" refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information..

15.2 Serious Adverse Events/Adverse Device Effect: Definition

Serious adverse event/adverse device effect refers to any of the following adverse events caused by medical devices used in clinical trials:

① Resulted in death or a life threatening illness or injury

② Required in-patient hospitalization or prolongation of existing hospitalization .

③ Resulted in a permanent impairment of a body structure or a body function

④ Resulted required in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment of a body structure or a body function

15.3 Evaluation of Adverse Events

15.3.1 Severity Evaluation

The severity of adverse events is assessed according to the NCI-CTCAE (Version 4.03) criteria. However, in case of an adverse event with no applicable item, 'Other' of appropriate 'Categories' shall be written and the details shall be recorded, and the appropriate grade shall be selected according to the definitions below.

Grade	Explanation
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse events.

15.3.2 Evaluation of Causal Relationships with Medical Device

Causality	Evaluation criteria
Definitely related	• The relationship between the occurrence of adverse events and the use of the medical device is reasonable, and is most likely explained by the use of the medical device than for any other reason. • Symptoms of adverse events disappear by discontinuance of the medical device, and hazardous cases appear when reused (performed only if reusable). • The occurrence of an adverse event is consistent with the information already known about the medical device or its affiliated medical device.
Probably related	• There is evidence that the medical device has been used, the time order of the use of the medical device and the occurrence of adverse events is reasonable, and is more likely to be explained by the use of the medical device than by other causes. • Symptoms of adverse events disappear by the discontinuation of the medical device

Possibly related	• There is evidence that the medical device has been used, and the time order of the use of the medical device and the occurrence of adverse events is reasonable, and it is deemed to be due to the use of the medical device at the same level as other possible causes. • Symptoms of adverse events disappear by the discontinuation of the medical device
Possibly not related	• There is evidence that the medical device has been used, there is a more likely other cause for adverse events, and disappearance of the symptoms of adverse events by discontinuation of the medical device is present or ambiguous • Symptoms of adverse events are not shown or ambiguous at reuse of the medical device (performed only if reusable)
Definitely not related	• The medical device is not used or the time order of use of the medical device and adverse event development is not appropriate; • There are other obvious causes for adverse events.
Unknown	• Cannot be determined because of insufficient or conflicting information and cannot be supplemented or verified;

The investigator shall evaluate the relevance of the medical device in the event of adverse events and describe the investigator's opinion according to the criteria above.

15.3.3 Evaluation Criteria .

In this clinical trial, an adverse event is defined as all undesirable medical findings that symptoms occur that are not observed before the start of the clinical trial. The predicted side effects are also classified as adverse events, and the degree of adverse events is classified into 5 grades according to the NCI-CTCAE (Version 4.03) criteria, and the use of terms is reported using the 'System Organ Class' and 'Preferred Term' of MedDRA (ver 17.0).

15.3.5 Serious Adverse Events/Adverse Device Effect Reporting

Subinvestigator shall immediately report all serious adverse device effects to the PI during the clinical trial period. The PI shall record the reported adverse events/adverse device effects in the Serious Adverse Event CRF and report them to the KFDA and the IRB within 24 hours, regardless of whether they are related to the use of medical devices for clinical trials. In such cases, the PI shall use the identification code on behalf of the subject's personal information, such as the subject's

name, social security number, and address, in order to protect the subject's confidential information, and shall comply with the instructions for reporting adverse events.

In addition, significant risks, taboos, side effects, or events requiring cautions that the PI considers critical or related to the use of the medical device shall be recorded as Serious adverse events/Adverse Device Effect CRFs and reported immediately to the KFDA and the IRB.

When reporting the case of death, the PI shall submit additional information, such as an autopsy report (applicable only to cases of autopsy) and a death certificate, to the KFDA and the IRB.

The PI shall report serious and unexpected adverse events (including adverse device effects, serious AE/ADE) to the KFDA as soon as possible within the period specified in the following:

1) In the event of death or life-threatening, additional information shall be reported within seven days from the date the PI receives or becomes aware of this fact, and the detailed information within eight days from the date of initial report.

2) In the event of all other serious or unexpected AEs, the PI shall report them within 15 days from the date the PI receives or becomes aware of them.

3) The PI shall regularly report additional safety information regarding serious AE/ADE until the relevant AEs are terminated (e.g., the loss of such AE or the inability to conduct follow-up investigations).

4) If the PI intends to report ADEs to the Minister of KFDA according to the 1) and 2) above, PI shall submit a ADE CRF in accordance with the Medical Device Clinical Trial Management Standards (No. 7 Camok 1 of KGCP's attached Form 56 ADE report), along with a prompt report on the ADE in accordance with attached Form 55.

16. Informed Consent

A written consent form must be received from each subject (or the subject's legal representative) before a screening assessment for clinical trials is conducted. Before starting the trial, clinical trial investigators should give patients who have met both inclusion and exclusion criteria and their guardians in-detail explanations of all aspects of the trial and sufficient time to enable to understand all foreseeable outcomes. A copy of the signed consent form shall be kept by the subject and the original by the researcher.

Clinical trial researchers shall prepare and keep a list of all patients who have agreed to participate in clinical trials.

Subjects should be informed of the fact that the subject's trial-related data will be used by the researchers and the level of disclosure in accordance with the relevant regulations for clinical trials.

It should also inform the subject that the subject's medical records may be reviewed by the clinical trial monitor personnel or auditors, IRB or health authorities on-site inspection personnel.

If the clinical trial plan is amended, the subject's consent form and the subject's consent manual may be amended to reflect the change in the plan. Where the subject's consent form and the consent documentation are amended, they shall be reviewed and approved by the IRB and the newly registered and currently participating subjects shall be explained according to revised content and sign on the revised consent form.

17. Protocol for Compensation for Victims

In the event of damage caused by the use of medical devices or clinical procedures that the subject would not have received if he did not participate in this clinical trial, all treatments will be taken in accordance with the hospital's standard procedures, and in the case of damage associated with the clinical trial, compensation for damage will be made in accordance with the victim's compensation protocol and the terms of the clinical trial insurance policy.

18. Matters Concerning Treatment of Subjects after Clinical Trial.

If the subjects are dropped out of the clinical trial due to AEs, or if there are any residual symptoms from side effects and AEs after completion of the clinical trial, sufficient treatment will be provided in accordance with the hospital's standard medical guidelines until recovery by performing appropriate medical measures for the AEs that have occurred, and those whose clinical trials have been completed without any AEs will be subject to general clinical observation following the hospital's standard procedures after the clinical trials.

19. Measures for Safety Protection of Subjects

19.1 Good Clinical Practice for Medical Devices (KGCP) and Helsinki Declaration

The procedures set out in this proposal are designed to ensure that the PI and investigators comply with the basic spirit of the ICH-GCP and the Helsinki Declaration in conducting, evaluating, and recording the results. This clinical trial will also be carried out in accordance with domestic laws (medical device clinical trial management standards, KGCP).

19.2 Institutional Review Board (IRB)

Prior to commencement of clinical trials, the researcher shall submit the clinical trial proposal, subject consent form, and materials and documents related to the recruitment of subjects (e.g., advertising) to the IRB for review and approval.

Any changes to the proposal that require approval from the IRB and the KFDA will not be applied to the clinical trial until the IRB reviews and approves the revised clinical trial proposal and, if

applicable, the revised subject consent from. Any changes of clinical trial proposal to eliminate immediate risk factors for subjects may be applied immediately on the condition that they are notified to the KFDA and the IRB and requested approval as soon as possible. Changes to the proposal related to administrative procedures, such as changes in monitor personnel, changes in subinvestigator, changes in emergency contact numbers, etc., may be applied immediately even before approval by the IRB.

The PI shall provide the clinical trial result report, latest information, and other information (e.g., safety update) to the IRB in accordance with the relevant regulations or procedures in the hospital.

19.3 Measures for Safety Protection of Subjects

Once new information is obtained that may affect the continuation of this clinical trial, it will be provided to subject or subject's representative in a timely manner, and the researchers will discuss with the subjects whether or not to continue participating in the clinical trial.

19.4 Clinical Trial Institution

The head of the institution shall ensure that clinical laboratories, equipment, and professional personnel necessary for carrying out the clinical trial are equipped and shall ensure that the clinical trials are carried out properly, such as allowing necessary measures to be taken in case of emergency.

19.5 Investigator

The term "investigator" means PI, co-investigator, and subinvestigator. The investigators shall conduct the clinical trials in compliance with the clinical trial plan approved by IRB and the Minister of KFDA.

① During or after a clinical trial, the investigator shall take measures to ensure that the subjects receive appropriate medical treatment for all AEs in the clinical trial, including clinically meaningful laboratory tests, and inform the subjects in case that medical treatment is required for the subjects' concurrent diseases that the investigators has become aware of.

② In accordance with paragraph 14.6.3. Serious AE/ADE, the PI shall be obliged to report AEs reported by the subinvestigator to the KFDA and the IRB.

③ The investigators shall accurately analyze and understand the clinical trial plan and actively respond to the subject's problems.

20. Others: Matters Necessary for Conducting Clinical Trial Safely and Scientifically

20.1 Confidentiality

20.1.1 Data

The investigators shall observe confidentiality of all information relating to the trial plan provided by the clinical trial monitor personnel. Exceptions are made to IRB, subjects, or health authorities that require disclosure in accordance with laws or related regulations.

20.1.2 Anonymity of Subjects

The anonymity of subjects involved in clinical trials must be ensured. The identification of the subject shall consist of the subject's initials and the subject number specified in the CRFs and other data submitted to the clinical trial monitor. Inform the subjects that all trial materials are stored on the computer and are strictly confidential. The signed consent forms shall be kept by the PI. The PI keeps a list of subjects' numbers and names so that they can find the records later. Subject consent forms and list of subjects shall be kept for three years.

Materials for identifying subjects should be strictly confidential by researchers. Exceptions shall be made if necessary for audit by health authorities, clinical trial monitors, or designated agents.

20.1.3 Privacy Protection Methods

The personal information of the subjects who participated in the clinical trial is used up to six months after the end of the study, and the collected information is properly managed in accordance with the Personal Information Protection Act. The personal information is not provided to other people except researchers but is kept confidential. Records that can be identified shall be anonymized by assigning a management number. Research-related data shall be kept in a place where there is a locking device, and access is prohibited other than those involved in the research. In addition, personal information will be kept for three years after the completion of the research and will be discarded afterwards.

Personal information, including research participation records and medical records, is provided only to those in charge. Exceptions shall be made if necessary for audit by health authorities, clinical trial monitors, or designated agents.

20.2 Compliance and Change in Clinical Trial Protocol

If it is necessary to change the contents of this proposal during clinical trials, the revised proposal shall be prepared by the PI. The investigators shall not apply any changes to the clinical trial until

obtaining approval from the IRB, except to immediately prevent harm to the subject. Significant proposal violations shall be recorded in the CRF.

If a modification or change of the clinical trial proposal is applied before obtaining approval from the IRB to prevent any immediate harm to the subject, such modification or change shall be submitted to the IRB (for future approval) and the KFDA (if required by relevant regulations) as soon as possible.

Significant changes in the clinical trial proposal include changes affecting the safety of the subject, changes in the scope of the study, changes in the scientific query of the clinical trial, changes in the experimental design, changes in evaluation variables, changes in the number of subjects, and changes in the inclusion criteria of subjects. These changes must be recorded and will be provided as data to demonstrate their validity.

The PI must prepare these changes with the revised clinical trial proposal, and the revised clinical trial proposal must be approved by the IRB or the relevant authorities before implementation.

Regarding the procedure for changing the clinical trial proposal, revised version of the original approved one will be submitted to the grant authority in parallel with the progress of IRB approvals. If the modified clinical trial proposal requires a change in the consent form, it must be approved by the IRB.

Urgent deviance from the clinical trial proposal to exclude obvious and urgent risks of a particular subject involved in a clinical trial is considered critical for the safety and well-being of the subject and can only be implemented for that particular subject.

If the changes in the clinical trial proposal are minor, it is sufficient for the PI to notify the IRB. However, if there is an inherent change in the clinical trial design or an increased risk to the subject, 1) the subject's consent form must be modified and submitted to the IRB for review and approval, 2) If such a change affects the subjects, new consent must be obtained from the subjects already recruited for the clinical trial with the newly modified consent form, and 3) new consent form should be used to obtain their consent from newly enrolled subjects.

20.3 Clinical Trial Monitoring

Monitoring Responsibility : PI Jae Young Lee, Prof.

Clinical Trial Monitor : Hyun-Ji Kim, CRA / Synex Consulting Ltd.

Prior to the start of the clinical trial, the PI, co-investigators and sub-investigators will hold a meeting of researchers or a meeting of clinical trial initiation for this clinical trial. The meeting will discuss in detail the clinical trial plan, the performance of clinical trial procedures, the preparation of CRFs, the methods of examination, etc. Researchers who are unable to attend such meetings or meetings or

who will later participate in clinical trials should be properly trained by the PI or by the person authorized by the PI.

The PI shall provide guidance and data to the co-investigators in a proper way and have the monitoring personnel responsible for this clinical trial monitor the progress and data before and during the clinical trial period. In order to ensure that the study is conducted in accordance with KGCP and that trial data can be recognized at home and abroad, the PI may conduct monitoring and auditing. The monitoring personnel explain the monitoring plan to the researchers before starting the clinical trial, and monitor the data and safety information at least three times during the clinical trial period to verify if the researchers perform the clinical trial in accordance with the clinical trial plan and the relevant regulations. Clinical trial monitors routinely visit and contact researchers, and are authorized to monitor various records of clinical trials.

It is the responsibility of the clinical trial monitor to monitor the CRFs regularly throughout the clinical trial period to demonstrate the completeness, consistency and accuracy of the recorded data and to demonstrate that the recorded data was faithful to the clinical trial plan. The findings should be properly discussed with the investigators. The investigators shall appropriately inform the clinical trial monitor personnel of any findings during the clinical trial and cooperate with the monitoring activities.

20.4 Record and Use of Trial Results

20.4.1 Case Report Form and Source Document

All information required for clinical trials should be recorded on the corresponding case report form (CRF) page. In addition, the investigators must sign the investigator's signature column in each CRF to ensure the accuracy of the data.

The investigators should allow direct access to source data and source documents during monitoring, inspection, IRB review and on-site inspection related to clinical trials. The original CRFs of each subject will be verified by the clinical trial monitor personnel against source documents in the clinical trial institution.

The PI shall maintain and provide clinical trial essential documents. Essential documents for clinical trials refer to documents that enable individual or overall evaluation of the performance of clinical trials and the quality of data obtained from them. Essential documents for clinical trials include source documents, which include hospital records, medical records, clinical laboratory test results, subjects logs, various examination papers and records kept by pharmacies, pathology laboratories, and medical and technical departments involved in clinical trials.

Source documents, CRFs, and other clinical trial-related documents shall be kept in the testing institution, and the PI shall retrieve the original copy and keep a copy in the testing institution. Investigators shall keep all records related to clinical trials until the KFDA completes inspection, and keep them until the deadline set by the PI after the inspection is completed.

20.4.2 Storage of Clinical Research Data

All CRFs and data and management logs provided shall be stored for three years from the end of the clinical trial. No clinical research material shall be destroyed or transferred to another location without prior written consent of the PI. If an investigator is excluded from the clinical trial due to relocation or retirement or other reasons, he/she shall notify the PI and agree to appropriate solutions.

Investigators shall retain the clinical medical device use records, copies of the CRFs and source data related to clinical trials for a period of three years as prescribed by local regulations.

In addition, all clinical research materials listed above shall be disposed of by requesting a disposal company after a list of disposal documents and reasons for disposal are written in the document disposal records in accordance with the agency's SOP after three years of preservation.

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