

Perioperative Stromal Depletion Strategies in Pancreatic Ductal Adenocarcinoma

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

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PROTOCOL SYNOPSIS

TITLE	Perioperative Stromal Depletion Strategies in Pancreatic Ductal Adenocarcinoma
RATIONALE	<p>Pancreatic ductal adenocarcinoma (PDAC) continues to be a challenging cancer to treat secondary to its advanced stage at the time of diagnosis, its aggressive behavior and its resistance to treatment [1, 2] While surgery provides the highest chance of cure for patients with localized PDAC, patients with either upfront resectable or borderline resectable disease may benefit from neoadjuvant therapy to select appropriate candidates for potentially curative operation, eradicate micrometastases, and increase the likelihood of R0 resection rate.</p> <p>The PDAC tumor microenvironment is complex and consists of multiple components including pancreatic stellate cells (PSC), endothelial cells, immune cells and fibroblasts with an extensive paracrine and autocrine network residing in a stiff extracellular matrix [2-5]. The desmoplastic reaction that is characteristic of the PDAC stroma [6, 7] has been associated with <u>increased cell proliferation and migration leading to metastasis</u> in PDAC [8-11], while it disturbs the pancreatic tissue architecture by <u>changing the layout of blood and lymphatic vessels</u> [7, 12]. Extracellular matrix in PDAC stroma also distorts the organization of capillary network, creating a hypoxic environment, which leads to “<i>disorganized, dysfunctional and permeable</i>” vasculature of PDAC [13]. As a component of the desmoplastic reaction, differentiation of PSC leads to accumulation of <u>hyaluronan (HA)</u> [14], a <u>glycosaminoglycan polymer</u>, which causes increased tumor interstitial fluid pressure (IFP) [15, 16]. The changes in pancreatic tissue architecture and increased IFP have been shown to <i>compress the tumor vasculature and hinder delivery of chemotherapy</i>, which may account for the resistance of PDAC to therapy [3, 17]. Preclinical studies with PEGPH20, which is pegylated recombinant human hyaluronidase and gemcitabine was associated with <u>reduction in IFP, increase in vessel diameter</u> and an <u>increase of 83% in median overall survival</u> in mice treated with gemcitabine and PEGPH20 [18].</p>
STUDY DESIGN	<p>This is a Phase II study investigating PEGPH20 in combination with gemcitabine and nab-paclitaxel in patients with both upfront resectable as well as borderline</p> <p>This trial will be conducted in two parts. In Part I, pre-treatment endoscopic ultrasound (EUS)-guided core biopsies of the</p>

	<p>pancreatic tumor and functional MRIs (fMRIs), including DCE-MRI and DWI-MRI, will be obtained for the first fifteen patients enrolled as outlined in Figure 1. After a 1-week run-in period with PEGPH20 on days 1 and 4, these patients will have repeat EUS-guided core biopsies, functional MRI, and undergo baseline CT/MRI of the chest, abdomen and pelvis.</p> <p>The following week after completing the 1 week run-in, patients in Part 1 will be started on treatment with PEGPH20, gemcitabine and nab-paclitaxel. PEGPH20, gemcitabine and nab-paclitaxel will be given weekly for 3 weeks, every 28 days. To evaluate the disease response to treatment, CA 19-9 levels will be checked monthly and restaging CT/MRI of the chest, abdomen and pelvis will be obtained every 8 weeks. If there is disease progression at any point in the study, patients will be taken off of study and alternative treatments will be offered. At the completion of 4 cycles of therapy, restaging CT/MRI scans will be obtained to determine resectability. If the patients are found to have resectable disease, an additional functional MRI will be obtained to evaluate the PDAC stroma. For patients who are able to have successful surgeries, tissue analyses will be performed on the resected pancreatic tumor. These patients may proceed to receive 2 cycles of adjuvant chemotherapy (physician’s choice). If the patients are deemed to be surgical candidates but are found to have unresectable disease in the operating room, an intraoperative core biopsy of the pancreatic tumor will be obtained for tissue analyses.</p> <p>At the time of initiation of therapy with PEGPH20, patients will be started on prophylactic dose of enoxaparin 1 mg/kg subcutaneous daily. This will be continued throughout the study until at least 14 days after the last infusion of PEGPH20. Patients will also take dexamethasone 1-2 hours before receiving PEGPH20, and 8-12 hours after completion of PEGPH20 infusion.</p> <p>Two interim safety assessments will be performed when the first 7 and 15 evaluable patients are enrolled in the study. Interim analyses and stopping rules are detailed later in this protocol.</p> <p>If the study enters Part II, an additional 21 patients will be enrolled. Patients in Part II will begin neoadjuvant therapy with PEGPH20, gemcitabine and nab-paclitaxel <i>without</i> the 1 week run-in of PEGPH20 (including pre- and post-run-in EUS-guided biopsies and fMRIs and post run-in CT scan).</p>
<p>TEST PRODUCT, DOSE, AND ROUTE</p>	<p>PEGPH20, pegylated recombinant HA degrading enzyme, is administered intravenously at MTD of 3 ug/kg on Days 1 and 4</p>

OF ADMINISTRATION	during the run-in period. Subsequently, patients will be treated with PEGPH20, gemcitabine and nab-paclitaxel on days 1, 8 and 15 of a 28 day cycle. Nab-paclitaxel will be infused prior to gemcitabine. Patients will begin taking enoxaparin 1 mg/kg subcutaneously upon initiating treatment with PEGPH20 and continue until at least 14 days after the final PEGPH20 infusion. Patients will also take dexamethasone 8mg PO 1-2 hours pre-PEGPH20 and again PO in 8-12 hours post-PEG.
NUMBER OF SUBJECTS	The required number of post-operative patients is 25 evaluable patients for the study. We expect to enroll 36 patients total for required sample size. We will enroll 15 patients in the first phase of the trial. 21 patients will be enrolled in the expansion cohort in the second phase.
RATIONALE FOR NUMBER OF SUBJECTS	With a sample size of 25 evaluable patients, we will be able to estimate the 90% CI to be [4.5%-19.89%] or 95% CI to be [3.36%-23.07%].
PRIMARY OBJECTIVES	<p>a) To evaluate development of clinically relevant pancreatic fistula within the 7-day post-operative period after neoadjuvant treatment with PEGPH20, gemcitabine and nab-paclitaxel.</p> <p>b) To evaluate pathologic complete response after neoadjuvant treatment with PEGPH20, gemcitabine and nab-paclitaxel.</p>
SECONDARY OBJECTIVES	To evaluate early efficacy measured by percent change of CA 19-9 response rate, R0 resection rate, overall response rate (ORR) and disease free survival (DFS).
EXPLORATORY OBJECTIVES	<p>1) To evaluate the sequential effect of PEGPH20 on the fibrotic character and vascular perfusion of PDAC via functional MRIs.</p> <p>2) To determine degree of stromal depletion and effects of PEGPH20 on cell proliferation and apoptosis.</p>
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	<p>Treatment: 4 months of chemotherapy followed by surgical resection if the patient's tumor is deemed resectable post-therapy.</p> <p>Follow-up: Patients will be followed after completion of study until death, by either in-person evaluation or telephone contact by study personnel at 2-3 month intervals (or more frequently as indicated by their disease state).</p>

<p>PRIMARY ENDPOINTS</p>	<p>The incidence of pancreatic fistula within the 7-day post-operative period after neoadjuvant treatment with PEGPH20, gemcitabine and nab-paclitaxel.</p> <p>Rate of pathologic complete response after neoadjuvant treatment with PEGPH20, gemcitabine and nab-paclitaxel.</p>
<p>SECONDARY ENDPOINTS</p>	<p>Percent change of CA 19-9 response rate</p> <p>R0 resection rate</p> <p>Overall response rate (ORR)</p> <p>Disease-free survival (DFS)</p>
<p>EXPLORATORY ENDPOINTS</p>	<p>1) Tissue analyses pre-treatment and post-treatment with standard IHC staining for actin, hyaluronic acid staining with binding protein probe, proliferation as measured by ki-67% and Phospho-histone H3 (Ph-H3); cell apoptosis as evaluated by IHC stain for cleaved caspase 3 (CC3) and TUNEL. If limited tissue sample is obtained via the core biopsies, the priority of tissue analysis will be as follows: (1) fixed in formalin for H&E and IHC (Ph-H3; CC3/TUNEL; HA binding); (2) fixed in OCT such that IHC with can be done with antibodies directed to conformational epitopes, or to potentially obtain mRNA or DNA.</p> <p>2) Functional MRIs including Dynamic Contrast Enhanced (DCE), Diffusion Weighted Imaging (DWI) will be obtained to evaluate intratumoral perfusion and stromal density pre-treatment and post-treatment prior to surgery. (Limited to patients <i>without</i> metallic biliary/enteral stents).</p>
<p>SAFETY EVALUATIONS</p>	<p>Post-operative complication of pancreatic fistula will be monitored per the standard clinical guidelines. Common clinical presentations of clinically relevant pancreatic fistula include abdominal pain, leukocytosis and fever (temperature >100.4 degrees). Diagnostic work-up of pancreatic fistula will be with CT abdomen with contrast, which has a sensitivity of 63% and specificity of 83% for detecting pancreatic fistula [33]. The pancreatic fistulas will be categorized into grades A, B or C as previously reported [34]. Clinically relevant pancreatic fistulas are categorized as grade B or C. Depending on the grade of pancreatic fistula, patients will be treated as indicated with conservative treatment options including bowel rest, medications and sometimes with interventional radiology assistance [34]. We will also track other relevant post-</p>

	operative complications such as delayed wound healing, development of wound dehiscence or wound infection.
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List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
mEq	milliequivalent
PI	Principal Investigator
PK	pharmacokinetic
SAE	serious adverse experience

1 BACKGROUND

1.1 Pancreatic Cancer: Overview of Resectable and Borderline Resectable Disease

Pancreatic ductal adenocarcinoma (PDAC) continues to be a challenging cancer to treat secondary to its advanced stage at the time of diagnosis, its aggressive behavior and its resistance to treatment[1]. Only a minority of patients present with localized, non-metastatic disease and may potentially represent surgical candidates. Such patients may be divided into two categories: those who have clearly resectable disease at initial diagnosis (herein referred to as upfront resectable), and those with borderline resectable pancreatic cancer (BRPC). BRPC represents an increasingly recognized, distinct clinical entity characterized by primary tumor involving surrounding vasculature with a high risk for margin-positive resection if resected de novo [35].

Neoadjuvant therapy is often considered for patients with both resectable and borderline resectable disease to eradicate any micrometastatic disease, to identify suitable candidates most likely to benefit from surgery, and to improve the likelihood of margin-negative (R0) resection. However, consensus regarding the optimal neoadjuvant approach, including the respective roles, necessity, sequencing, and duration of neoadjuvant chemotherapy and chemoradiation (chemoRT), is lacking (reviewed in [36]). The neoadjuvant setting also represents an ideal setting to evaluate novel therapies to assess their on-target/pharmacodynamic effects, given that the majority of patients will ultimately be taken to surgery and be able to provide abundant tumor material for analyses.

1.2 Targeting the Tumor Stroma: PEGPH20

The PDAC tumor microenvironment is complex and consists of multiple components including pancreatic stellate cells (PSC), endothelial cells, immune cells and fibroblasts with an extensive paracrine and autocrine network residing in a stiff extracellular matrix [2-5]. The desmoplastic reaction that is characteristic of the PDAC stroma [6, 7] has been associated with increased cell proliferation and migration leading to metastasis in PDAC [8-11], while it disturbs the pancreatic tissue architecture by changing the layout of blood and lymphatic vessels [7, 12]. Extracellular matrix in PDAC stroma also distorts the organization of capillary network, creating a hypoxic environment, which leads to “disorganized, dysfunctional and permeable” vasculature of PDAC [13]. As a component of the desmoplastic reaction, differentiation of PSC leads to accumulation of hyaluronan (HA) [14], a glycosaminoglycan polymer, which causes increased tumor interstitial fluid pressure (IFP) [15, 16]. The changes in pancreatic tissue architecture and increased IFP have been shown to compress the tumor vasculature and hinder delivery of chemotherapy, which may account for the resistance of PDAC to therapy[3, 17] Preclinical studies with PEGPH20, which is pegylated recombinant human hyaluronidase and gemcitabine (G) was associated with reduction in IFP, increase in vessel diameter and an increase of 83% in median overall survival in mice treated with gemcitabine and PEGPH20 [18].

In addition to the preclinical studies, phase I studies investigating the effect of PEGPH20 have shown that it is well tolerated when used alone or in combination with gemcitabine and nab-paclitaxel. The most commonly reported adverse event in phase I trials was Grade 3 myalgia which improved after the use of dexamethasone [19, 20]. Of note, there was no evidence of inflammation or muscle damage in patients treated with PEGPH20 as measured by human

inflammation multi-analyte profile of 46 different cytokines, chemokines and acute-phase reactants [21]. A phase 1b study (NCT01453153) testing PEGPH20 with gemcitabine was complete recently. Preliminary data from the phase 1b trial studying PEGPH20 plus gemcitabine in patients with metastatic pancreatic cancer showed that the most commonly reported adverse event was fatigue and musculoskeletal events [37]. In this study, patients whose tumors had high HA staining had an overall response rate of 83% [22]. The final results of the Phase 1B study may be available prior to our trial's tentative initiation date. In addition, two phase II clinical trials are now in progress assessing the safety and efficacy of PEGPH20 plus nab-paclitaxel and gemcitabine (NCT01839487) and PEGPH20 combined with MFOLFIRINOX (NCT01959139) in patients with metastatic pancreatic cancer.

We selected gemcitabine and nab-paclitaxel as the chemotherapy backbone due to the safety and efficacy profile reported in preclinical and clinical studies. In earlier preclinical studies, nab-paclitaxel was thought to work by binding of albumin to SPARC-positive fibroblasts and targeting the tumor microenvironment directly [23]. This resulted in approximately 3-fold increase in the intratumoral gemcitabine concentration. However, a recent study demonstrated that reduction of cytidine deaminase impaired gemcitabine metabolism and lead to increased gemcitabine concentration in the tumor [24]. While both of these studies demonstrated increased intratumoral concentration of gemcitabine, the latter study did not demonstrate stromal depletion with the use of nab-paclitaxel. Following the preclinical findings of overexpression of SPARC in pancreatic cancer, a phase I/II study enrolled patients with advanced pancreatic cancer for treatment with gemcitabine and nab-paclitaxel [19]. This study noted a median overall survival of 12.2 months and 1-year survival of 48%. The subsequent phase III clinical trial with gemcitabine and nab-paclitaxel reported median overall survival of 8.5 months compared to 6.7 months with single-agent gemcitabine [38]. Recently, gemcitabine and nab-paclitaxel was found to be feasible in the preoperative setting for resectable PDAC and showed pathologic down-staging [26]. Radiologic partial response was reported as 16% and there was a >50% decline in CA 19-9 in 60% of the patients.

We plan to evaluate the effect of PEGPH20 with functional MRI, including DCE-MRI and DWI-MRI. Functional imaging became a measure of treatment response with the introduction of anti-angiogenic therapy [27]. Multiple studies have reported the feasibility and validity of DCE-MRI, including a study that compared primary PDAC, benign pancreatic tumors and normal pancreatic tissue histologically and with DCE-MRI [28]. Malignant pancreatic tumors had a significantly lower K_{trans} (i.e. decreased perfusion) compared to benign pancreatic lesions and normal pancreatic tissue. In addition, DWI-MRI has been used for the study of pancreatic lesions as it is able to detect "dense cellularity and extracellular fibrosis" by demonstrating low apparent diffusion coefficient (ADC) values [29]. Functional MRIs have also been used as correlative studies in the phase I studies with PEGPH20 and showed increase in K_{trans} and ADC 48 hours post-treatment relative to baseline [21, 30, 39]. Our project will address the sequential effect of PEGPH20 on stroma character and vascular perfusion. As a part of the clinical trial protocol, we will obtain tissue biopsies pre-treatment, post-treatment after a run-in period with PEGPH20 and again post-treatment after treatment with PEGPH20, gemcitabine and nab-paclitaxel. To study the relationship between the potential tissue and radiographic modifications in the stroma, we will also utilize DCE-MRI and DWI-MRI pre-

treatment, post-treatment after a run-in period with PEGPH20 and again on day 14 after initiation of treatment with PEGPH20, gemcitabine and nab-paclitaxel.

The role of tumor microenvironment in formation of desmoplastic reaction, cell proliferation, migration and metastatic potential makes it an important target for therapeutic intervention. We hypothesize that preoperative treatment with PEGPH20 will deplete the stroma, increase intratumoral perfusion (and hopefully drug delivery) without increased risk of post-operative complication of pancreatic fistula formation in patients with borderline resectable PDAC. We will address this by (1a) investigating the effect of preoperative treatment with the combination of PEGPH20, gemcitabine and nab-paclitaxel on the risk of post-operative clinically relevant pancreatic fistula formation (1b) evaluating pathologic complete response after neoadjuvant PEGPH20, gemcitabine and nab-paclitaxel treatment (2) evaluating the sequential effect of PEGPH20 on the fibrotic character and vascular perfusion of PDAC via functional MRIs. In addition, we will investigate (3) the degree of stromal depletion and the effects of PEGPH20 on cell proliferation and apoptosis.

1.3 Pancreatic Fistula Definition

Pancreatic fistula is the “failure of healing/sealing of pancreatic-enteric anastomosis or it may represent a parenchymal leak not directly related to an anastomosis”. It is considered to be a common post-operative complication following pancreatic surgery with a frequency ranging from 5-30% [40-47]. Development of pancreatic fistula may affect timely initiation of adjuvant therapy following surgery due to possible longer hospital stays. A universally accepted Definition of pancreatic fistula was developed by the International Study Group on Pancreatic Fistula (ISGPF) in 2005 and classified pancreatic fistulas to 3 grading systems; A, B and C[48]. According to this definition, pancreatic fistula is defined as “any appreciable drainage from an operatively placed drain with an amylase content greater than 3 times the upper limit of normal serum amylase level measure on, or after, postoperative day 3”[49]. Grade A fistulas are diagnosed biochemically with elevated amylase but do not have any associated symptoms and therefore are not clinically relevant. Grade B and C fistulas on the other hand are symptomatic fistulas, which require diagnostic evaluation and therapeutic interventions. Patients often present with “abdominal pain, fever, nausea and intolerance to oral intake” and diagnostic imaging studies may show peripancreatic fluid collection[50]. The degree of intervention is more intense with grade C fistulas as these patients are often in critical condition with possible sepsis and organ dysfunction. While patients with grade B pancreatic fistulas may be treated with antibiotics and percutaneous drainage, patients with grade C pancreatic fistulas may require ICU admission, surgical re-exploration, antibiotics and somatostatin analogues. In the current study, we will be evaluating clinically relevant pancreatic fistulas, i.e. pancreatic fistulas graded as B or C, within in the first week following surgery.

1.4 Background on the Compounds

1.4.1 Gemcitabine and nab-Paclitaxel for Pancreatic Cancer

Gemcitabine became the standard of care for systemic treatment of advanced pancreatic cancer in 1997 when it was shown to have clinical response and survival benefit over 5-fluorouracil [51]. Since then, multiple combinations of other cytotoxic agents and targeted therapies have been studied in combination with gemcitabine. However, only erlotinib, an EGFR inhibitor, showed a marginal survival benefit in a Phase III clinical trial, when combined with gemcitabine[52]. While the recent randomized controlled trial with FOLFIRINOX revealed improved response in overall and progression free survival over single-agent gemcitabine in metastatic pancreatic cancer, there is much needed advancement in the systemic treatment of pancreatic cancer[53].

One recent phase I/II study investigated gemcitabine in combination with nab-paclitaxel, an albumin-bound form of paclitaxel, in patients with advanced pancreatic cancer [19]. This study was undertaken after molecular profiling of pancreatic adenocarcinoma tumors revealed overexpression of secreted protein acidic and rich in cysteine (SPARC), which is an albumin-binding protein which is secreted by tumors [54]. It is believed that SPARC is able to bind albumin and then releases the active drug at the tumor cell membrane allowing for increased concentration of the agent at the target site of action [55]SPARC is also overexpressed in other tumor types including breast, lung and melanoma and nab-paclitaxel was shown to have antitumor effect in these tumor types secondary to its association with SPARC[56-58]

Following the preclinical findings of overexpression of SPARC in pancreatic cancer, the aforementioned phase I/II study enrolled patients with advanced pancreatic cancer for treatment with gemcitabine and nab-paclitaxel [19]. Phase I study found the MTD of gemcitabine to be 1000 mg/m² and nab-paclitaxel to be 125 mg/m² administered weekly for 3 weeks in a 28-day cycle. Subsequently, a phase III clinical trial showed a median overall survival of 8.5 months compared to 6.7 months with single-agent gemcitabine [38].

1.4.2 Pegylated Recombinant Human Hyalurodinase (PEGPH20)

A potential limitation of chemotherapy in pancreatic cancer treatment has been the thick stromal matrix, characteristic of this disease. A pivotal preclinical study showed that the stroma impedes drug delivery and it was proposed that drugs that are able to disrupt the desmoplastic stroma may “facilitate delivery and enhance the efficacy of gemcitabine” [23]. Hyaluronan (HA), a glycosaminoglycan polymer may accumulate in the tumor stroma causing increased tumor interstitial fluid pressure (IFP) compressing tumor vasculature[59, 60]. These observations led to the hypothesis that depletion of HA may lead to decreased tumor IFP and increased vascular area with improved perfusion and drug delivery to the tumor. Preclinical studies with gemcitabine monotherapy plus PEGPH20, which is pegylated recombinant human hyalurodinase, showed decreased proliferation, increased apoptosis and decreased metastatic tumor burden in pancreatic cancer [18]. In this study, the use of PEGPH20 was associated with reduction in IFP, increase in vessel diameter and an increase of 83% in median overall survival in mice treated with gemcitabine and PEGPH20 compared to gemcitabine and placebo. PEGPH20 may serve as a

novel agent in treatment of tumors with high HA concentration, such as pancreatic cancer, by “enzymatically remodeling” the tumor stroma.

Two Phase I studies (N=40) using PEGPH20 were conducted to determine its safety and tolerability. In a phase I clinical trial studying PEGPH20, the most commonly reported adverse event was Grade 3 myalgia at higher doses (50 ugram/kg) or higher frequency (twice a week rather than once a week) [21]. The musculoskeletal events were also observed in canines in a dose-dependent fashion as the canines had difficulty with standing and mobility. With the addition of dexamethasone, the musculoskeletal events were prevented in the canines without altering PEGPH20 pharmacokinetics. When dexamethasone was used in Phase I studies in addition to PEGPH20, muscle stiffness and pain were improved [21, 30]. Of note, a phase I study measured human inflammation multi-analyte profile (MAP) of 46 different cytokines, chemokines, and acute-phase reactants and did not find any evidence of inflammation or muscle damage [21]. A phase Ib clinical trial in subjects with Stage IV pancreatic cancer showed that PEGPH20 plus gemcitabine in the first-line setting was safe and showed promising results. In this study, patients whose tumors had high HA staining had an overall response rate of 56% [20].

In the over 145 subjects exposed to PEGPH20, either in the monotherapy or combination setting, the most frequently reported adverse events are of musculoskeletal origin (MSE) (e.g., muscle spasms, arthralgia, and myalgia), as well as peripheral oedema. The majority of these types of events are Grade 1/2 in severity. Other AEs that have been identified in both the monotherapy and combination therapy settings include nausea, diarrhea, and dysphonia. The majority of the events are Grade 1/2. Please refer to the Investigator’s brochure for additional safety information.

Halozyme has recently completed enrollment to a randomized Phase 2 clinical study (HALO-109-202) in which approximately 253 subjects with Stage IV previously untreated pancreatic cancer were assigned to receive either nab-paclitaxel plus gemcitabine, or this same chemotherapy regimen plus PEGPH20. Interim safety analysis suggested the possibility of an increase in thromboembolic events in the PEGPH20 plus nab-paclitaxel and gemcitabine (PAG) arm compared to the nab-paclitaxel and gemcitabine arm (AG). The majority of the TE events were of venous origin (deep vein thrombosis and pulmonary embolism); however, arterial events were also reported. It has been well cited in the medical literature that pancreatic cancer is one of the most thromboegenic malignancies; in a retrospective analysis of TE rates in this patient population, Epstein and colleagues (Epstein, 2012) identified a TE event rate at approximately 36%. Based on this review, the study protocol was amended to exclude new subjects, as well as those who were previously on PAG treatment, who may be at a higher risk for developing TE events, and prophylactic treatment with low molecular-weight heparin for all subjects on study (PAG and AG) was added. With these mitigation strategies, no excess rates of TE events were observed with continuation and completion of study enrollment. Based on promising early results reported in this phase II study specific to patients with elevated intratumoral expression of HA[61], a subsequent phase III trial (HALO-301) is now underway evaluating this same strategy, again in the metastatic setting, with enrollment limited exclusively to patients with HA-high tumors.

2 STUDY RATIONALE

Because of its mechanism of action as mentioned above, we believe that PEGPH20 could have a role in the neoadjuvant setting for patients with upfront and borderline resectable pancreatic ductal adenocarcinoma. While this agent already has an established safety profile in combination with gemcitabine and nab-paclitaxel in the metastatic setting, we wish to assess both its safety and efficacy in this preoperative context.

Hyaluronan and HA metabolites—medium, low, and very small molecular weight products of hyaluronidase degradation—are important mediators of the inflammatory and tissue-regenerative processes of wound repair[62]. It is currently unknown what effects, if any, exogenously administered hyaluronidase would have on the natural rate of hyaluronan turnover and the dynamics of wound healing [62, 63]. As safety and toxicity will be a critical factor in this trial, we have chosen to include as a co-primary endpoint the development of pancreatic fistula, which represents the most common post-operative complication following pancreatic surgery. PEGPH20, whose mechanism involves breakdown of a key component of connective tissue, may potentially affect wound healing and anastomotic integrity and could theoretically increase the risk of fistula formation.

3 STUDY OBJECTIVES

3.1 Primary Objectives

- To evaluate development of clinically relevant pancreatic fistula in the post-operative period after neoadjuvant treatment with PEGPH20, gemcitabine and nab-paclitaxel.
- To evaluate pathologic complete response after neoadjuvant PEGPH20, gemcitabine and nab-paclitaxel treatment.

3.2 Secondary

To evaluate early efficacy measured by percent change of CA 19-9 response rate, R0 resection rate, overall response rate (ORR) and disease free survival (DFS).

3.3 Exploratory Objectives, Other Assessments

- To evaluate the sequential effect of PEGPH20 on the fibrotic character and vascular perfusion of PDAC via functional MRIs.
- To determine degree of stromal depletion and effects of PEGPH20 on cell proliferation and apoptosis.

4 STUDY DESIGN

4.1 Study Overview

This is a Phase II study investigating PEGPH20 in combination with gemcitabine and nab-paclitaxel in patients with both upfront and borderline resectable pancreatic ductal adenocarcinoma (PDAC).

This trial will be conducted in two parts. In Part I, pre-treatment endoscopic ultrasound (EUS)-guided core biopsies of the pancreatic tumor and functional MRIs (fMRIs), including DCE-MRI and DWI-MRI, will be obtained for the first fifteen patients enrolled as outlined in Figure 1. After a 1-week run-in period with PEGPH20 on days 1 and 4, these patients will have repeat EUS-guided core biopsies, functional MRI, and undergo baseline CT/MRI of the chest, abdomen and pelvis.

After completing the 1 week run-in, patients in Part 1 will be started on treatment with PEGPH20, gemcitabine and nab-paclitaxel (within 1-2 weeks). PEGPH20, gemcitabine and nab-paclitaxel will be given weekly for 3 weeks, every 28 days. To evaluate the disease response to treatment, CA 19-9 levels will be checked monthly and restaging CT/MRI of the chest, abdomen and pelvis will be obtained every 8 weeks. If there is disease progression at any point in the study, patients will be taken off of study and alternative treatments will be offered. At the completion of 4 cycles of therapy, restaging CT/MRI scans will be obtained to determine resectability. If the patients are found to have resectable disease, an additional functional MRI will be obtained to evaluate the PDAC stroma. For patients who are able to have successful surgeries, tissue analyses will be performed on the resected pancreatic tumor. These patients may receive further adjuvant chemotherapy post-operatively based on the physician's clinical judgement. If the patients are deemed to be surgical candidates but are found to have unresectable disease in the operating room, an intraoperative core biopsy of the pancreatic tumor will be obtained for tissue analyses.

At the time of initiation of therapy with PEGPH20, patients will be started on prophylactic dose of enoxaparin 1 mg/kg subcutaneous daily. This will be continued throughout the study until at least 14 days after the last infusion of PEGPH20. Patients will also take dexamethasone 1-2 hours before receiving PEGPH20, and 8-12 hours after completion of PEGPH20 infusion.

Two interim safety assessments will be performed when the first 7 and 15 evaluable patients are enrolled in the study. Interim analyses and stopping rules are detailed later in this protocol.

If the study enters Part II, an additional 21 patients will be enrolled. Patients in Part II will begin neoadjuvant therapy with PEGPH20, gemcitabine and nab-paclitaxel *without* the 1 week run-in of PEGPH20, the pre- and post-run-in EUS-guided biopsies and fMRIs, or the post run-in CT/MRI scan.

For Specific Aim 1, we will be monitoring the post-operative complication of clinically relevant pancreatic fistula within one week of surgery per the standard clinical guidelines as noted above. Common clinical presentations of pancreatic fistula include abdominal pain, leukocytosis and fever (temperature >100.4 degrees). Diagnostic work-up of pancreatic fistula will be with CT

abdomen with contrast, which has a sensitivity of 63% and specificity of 83% for detecting pancreatic fistula [33]. The pancreatic fistulas will be categorized into grades A, B or C as previously reported [34]. Our study will be investigating only clinically relevant pancreatic fistulas, i.e. grades B or C. Depending on the grade of pancreatic fistula, patients will be treated as indicated with conservative treatment options including bowel rest, antibiotics, somatostatin analogues and percutaneous drainage or surgical re-exploration[34]. We will also track other relevant post-operative complications such as delayed wound healing, development of wound dehiscence or wound infection.

The tissue analyses will include review of the immunohistochemical (IHC) stains for actin, hyaluronic acid staining with binding protein probe, proliferation as measured by ki-67% and Phospho-histone H3 (Ph-H3); cell apoptosis as evaluated by IHC stain for cleaved caspase 3 (CC3) and Tunel. If limited tissue sample is obtained via the core biopsies, the priority of tissue analysis will be as follows: (1) fixed in formalin for H&E and IHC (Ph-H3; CC3/Tunel; HA binding); (2) fixed in OCT such that IHC with difficult antibodies can be done (to potentially obtain mRNA or DNA). The IHC studies will be done at the UCSF Helen Diller Family Comprehensive Cancer Center Immunohistochemistry and Molecular Pathology Core, led by Dr. Rick Baehner (see letter of support).

The CT and MR imaging analyses will be performed at a University of California (UC) campus. To decrease the impact that metal stents may have on the functional MRI results, any patients who has a metallic stent (biliary and/or enteral) will not participate in this MRI component of the study. In addition, to reduce variability in results, the DCE-MRI and DWI-MRI will be obtained on the same MR machine at a similar time of day as the baseline scan. The DCE-MRI images will be analyzed by calculating Ktrans and DWI-MRI images will be analyzed by calculating ADC as described elsewhere [41, 44]. We will scan patients in a torso coil on a 3T clinical MR scanner. Imaging will include MR diffusion with b-values of 0, 125, and 500 for estimates of perfusion and tumor, and dynamic contrast-enhanced MR imaging (DCE-MRI) for measurement of Ktrans, blood volume, and blood flow. The region of tumor will be determined by MR imaging in reference to the baseline CT scans. The native T1 of the pancreas and liver will be calculated from a series of four, 3D, spoiled gradient recalled echo (SPGR) sequences with different flip angles. The conventional DCE-MRI will be acquired as a 3D, fast spoiled gradient echo sequence, covering the targeted areas of the pancreas or liver, at a temporal resolution of 5 sec over 6 minutes after the administration of 0.1 mmol/kg gadobenate dimeglumine. DCE-MRI images will be post-processed using MISTar software [redacted] which allows for motion correction to account for any shifts in data. Datasets with artifacts will be eliminated before further post processing. After contrast delivery, the new T1 is calculated and is presumed to change with the Gd concentration such that $[Gd] = (1/T1 - 1/T10)/R1$ where R1 is assumed to be 4.5 sec⁻¹ mmol/L⁻¹ at 3T.

Run-in Period with PEGPH20

Days 1, 4	PEGPH20 3 ug/kg over a 10 minute period (+2 minute window, i.e. infusion may be 10-12 minutes)
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	<p>Dexamethasone 8mg PO 1-2 hours pre-PEGPH20 and PO 8-to-12 hours post-PEGPH20</p> <p>*Start enoxaparin 1 mg/kg subcutaneous daily on day 1 (to be continued throughout the trial during treatment with PEGPH20, and at least 14 days after the last infusion of PEGPH20)</p>
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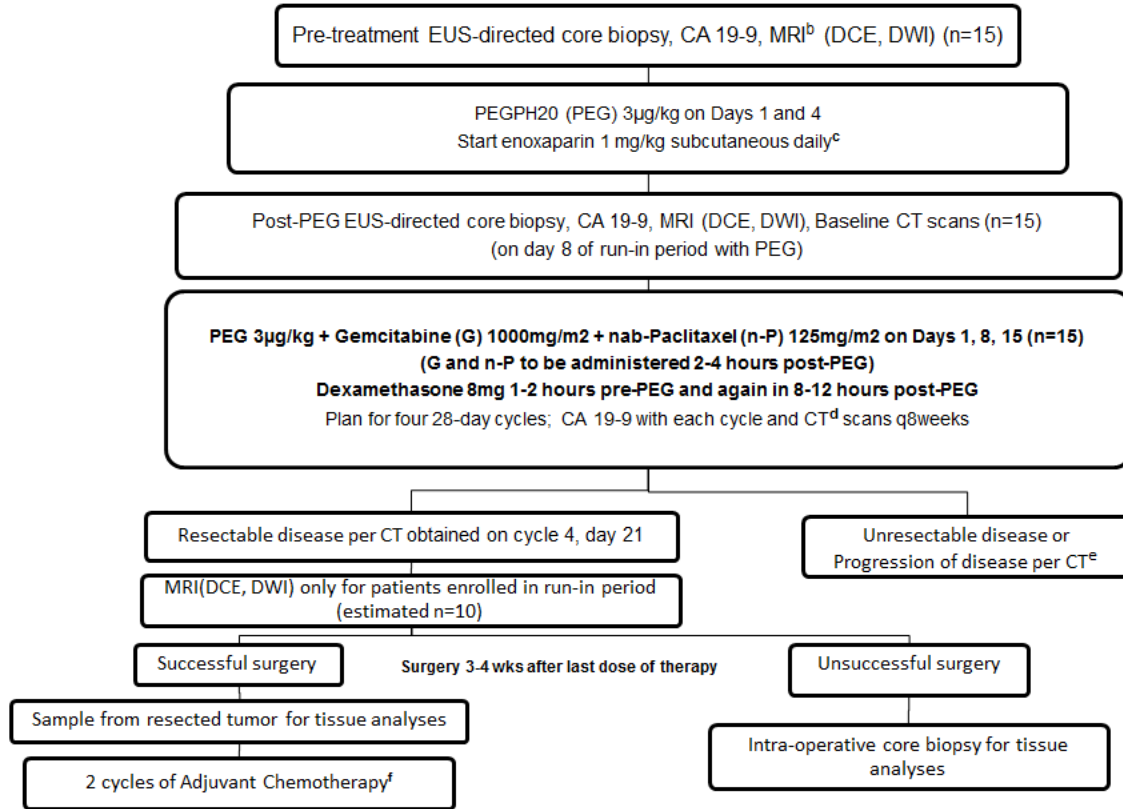
- On day 8 (\pm 1 day) of run-in period with PEGPH20, EUS-directed core biopsy, functional MRI (except for patients with metallic stents) and CT/MRI of the chest, abdomen (pancreatic protocol) and pelvis will be obtained.

Cycle 1 and onward

<p>Days 1, 8, 15 out of a 28-day cycle</p>	<p>PEGPH20 3 ug/kg over a 10 minute period (+2 minute window, i.e. infusion may be 10-12 minutes) + Gemcitabine 1000mg/m² + nab-Paclitaxel 125mg/m². Infuse nab-Paclitaxel prior to gemcitabine.</p> <p>Dexamethasone 8mg PO 1-2 hours pre-PEGPH20 and PO 8-to-12 hours post-PEGPH20</p>
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- Gemcitabine and nab-paclitaxel will be administered 2-4 hours post-PEGPH20.
- Neoadjuvant therapy will be four 28-day cycles with CA 19-9 measurements every 4 weeks, and CT/MRI of the chest, abdomen and pelvis every 8 weeks. Patients will be taken off of the study if there is any evidence of disease progression.
- Patients will be evaluated for surgical resection depending on imaging obtained on Cycle 4 Day 21.
 - Patients who are found to have resectable disease will have a functional MRI following the restaging CT scan. If patients continue on to have successful resection, they may receive 2 additional cycles of chemotherapy without PEGPH20 (physician’s choice). If a patient is found to have unresectable disease in the operating room, an intra-operative core biopsy will be obtained.
 - Patients who are found to have unresectable disease on the restaging scans following 4 cycles of therapy will be taken off of the study.

4.2 Schema of Phase II clinical trial in patients with either upfront or borderline resectable pancreatic cancer based on the baseline pancreatic protocol CT scan, Part Ia.



- DCE:** Dynamic contrast enhanced
DWI: Diffusion weighted imaging
- In Part II, an additional 21 patients will be enrolled, and will begin neoadjuvant therapy with PEGPH20, gemcitabine and nab-paclitaxel without the 1 week run-in of PEGPH20-only, the pre- and post-run-in EUS-guided biopsies, or fMRI.
 - MRIs only to be performed in patients without existing metallic stent
 - 1 mg/kg enoxaparin injected daily until 14 days after the last dose of PEG is administered.
 - CT chest, abdomen (pancreatic protocol) and pelvis
 - If disease progression at any time, patients will be taken off of study and alternative treatments will be offered.
 - Adjuvant chemotherapy is at the discretion of the treating physician.

5 CRITERIA FOR EVALUATION

5.1 Primary Endpoints

- Clinically relevant pancreatic fistula in the post-operative period after neoadjuvant treatment with PEG, gemcitabine and nab-paclitaxel.
- Pathologic complete response after neoadjuvant PEG, gemcitabine and nab-paclitaxel treatment

5.2 Secondary Endpoints

- Percent change of CA 19-9 response rate,
- R0 resection rate
- Overall response rate (ORR)
- Disease free survival (DFS)

5.3 Safety Evaluations

- Safety and tolerability (adverse events, categorized and graded according to NCI CTC v. 4.0)
- Other relevant post-operative complications, including:
 - delayed wound healing
 - wound dehiscence
 - wound infection

5.4 Correlative Endpoints

- 1) Tissue analyses pre-treatment and post-treatment with standard IHC staining for actin, hyaluronic acid staining with binding protein probe, proliferation as measured by ki-67% and Phospho-histone H3 (Ph-H3); cell apoptosis as evaluated by IHC stain for cleaved caspase 3 (CC3) and TUNEL. If limited tissue sample is obtained via the core biopsies, the priority of tissue analysis will be as follows: (1) fixed in formalin for H&E and IHC (Ph-H3; CC3/TUNEL; HA binding); (2) fixed in OCT such that IHC with difficult antibodies can be done (to potentially obtain mRNA or DNA).
- 2) Functional MRIs including Dynamic Contrast Enhanced (DCE), Diffusion Weighted Imaging (DWI) will be obtained to evaluate intratumoral perfusion and stromal density pre-treatment and post-treatment prior to surgery (excluding patients with pre-existing metallic stents).

6 SUBJECT SELECTION

6.1 Inclusion Criteria

1. Greater than or equal to 18 years old.
2. Histologically confirmed pancreatic adenocarcinoma
3. One of the following:
 - a. **Upfront resectable disease.** This is defined as:
 - i. No arterial tumor contact (celiac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA)); AND

- ii. No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV), or $\leq 180^\circ$ contact without vein contour irregularity.
- b. **Borderline resectable disease.** There are multiple definitions of borderline resectable PDAC including the MD Anderson definition [32] and the criteria developed during the Consensus Conference sponsored by the American Hepato-Pancreato-Biliary Association, Society of Surgical Oncology, and Society for Surgery of the Alimentary Tract [33]. Borderline resectable PDAC cases will be identified per the definition developed in the currently running inter-group pilot trial for borderline resectable pancreatic cancer (NCT01821612). Per this trial, borderline resectable PDAC is defined as the presence of any one or more of the following on CT or MRI:
 - i. An interface between the primary tumor and the superior mesenteric vein or portal vein (SMV-PV) measuring $\geq 180^\circ$ of the circumference of the vessel wall
 - ii. Short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction
 - iii. Short segment interface (of any degree) between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and reconstruction.
 - iv. An interface between the tumor and SMA measuring $< 180^\circ$ of the circumference of the vessel wall.
- 4. Performance status of ECOG of 0-1
- 5. No prior treatment for pancreatic cancer
- 6. Adequate organ function including:
 - a. Bone marrow: ANC $\geq 1500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$ and hemoglobin ≥ 9 g/dL
 - b. Hepatic: Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN), ALT (SGPT) and AST (SGOT) ≤ 2.5 x ULN, Alkaline phosphatase ≤ 2.5 x ULN
 - c. Renal: Serum creatinine (sCr) ≤ 1.5 x ULN, or creatinine clearance (Ccr) ≥ 40 mL/min as calculated by the Modified Cockcroft-Gault formula.
- 7. Peripheral neuropathy $<$ grade 2
- 8. Biliary stents (plastic or metallic) are allowed; however, those patients with metallic stents will *not* undergo the functional MRI correlative component of this study.

6.2 Exclusion Criteria

- 1. Age younger than 18 years old
- 2. Locally advanced (clearly unresectable) or metastatic disease
- 3. Known allergy to hyaluronidase
- 4. Contraindications to prophylactic dose LMWH, including:
 - a. Patients with recent gastrointestinal bleeding,
 - b. History of heparin induce thrombocytopenia on LMWH

- c. Subjects with previous severe hemorrhagic events on LMWH
 - d. Recent central nervous system bleed, intracranial or spinal lesion at high risk for bleeding
 - e. Active bleeding (major): more than 2 units transfused in 24 hours
 - f. Spinal anesthesia/lumbar puncture
 - g. Chronic, clinically significant measurable bleeding > 48 hours
 - h. Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)
Recent major operation at high risk for bleeding
 - i. Underlying hemorrhagic coagulopathy
 - j. High risk for falls (head trauma)
5. Known status of HIV which is not well-controlled at the time of study eligibility
 6. Untreated Hepatitis B infection
 7. Active infection or antibiotics within 48 hours prior to study
 8. Currently active second primary malignancy or history of malignancy less than 5 years prior to the time of study eligibility (Patients with history of skin cancers excluding melanoma will be eligible for participation).
 9. Serious medical comorbidities such as New York Heart Association Class III/IV cardiac disease, uncontrolled cardiac arrhythmias, myocardial infarction over the past 12 months.
 10. Known, existing uncontrolled coagulopathy. Patients who have had a venous thromboembolic event (e.g., pulmonary embolism or deep vein thrombosis) requiring anticoagulation are eligible IF: they are appropriately anticoagulated and have not had a Grade 2 or greater bleeding episode in the 3 weeks before Day 1.
 11. Current use of warfarin (patients will be eligible if warfarin is discontinued and low-molecular weight heparin is used instead).
 12. Intolerance to dexamethasone
 13. Prior history of cerebrovascular accident or transient ischemic attack, or pre-existing carotid artery disease.
 14. Known pregnancy, nursing women or positive pregnancy test.
 15. Any condition that would preclude informed consent, consistent follow-up and compliance for the study participation.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Medications Allowed:

- Medications used for supportive therapy such as anti-emetics, anti-diarrheals, analgesics, bisphosphonates and antibiotics are allowed as indicated.

- Thromboembolic events will be managed with low-molecular weight heparin.
- In addition to study medication, all subjects will be administered dexamethasone to reduce potential musculoskeletal symptoms, which have been reported to be associated with PEGPH20. Dexamethasone 8 mg will be administered, preferably orally (PO), within 2 hours prior to the beginning of each PEGPH20/placebo infusion and 8 to 12 hours after completion of the randomized study medication infusion (total dose 16 mg on dosing days). Parenteral administration is allowed if the subject cannot tolerate oral dexamethasone. Additional doses of dexamethasone may be given 24 hours prior to infusions of randomized study medication or at any other time at the discretion of the Investigator based on tolerability. The Investigator may adjust (increase or decrease) the dose and/or frequency of dexamethasone based on the clinical need (e.g., tapering off if subject is tolerating study medication).
- At the first occurrence of fever > 38.5C (regardless of neutrophil count), either oral levofloxacin (500 mg daily) or amoxicillin/clavulanate (500 mg tid) will be initiated.
- For febrile neutropenia, interrupt nab-paclitaxel and gemcitabine until fever resolves and ANC \geq 1500 then resume treatment at a reduced dose.

Medications Prohibited:

- Warfarin
- Patients may not be on any therapy for their pancreatic cancer other than the current study's treatment drugs.

8 STUDY TREATMENTS

8.1 Study Agent Administration

Each treatment cycle consists of 28 days as mentioned in Section 4.1.

PEGPH20 3 ug/kg will be administered intravenously over a 10 minute period (+2 minute window, i.e. infusion may be 10-12 minutes) on days 1 and 4 during the one week run-in period. Starting cycle 1, PEGPH20 will be administered on days 1, 8 and 15. PEGPH20 will be administered 2-4 hours prior to nab-paclitaxel and gemcitabine.

Nab-paclitaxel 125 mg/m² will be administered on days 1, 8, 15 of each cycle over 30 minutes. It will be administered 2-4 hours after PEGPH20. Nab-paclitaxel will be infused prior to gemcitabine.

Dexamethasone 8 mg will be administered PO 1-2 hours pre-PEGPH20 and PO 8-12 hours post-PEGPH20.

Gemcitabine 1000 mg/m² will be administered intravenously on days 1, 8, 15 of each cycle over 30 minutes. Gemcitabine will be administered after nab-paclitaxel.

Enoxaparin 1 mg/kg subcutaneous daily will be started at the time of initiation of therapy with PEGPH20. This will be continued throughout the study participation. Enoxaparin will be stopped the day before any biopsy procedure and will resume the day after the procedure.

8.2 Formulation of Study Agents

8.2.1 Nab-paclitaxel

Abraxane (*nab*-paclitaxel, nanoparticle albumin-bound paclitaxel), when released as the active drug (paclitaxel), blocks cell replication in the G2 mitotic phase by promoting microtubule assembly, stabilizing existing microtubules, and inhibiting disassembly of microtubules. Binding of abraxane by an albumin-specific receptor (gp60) leads to activation of caveolin-1, a protein which mediates internalization of the compound into the endothelial cell and transport to the tumor interstitium. SPARC (Secreted Protein And Rich in Cysteine), a tumor-secreted protein, binds albumin, releasing the active drug at the tumor cell membrane, thereby increasing its concentration at the target site of action.

Drug Storage and Stability

Nab-Paclitaxel (Abraxane) is supplied in single-use 50 mL vials, each vial containing paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Unreconstituted Abraxane should be stored at controlled room temperature (20° to 25° C or 68° to 77°F) in its carton, and should be protected from bright light. Unopened vials of Abraxane are stable until the date indicated on the package when stored at the above temperatures in the original package. Reconstituted Abraxane should be used immediately, but may be refrigerated at 2° to 8°C (36° to 46 °F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Also, after the suspension for infusion reconstituted as recommended is stable in an IV bag at room temperature 20° to 25° C (68° to 77°F) and ambient lighting conditions for up to 8 hours if necessary.

Drug Administration

The number of vials required will be calculated using the following formula:

$$\text{Total number of vials} = \text{Total dose} / 100 \text{ (mg/vial)}$$

If a fractional number of vials is obtained using this formula, it should be rounded-up to the next higher whole number. The vials should be prepared for reconstitution using sterile technique. Each Abraxane vial should be reconstituted by injecting 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the inside wall of the vial. The 0.9% Sodium Chloride Injection, USP solution should not be injected directly onto the lyophilized cake as this will result in foaming. Once the injection is complete, the vial should sit for a minimum of 5

minutes to ensure proper wetting of the lyophilized cake/powder. The vial should be gently swirled and/or inverted for at least 2 minutes until complete dissolution of any cake/powder occurs. Rapid agitation or shaking will result in foaming. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides. Each ml of reconstituted product will contain 5 mg of paclitaxel. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:

$$\text{Dosing volume (ml)} = \text{Total dose(mg)} / 5 \text{ (mg/ml)}$$

The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be gently inverted again to ensure complete resuspension, prior to use. Once the exact volume of reconstituted Abraxane has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted Abraxane suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag. Administer the calculated dosing volume of reconstituted Abraxane suspension by IV infusion over 30 minutes. The use of in-line filters is not necessary. If used, in-line filters with pore sizes of < 15 μ should not be used. Use within 8 hours of reconstitution.

Albumin-bound paclitaxel should be administered by IV over 30 minutes.

Side Effects

Most common side effects include myelosuppression, nausea/vomiting, diarrhea, mucositis, sensory neuropathy, myalgia/arthralgia, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, bilirubin/liver enzyme elevations, allergic reactions, alopecia, asthenia. Rare but serious side effects include hypersensitivity reactions and cardiovascular events.

8.2.2 Gemcitabine

Gemcitabine (2'-Deoxy-2',2'-difluorocytidine monohydrochloride, Gemzar) exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potential). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition

of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Drug Storage and Stability

Unreconstituted drug vials are stored at controlled room temperature. Gemcitabine is commercially available in 200 mg and 1 gm vials. Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Reconstitute the 200 mg vial with 5ml and the 1 gm vial with 25 ml preservative free normal saline to make a solution containing 38 mg/ml. Shake to dissolve. Solutions of gemcitabine should not be refrigerated; crystallization may occur. The unused portion should be discarded.

Drug Administration

The drug may be administered as prepared above or further diluted with normal saline to a minimum concentration of 0.1 mg/ml. Gemcitabine is commonly diluted in 500 ml of saline. The drug will be infused over 30 mins. Gemcitabine will be paid for by the patient or his/her insurance.

Side Effects

Most common side effects include myelosuppression, rash, nausea/vomiting, fever, fatigue, flu-like symptoms, fluid retention, diarrhea, and transaminitis. Rare but serious side effects include pulmonary syndromes, bronchospasm, and hemolytic-uremic syndrome.

8.2.3 PEGPH20

The investigational material in PEGPH20 is a PEGylated, neutral-pH-active human hyaluronidase PH20 produced by recombinant DNA technology. Recombinant human hyaluronidase PH20 (rHuPH20) degrades HA under physiologic conditions and acts as a spreading factor in vivo.

PEGPH20 is a multi-site PEGylated enzyme generated by conjugating N-hydroxysuccinimidyl ester of methoxypoly(ethylene glycol)-butanoic acid (MSBA30K or PEG) and PH20. PH20 and PEG are covalently linked via a stable amide bond between PEG and the N-terminal amino group or the ϵ -amino groups present on lysine amino acid side chains of PH20.

Chemical Name

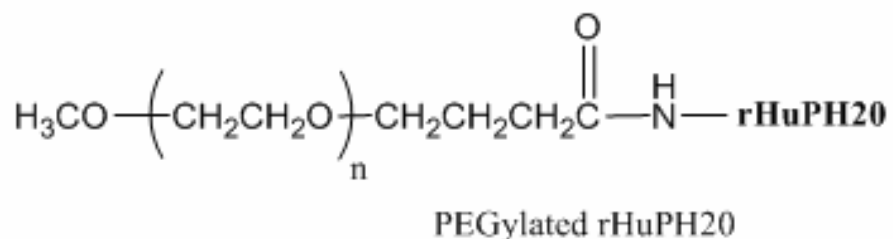
PEGPH20 (PEGylated recombinant human hyaluronidase: 36-482-hyaluronoglucosaminidase PH20 [human])

Structural Formula

The structure of PEGPH20 is represented in .

Figure .

Figure 2: Structure of PEGPH20



The empirical formula for PEGPH20 is rHuPH20: C₂₃₂₇H₃₅₆₅N₅₈₉O₆₆₇S₂₀ (based on amino acid sequence) and PEG: C₁₃₇₁H₂₇₃₇NO₆₈₆ (based on PEG with n = 681). PEGPH20 is a multi-site PEGylated enzyme. Its measured molecular weight is generally between 100,000 and 270,000 Da.

Drug Packaging and Labeling

The PEGPH20 drug product is supplied as a refrigerated, sterile, single-use, injectable liquid. PEGPH20 drug product (clinical test article) is an aqueous solution containing 0.3 mg/mL PEGPH20 with 10 mM succinate, 130 mM NaCl, and 10 mM Methionine at a pH of 6.2. Each vial contains 1.2 mL (0.36 mg) of PEGPH20 drug product. PEGPH20 drug product will be packaged in clear, Type I, 2 mL glass vials with a 13 mm chlorobutyl Flurotec® coated stopper and 13 mm flip-off overseal. It should be stored at 2-8°C before use.

Drug Storage

PEGPH20 drug product is a liquid formulation and should be stored at 2-8°C before use. Stability testing of PEGPH20 drug product was initiated following general International Conference on Harmonisation (ICH) guidelines at 5°C ± 3°C, and concurrent stability evaluation is ongoing. The Sponsor will monitor drug stability and provide updates on an ongoing basis.

Drug Preparation

PEGPH20 should be stored at 2-8°C prior to use. Each vial is intended for single use. All used and unused study drug must be stored and kept for reconciliation by the study monitor, unless clinic policy requires immediate disposal. If this is the case, the Sponsor should be notified in advance, and reconciliation procedures will be agreed upon. Instructions for preparing the PEGPH20 can be found in the pharmacy manual.

Side Effects

Most common side effect was grade 3 muscle stiffness and pain in preclinical and phase I studies. These symptoms were dose and frequency related with the higher doses and twice a week dosing causing more muscle stiffness and pain compared to lower doses or once a week dosing. Phase I studies reported that 7 days after the discontinuation of PEGPH20, myalgia resolved[30]. In addition, they reported that there was no increase in the inflammatory markers from the serum of patients who experienced myalgias. With the use of dexamethasone 8mg 1-2 hours prior to the administration of PEGPH20 and 8-12 hours after the administration of PEGPH20, symptoms of myalgia improved.

Recently, increased rates of venous thromboembolic events (VTE) were reported in the Phase II trial investigating the combination of PEGPH20 with gemcitabine and nab-paclitaxel. Patients treated in the combination arm were reported to have approximately doubled the rate of VTE compared to patients treated with gemcitabine and nab-paclitaxel alone. Per the advisory board and FDA recommendations, this trial resumed with implementation of prophylactic dosing of enoxaparin 1 mg/kg subcutaneous daily in the treatment arm receiving PEGPH20. Due to this reported adverse event, patients in the current trial will start receiving a prophylactic dose of enoxaparin 1 mg/kg subcutaneous daily at the time of initiation of therapy with PEGPH20. This will be continued throughout the study during treatment with PEGPH20. Daily injections of enoxaparin should stop at least 14 days after the last dose of PEGPH20 is administered. Please see Appendix 1 for recommended dosing. Thromboembolic events will be managed with therapeutic doses of low-molecular weight heparin.

Allergic reactions are not considered a likely source of toxicity for this recombinant human-derived molecule, and current human experience with PEGPH20 shows that allergic reactions during the use of PEGPH20 are uncommon. To date, infusion reactions have been observed in less than 5% of subjects treated with PEGPH20 in [REDACTED] sponsored clinical studies.

Other potential adverse reactions for PEGPH20 based on cumulative clinical data include neutropenia and thrombocytopenia, edema, and rash.

8.2.4 Rules for Dose Omissions and Modified Schedules

Gemcitabine, nab-Paclitaxel and PEGPH20

Day 1 (+/- 1 day) dose missed:

If the dose held or missed was to be given on Day 1 (+/- 1 day) of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (i.e., 1-2-3-Rest, X-1-2-3-Rest, etc.). All components of study treatment should be held and resumed at the same time.

Day 8 (+/- 1 day) dose is missed:

Cycle continues per protocol, with one dose not given (i.e., 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc.). The missed dose will not be made up. Day 15 is administered as per cycle calendar if counts and chemistries permit. Depending on the specific toxicity, PEGPH20 may be

administered on Day 8 even if gemcitabine/nab-paclitaxel have to be held, or can also be held at the discretion of the treating physician.

Day 15 (+/- 1 day) dose missed:

That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a x2q3 (21-day) cycle (i.e., 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc.). Depending on the specific toxicity, PEGPH20 may be administered on Day 15 even if gemcitabine/nab-paclitaxel have to be held, or can also be held at the discretion of the treating physician.

Doses will be reduced for hematologic and other non-hematologic toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.03. If recurrent toxicities require dose modifications below those listed in Tables 1 and 2 below, the patient should be removed from study treatment. If patients experience study drug-related toxicities that require all treatment to be held for ≥ 14 days from their scheduled dose, they will be discontinued from further participation in this study. In special circumstances noted below, one component of study treatment may be permanently discontinued but the patient may remain on study. When the dose of one or more drugs is reduced due to toxicities, dose re-escalation will not be permitted for the duration of study treatment.

Table 1. Dose Reductions for Gemcitabine and Nab-paclitaxel

	Nab-Paclitaxel	Gemcitabine
Starting dose level	125 mg/m ²	1000 mg/m ²
Dose level -1	100 mg/m ²	800 mg/m ²
Dose level -2	75 mg/m ²	600 mg/m ²

Table 2. Dose Reductions for PEGPH20

	28-day dosing cycle in combination with gem/Abrax
Starting dose level	3 µg/kg on days 1, 8, and 15
Dose level -1	1.6 µg/kg on days 1, 8, and 15
Dose level -2	na

During the initial one-week run-in period, PEGPH20 is to be administered at a dose of 3 µg/kg on days 1 and 4. Depending on AEs that occur following the day 1 dose (refer to Tables 3 and 4), the scheduled day 4 dose can be reduced to 1.6 µg/kg and administered with a delay of up to 7 days. Patients who cannot receive their second dose of PEGPH20 during this run-in period will be removed from study and replaced.

Doses of study drugs may be held or adjusted as detailed in Tables 3 and Table 4 below. The start of a new treatment cycle should be held until ANC >1500 and platelet count > 100,000, and until toxicities from the prior cycle have improved to grade 1 or baseline. If the start of a new cycle is delayed, all components of study treatment should be held and resumed at the same time.

Table 3. Dose Modifications for Hematologic Toxicities at the Start of Each Cycle or Within a Cycle

Cycle Day	ANC (cells/mm ³)		Platelet count (cells/mm ³)	Nab-Paclitaxel, Gemcitabine and PEGPH20
Day 1	<1500	OR	<100,000	Delay doses until recovery
Days 8 and 15	500 to <1000	OR	50,000 to <75,000	Withhold nab-Paclitaxel and gemcitabine; resume at one dose level lower once counts adequately recover. Continue PEGPH20 at same dose. Consider growth factor support.
	< 500	OR	<50,000	Withhold all doses (including PEGPH20). Resume nab-Paclitaxel and gemcitabine at one dose level lower, and PEGPH20 at same dose level, once counts adequately recover. Consider growth factor support.

Abbreviations: ANC = Absolute Neutrophil Count

Table 4. Dose Modifications for Non-Hematologic Toxicity

For grade 3 or higher clinically relevant non-hematologic toxicities, treatment cycles will be delayed. Therapy may be resumed when the toxicity improves to grade 0-1 (or baseline). If the patients are unable to resume therapy within 2 weeks of a planned dose, they will be removed from the study. Dose adjustments in subsequent cycles will be made as follows depending on the highest grade of toxicity observed in prior cycles.

	nab-Paclitaxel	Gemcitabine	PEGPH20
Diarrhea			
Grade 1 -2	Continue at same dose		
Grade 3	Interrupt until grade 0-1 1 st = Resume at same dose 2 nd = Decrease dose to level-1	Interrupt until grade 0-1 1 st = Resume at same dose 2 nd = Decrease dose to level-1	Continue at same dose

	nab-Paclitaxel	Gemcitabine	PEGPH20
Grade 4	Interrupt until grade 0-1 1 st = Decrease dose to level-1	Interrupt until grade 0-1 1 st = Resume at same dose	Interrupt until gemcitabine and nab-paclitaxel resumed*
Symptomatic management of diarrhea: IV hydration and loperamide. Loperamide can be used at 4 mg at the first onset of loose stools and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. If control takes longer than 2 days, medical evaluation including relevant diagnostic procedures and alternative treatments should be considered.			
Nausea/Vomiting			
Grade 1-2	Continue at same dose		
Grade 3	Interrupt until grade 0-1 1 st = Decrease dose to level-1 2 nd = Decrease dose to level-2	Interrupt until grade 0-1 1 st = Resume at same dose 2 nd = Decrease dose to level-1	Continue at same dose
Grade 4	Interrupt until grade 0-1 1 st = Decrease dose to level-1 2 nd = Discontinue study treatment	Interrupt until grade 0-1 1 st = Decrease dose to level-1 2 nd = Discontinue study treatment	Interrupt until gemcitabine and nab-paclitaxel resumed*
Liver Function Tests (AST, ALT, total bilirubin, NOT alkaline phosphatase)			
Grade 1-2	Continue at same dose		
Grade 3	Interrupt until grade 0-1 1 st = Decrease dose to level-1 2 nd = Resume at same dose	Interrupt until grade 0-1 1 st = Resume at same dose 2 nd = Decrease dose to level-1	Continue at same dose
Grade 4	Interrupt until grade 0-1 1 st = Decrease dose to level-1 2 nd = Off study	Interrupt until grade 0-1 1 st = Decrease dose to level-1 2 nd = Off study	Interrupt until gemcitabine and nab-paclitaxel resumed*
nab-Paclitaxel is not recommended for patients with moderate to severe hepatic impairment and the nab-Paclitaxel starting dose of 125mg/m ² is recommended for patients with mild hepatic impairment, defined as (total bilirubin greater than ULN and less than or equal to 1.5 X ULN and AST less than or equal to 10 X ULN). Do not administer Abraxane to patients with total bilirubin greater than 5 X ULN or AST greater than 10 X ULN.			
Peripheral neuropathy <u>Note:</u> As observed in other clinical trials, ≥ Grade 3 neuropathy related to nab-Paclitaxel is usually seen in later phases of the treatment (cycle 6 and beyond). If ≥ Grade 3 neuropathy occurs in early treatment cycles, other factors predisposing the patient to neuropathy might be present (e.g., Diabetes, alcohol consumption, concomitant medications). To maintain dose intensity during the first 4 treatment cycles, careful consideration should be exercised when these predisposing factors are present.			

	nab-Paclitaxel	Gemcitabine	PEGPH20
Grade 1-2	Continue at same dose		
Grade 3	<p>Interrupt until grade 0-1 1st = Decrease dose to level-1 2nd = Decrease dose to level-2</p> <p>Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-Paclitaxel dosing for ≥ 21 days should have their nab-paclitaxel permanently discontinued, but may remain on gemcitabine and PEGPH20.</p>		
Grade 4	<p>Interrupt until grade 0-1 1st = Decrease dose to level-2 2nd = Off study</p> <p>Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-Paclitaxel dosing for ≥ 21 days should have their nab-paclitaxel permanently discontinued, but may remain on gemcitabine and PEGPH20.</p>	Continue at same dose	Continue at same dose
Musculoskeletal events (i.e. myalgias)			
Grade 1	Continue at same dose		Continue at same dose. May give additional dexamethasone, muscle relaxer, or pain medication.
Grade 2	Continue at same dose		Continue at same dose OR reduce dose to 1.6 ug/kg. May give additional dexamethasone, muscle relaxer, or pain medication.
Grade 3-4	Interrupt until grade 0-1, then resume at one dose level lower.		Hold treatment. If resolved to ≤ Grade 2 within 14 days, may resume treatment at 1.6 µg/kg For Grade 4 events,

	nab-Paclitaxel	Gemcitabine	PEGPH20
			patient may be removed from the study at the discretion of the Investigator. If lasts > 14 days, patients should be removed from study treatment.
Cutaneous toxicity			
Grade 1	Continue at same dose.		Continue at same dose.
Grade 2-3	Continue treatment but reduce to next lower dose level; discontinue treatment if toxicity persists		Continue at same dose.
Grade 4	Hold treatment until toxicity resolves to grade 2 or less, then reduce to next lower dose level. Discontinue treatment if toxicity persists.		Hold treatment. Resume at same dose level when gemcitabine/nab-paclitaxel is resumed.
Other non-hematologic toxicity			
Grade 1-2	Continue at same dose		Continue at same dose
Grade 3	Interrupt until grade 0-1; Decrease dose for both drugs to level-1 Maximum of two dose reductions allowable.		Hold treatment if deemed potentially related to PEGPH20. Treatment may resume at the same dose level if toxicity is resolved to 0-1 (or baseline) within 14 days. For second event, dose should be decreased to 1.6 µg/kg.
Grade 4	Interrupt until grade 0-1; Decrease dose for both drugs to level-1. For repeated grade 4 event, discontinue from study.		Hold treatment. Treatment may resume at 1.6 µg/kg if toxicity is resolved to 0-1 (or baseline) within 14 days.

* If PEGPH20 dosing is interrupted, daily self-administration of enoxaparin should be continued until the patient is off study, for at least 14 days after the last dose of PEGPH20.

Toxicities of special note

- For any grade 2 or higher **thromboembolic event**, regardless of relatedness to PEGPH20, patients will discontinue PEGPH20 treatment permanently and should be treated per NCCN guidelines. Patients may remain on study and continue receiving nab paclitaxel and gemcitabine according to standard practice and the treating physician’s clinical judgment.

- Patients who develop Grade 3 or higher pulmonary toxicity or hemolytic uremic syndrome will be taken off study.
- Hypersensitivity reactions with nab-paclitaxel are rare. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience severe hypersensitivity reactions to nab-paclitaxel should not be re-challenged. They may continue on study with just gemcitabine/PEGPH20. It is not recommended to administer nab-paclitaxel to patients with prior hypersensitivity to a taxane.
- All treatment should be held for grade 3 or 4 febrile neutropenia, and not resumed until the fever has resolved and ANC \geq 1500. Gemcitabine and nab-paclitaxel should then be resumed at the next lower dose level, while PEGPH20 may be resumed at the same dose level as previously.
- Patients who experience any other unexpected Grade 4 toxicities may be taken off study at the first or second episode, at the discretion of the investigator, per Table 4 above.

8.3 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The study monitor will verify these documents throughout the course of the study.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is presented in Section 10.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening/pre-treatment and on day 1 during the clinical assessment by the physician, and at early termination

when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a qualified delegate on day 1 of each cycle.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse, oximetry and respirations will be performed after resting for 5 minutes on each day that the patient receives PEGPH20, nab-paclitaxel and gemcitabine.

9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Hematology

Blood will be obtained and sent to clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count). Hematology labs should be drawn within 2 days before each infusion (days 1, 8 and 15 of each cycle).

9.2.2 Blood Chemistry Profile

Blood will be obtained and sent to clinical chemistry lab for determination of serum albumin, alkaline phosphatase, total and direct bilirubin, bicarbonate, BUN, chloride, creatinine, glucose, potassium, SGOT [AST], SGPT [ALT], calcium, sodium. Blood chemistry profiles should be drawn within 2 days before each infusion (days 1, 8 and 15 of each cycle).

9.2.3 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within (insert time-frame which must be at least 28 days of the subject's last dose of IP), are considered immediately reportable events. IP is to be discontinued immediately.

The Investigator will follow the female subject until completion of the pregnancy. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

9.2.4 Pregnancy Test

A urine or serum pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

9.3 Tumor marker

CA19-9 levels will be measured during screening (prior to initiation of therapy) and then monthly (i.e., first day of every cycle).

9.4 Research Tissue Analyses

EUS-guided core biopsies will be obtained at baseline and after a run-in period with PEGPH20 from the 15 patients enrolled in the run-in/Part 1 of the study. Three core biopsies via 22-gauge “Pro-Core” needle will be obtained and will be submitted for research analyses purposes. Tissue will be placed in OCT in the EUS suite and will be picked up by the CC Tissue Bank for storage. Tissue analyses will include standard IHC staining for actin, hyaluronic acid staining with binding protein probe, proliferation as measured by ki-67% and Phospho-histone H3 (Ph-H3); cell apoptosis as evaluated by IHC stain for cleaved caspase 3 (CC3) and Tunel. If limited tissue sample is obtained via the core biopsies, the priority of tissue analysis will be as follows: (1) fixed in formalin for H&E and IHC (Ph-H3; CC3/Tunel; HA binding); (2) fixed in OCT such that IHC with difficult antibodies can be done (to potentially obtain mRNA or DNA).

9.5 Functional MRI

The CT and MR imaging analyses will be at a UC campus. To decrease the impact that metal stents may have on the functional MRI results, those patients who have existing metallic stents (biliary or enteral) will *not* partake in the fMRI component of this study. In addition, to reduce variability in results, the DCE-MRI and DWI-MRI will be obtained on the same MR machine at a similar time of day as the baseline scan. The DCE-MRI images will be analyzed by calculating Ktrans and DWI-MRI images will be analyzed by calculating ADC as described elsewhere[41, 44]. We will scan patients in a torso coil on a 3T clinical MR scanner. Imaging will include MR diffusion with b-values of 0, 125, and 500 for estimates of perfusion and tumor, and dynamic contrast-enhanced MR imaging (DCE-MRI) for measurement of Ktrans, blood

volume, and blood flow. The region of tumor will be determined by MR imaging in reference to the baseline CT scans. The native T1 of the pancreas and liver will be calculated from a series of four, 3D, spoiled gradient recalled echo (SPGR) sequences with different flip angles. The conventional DCE-MRI will be acquired as a 3D fast spoiled gradient echo sequence, covering the targeted areas of the pancreas or liver, at a temporal resolution of 5 sec over 6 minutes after the administration of 0.1 mmol/kg gadobenate dimeglumine. DCE-MRI images will be post-processed using MISTar software (Apollo Medical Imaging, Melbourne, Australia), which allows for motion correction to account for any shifts in data. Datasets with artifacts will be eliminated before further post processing. After contrast delivery, the new T1 is calculated and is presumed to change with the Gd concentration such that $[Gd] = (1/T_1 - 1/T_{10})/R_1$ where R1 is assumed to be $4.5 \text{ sec}^{-1} \text{ mmol/L}^{-1}$ at 3T.

10 EVALUATIONS BY VISIT

Patients will have baseline clinical and laboratory screening evaluations within 21 days prior to start of protocol therapy. Scans must be performed within 4 weeks prior to initiation of therapy. Patients' clinical assessment may take place on day 1 of each cycle. Laboratory measurements should be done within 48 hours prior to the day of treatment with nab-paclitaxel and gemcitabine.

Table 5. Timeline of Clinical Assessment, Studies and Treatment

	Pre-Treatment Period	Run-in ^d Period (n=15)	Chemotherapy Cycle (n=36)				End of Treatment ⁿ
			1	2	3	4	
PEGPH20		X (days 1, 4)	X	X	X	X	
Enoxaparin ^a 1 mg/kg subcutaneous daily		X ^a	X	X	X	X	
Dexamethasone 8mg (PO 1-2 hours pre- and PO 8-12 hours post-PEGPH20)		X (days 1, 4)	X	X	X	X	
Nab-paclitaxel ^k			X	X	X	X ^l	
Gemcitabine ^k			X	X	X	X ^l	
Informed Consent and Eligibility Review	X						
Demographics (date of birth, gender, race)	X						
Medical History	X						
Review of Concurrent Medications ^h	X		X	X	X	X	X
Physical Examination ^h	X		X	X	X	X	X
Vital Signs ^b	X		X	X	X	X	
Height	X						
Weight ^b	X		X	X	X	X	X
ECOG Performance Status ^h	X		X	X	X	X	X
CBC with Differential ^b	X		X	X	X	X	X
Blood Chemistry Profile ^{c, b}	X		X	X	X	X	X
CA 19-9	X		X	X	X	X	X
Plasma HA level ⁱ		X (days 1, 4)	X	X	X	X	
Hepatitis B serology (Hepatitis B core Antibody, Hepatitis B surface Antibody, Hepatitis B surface Antigen)	X						
Serum or urine β -hcG	X						
Adverse Event Evaluation	X	X	X	X	X	X	X
CT/MRI Chest, Abdomen, Pelvis with Contrast	X ^j			X		X (day 21)	
Run-in Cohort: CT/MRI Chest, Abdomen, Pelvis with contrast ^d (n=15)		X (day 8 \pm 1 day)					
Run-in Cohort: Functional MRI ^d (n=15)	X	X (day 8 \pm 1 day)				X ^e	
Run-in Cohort: EUS-guided Core Biopsy ^d (n=15)	X	X (day 8)					

a. Enoxaparin administration will commence on day 1 of run-in period. Daily self-administration will stop 24 hours before and resume 24 hrs after the post-run-in biopsy, and continue throughout neoadjuvant therapy. Enoxaparin will be administered subcutaneously (SC) at a dose of 1 mg/kg/day. Rounding of the dose may be done per Institution policy and when using prefilled syringes. All efforts should be made to administer the calculated 1 mg/kg dose (\pm 10%); however, if prefilled syringes

are used, the treating physician may use medical judgment regarding the appropriate pre-filled syringe. If the rounded dose is greater than 20% of the expected dose based on weight, the Sponsor should be consulted. Refer to Table 8 in Appendix 1 for examples of rounding based on the expected enoxaparin dose.

b. These measurements will be obtained before infusion on days 1, 8 and 15 (drawn within 2 days of infusion) while receiving chemotherapy.

c. Basic metabolic panel: Albumin, alkaline phosphatase, total and direct bilirubin, bicarbonate, BUN, chloride, creatinine, glucose, potassium, SGOT [AST], SGPT [ALT], calcium, sodium.

d. The 7 day PEGPH20 run-in, pre- and post-run-in EUS guided biopsies, and Functional MRIs, and post run-in CT/MRI only apply to the 15 patients enrolled in Part I. fMRIs will *not* be performed in patients with metallic (biliary or enteral) stents.

e. Functional MRI will be obtained only in those patients who were enrolled in the run-in period and who are found to have resectable disease on cycle 4, day 21 CT scan (n=10).

f. Enoxaparin administration will be stopped 24 hours before surgery.

h. Physical examination, with concomittant medicines and ECOG, will be performed by the treating MD or qualified delegate on day 1 of each cycle of neoadjuvant chemotherapy (or more frequently at the treating provider's discretion).

i. EDTA plasma (1-2 mls) to be drawn prior to each PEGPH20 dose.

j. The diagnostic CT scan or MRI confirming borderline resectability must have been performed within 4 weeks prior to the day of the initiation of therapy.

k. After the first week of loading doses of PEGPH20 alone, the combination therapy of nab-paclitaxel, gemcitabine and PEGPH20 should start the following week, preferably on Monday, (but within a 2 days window without protocol violation). The allowable window for all subsequent chemotherapy treatment timepoints is +/- 1 day.

l. Surgery should be scheduled no earlier than 2 weeks and, ideally, no later than 4 weeks post-neoadjuvant therapy.

Scheduling of surgery is at the discretion of the physician according to the clinical condition of the patient.

m. Adjuvant chemotherapy should start no earlier than 8 weeks and no later than 12 weeks post-surgery. Choice of therapy will be made according to the treating MD's discretion.

n. For patients having surgery, End of Treatment assessments should be performed post-surgery.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator and the study team will record any occurrences of AEs reported during conversations with the patients or their family members or care providers.. This will occur from the signing of the informed consent to 28 days after the last dose of study drug, or longer if the PI deems the event is related to the drug. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 5 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

IND Annual Reports

Since the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CFR 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided [REDACTED] supporter of this study as follows.

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

Table 6. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.
Death related to adverse events (5)	While the subject is on study, death attributed to any cause will be reported.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in [NCI CTCAE v. 4.03](#).

Table 7. AE Relationship to Study Drug

Relationship to Drug	Comment

Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.1 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events (e.g. secondary cancer, etc.) may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.1.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF IRB Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed and at 28 days after the last dose of study drug or longer if the PI determines the event is related to the study drug.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

Expedited Reporting

Reporting to the UCSF Data and Safety Monitoring Committee (DSMC)

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF's Institutional Review Board (IRB)

The Study Chair must report events meeting the IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Guidance on Adverse Event Reporting to the IRB is available online at the UCSF Human Research Protection Program website.

Expedited Reporting to the Food and Drug Administration (FDA)

As this study is being conducted under an Investigational New Drug Application (IND), the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeframe for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report must be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

The investigator (or designee) should prepare Form FDA 3500A (MedWatch) detailing the event, and contact the Institutional Trials Unit for assistance in the preparation of the IND Safety Report.

11.1.2 Reporting of Serious Adverse Events to Halozyme

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and during the study period will be reported to [REDACTED] within 24 hours of learning of its occurrence. SAEs will be reported to [REDACTED] by completed SAE Form or MedWatch 3500A form via email at [REDACTED]. The form should include a description of the event, subject number/initials, criteria for seriousness, severity, assessment of relationship to study drug(s), whether the event was expected or unexpected per the Investigator's Brochure or package insert, and other available information relevant to the event. Any new information about a previously reported SAE must also be sent to Halozyme within 24 hours of the initial awareness. The investigator must also provide [REDACTED] with a copy (MedWatch 3500A form) of any FDA submissions (expedited 7-Day or 15-Day initial and follow-up safety reports) within 24 hours of submission.

Thromboembolic events will be considered Adverse Event of Special Interest (AESI) and will also be reported [REDACTED] at the above number or email. AESI will be reported using an AESI form.

11.2 Data and Safety Monitoring Committee (DSMC) Contacts

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment. This includes unexpected delay in wound healing, development of wound dehiscence or pancreatic anastomotic leak.
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)
- Initiation of other anticancer therapy

- Development of intercurrent medical condition or need for concomitant treatment that precludes further safe participation in the trial such as the occurrence of any Grade thromboembolic event.

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 9 for early termination procedures.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to visit 2) should have an early discontinuation visit. Refer to Section 9 for early termination procedures. Subjects who withdraw after first cycle with study therapy but prior to second treatment cycle should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.3 Replacement of Subjects

Patients will be included in the primary AE evaluation if the full 28-day treatment cycle is completed. In the event that a patient is unable to complete the 28-day cycle unrelated to treatment toxicity, this patient will be removed from study and will be replaced for primary MTD evaluation. In the event that a patient withdraws from study due to treatment-related toxicity, this patient will be included in the AE evaluation for this study and will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or the investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria

- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. A copy of the form will be filed in the site's regulatory binder.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All eligible patients who are enrolled into the study and receive at least one complete, 28-day cycle of the study drugs will be included in the safety analysis. If the patient withdraws from the study prior to completing the first cycle of chemotherapy secondary to reasons other than toxicity related to the study therapy, they will not be included in the primary analysis. However, if the patients' enrollment in the trial is terminated secondary to toxicity secondary to the study drugs, they will be evaluated as having an AE and will be included in the analyses.

In addition, the patients who have received at least 2 complete, 28-day cycles of study drugs will be included in the secondary analyses as they will have had monthly CA 19-9 measurements and restaging scans which would be obtained after 8 weeks of therapy.

14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, gender, age, height and weight.

14.3 Analysis of Primary Endpoint

The primary endpoint of the study is to evaluate development of clinically relevant pancreatic fistula in the post-operative period after neoadjuvant treatment with PEG, gemcitabine and nab-paclitaxel. The co-primary endpoint is to evaluate pathologic complete response after neoadjuvant PEG, gemcitabine and nab-paclitaxel treatment. Descriptive statistics with frequency and proportion will be used to evaluate the primary endpoints.

14.4 Analysis of Secondary Endpoint

Secondary endpoints include early efficacy as measured by percent change of CA 19-9 response rate, R0 resection rate, overall response rate (ORR) and disease free survival (DFS). Descriptive

statistics with frequency and proportion will be used to analyze the CA19-9 response rate and ORR. Kaplan-Meier methods will be used to analyze DFS with median and 95% CI.

14.5 Analyses of the Correlative Studies

Tissue Analyses:

We will examine the tissue from baseline to post-therapy at the time of surgery. We will use descriptive statistics and graphical displays to compare the percent change in stromal depletion overall and to describe the association with cell proliferation and death.

Imaging Studies:

The images will be analyzed using MISTar software [REDACTED] using a modified Tofts model. We will explore the percent change in Ktrans and ADC from baseline to post-therapy as reported from the DCE-MRI and DWI-MRI, respectively, using descriptive statistics. Due to substantial interscan variability, a **50% change** in DWI or DCE parameters is considered significant.

14.6 Additional Stopping Rules for Safety

In order to ensure patient safety, this trial includes early stopping rules in the event of unexpected postoperative complications such as development of pancreatic fistula. Two interim safety assessments will be performed when the first 7 and 15 evaluable patients are enrolled in the study. If three out of first 7 patients or four out of first 15 patients show unexpected postoperative complications with delayed wound healing, development of wound dehiscence, wound infection or pancreatic fistula, this trial will be stopped. The early stopping rules of declaring the trial unsafe based on assumed postoperative complications of < 11% and type I alpha of 10% are described in Table 9.

Table 9. Early Stopping Criteria (assuming %complications < 11%)

# of evaluable patients enrolled	7	15	
Alpha (Type I error rate)	10%	10%	5%
# of post-op complications	3	4	5

Furthermore, the development of venous thromboembolic events (DVT and/or PE) or arterial thromboembolic events during the preoperative treatment period may affect the safety and timing of surgery. Therefore, at the same interim assessment time points as above, we will consider the development of VTE/ATEs in 3 or more of the first 7 patients, or 4 or more of the first 15 patients, occurring during the preoperative treatment period through one week postoperatively, as a signal to stop the trial early.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. *For EDC studies:* Queries are entered, tracked, and resolved through the EDC system directly. *For paper studies:* Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.4.1 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the investigator is required to maintain study records and, therefore, the investigator should be contacted prior to removing study records for any reason.

15.5 Monitoring

Data and Safety Monitoring Plan for Multicenter Institutional Study (Phase 2 or 3 Institutional Study)

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data
- Review of suspected adverse reactions considered “serious”
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject’s treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be sent electronically or faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

Adverse Event Monitoring

All Grade 3-5 Adverse Events, whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data and Safety Monitoring Committee Contacts:

<p>██████████ ██████████ ██████████ ██████████</p>	<p>██████████████████ ████████████████ ██████████████████ ██████████ ██████████ ██████████████████</p>	<p>██████████████████ ██████████ ██████████████████ ██████████████████ ██████████ ██████████████████</p>
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15.5.1 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center and Halozyme prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to Halozyme Therapeutics prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the

standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF IRB. Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

16.5 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

16.6 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the Halozyme and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.7 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB, [REDACTED], (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).

9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

17 Recommended Dosing of Enoxaparin

Enoxaparin will be administered to all subjects to minimize the risk of thromboembolic events (TE) events. Enoxaparin will be administered subcutaneously (SC) at a dose of 1 mg/kg/day. Rounding of the dose may be done per Institution policy and when using prefilled syringes supplied [REDACTED]. Refer to Table 8 for examples of rounding based on the expected enoxaparin dose. If the rounded dose is greater than 20% of the expected dose based on weight, the Sponsor should be consulted.

Table 8 Rounding of Enoxaparin with Using Pre-filled Syringes

Enoxaparin Expected Dose (mg)	Rounded Enoxaparin Dose (mg)	Syringes Dispensed
50-69	60	60 mg x1
70-89	80	80 mg x1
90-109	100	100 mg x 1
110-134	120	120 mg x 1

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Appendix 1 UCSF Policy/Procedure for Required Regulatory Documents for UCSF Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore[®], as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Committee for Human Research (IRB) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to IRB with supporting fax documentation

Documents Filed in OnCore[®]:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore[®] Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

Appendix 2 UCSF Policy/Procedure for Required Regulatory Documents for Single Site and Multicenter Investigator-Initiated Oncology Clinical Trials

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) for both IND and IND-exempt trials.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iRIS and OnCore[®], as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. Single Site (HDFCCC) Therapeutic Essential Regulatory Documents:

Documents Filed in iRIS:

- Current and prior versions of the Informed Consent Form(s) (ICFs).
- IRB approvals for initial submission of application, all modifications, and continuing annual renewals.
- Current and prior approved protocol versions.
- Current IRB roster
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event (SAE) Reports.
- Subject diary and handouts (if applicable).
- Single Patient Exception (SPE) Report(s) to IRB with Approval Letter(s) from IRB.
- Protocol Violation (PV) Reports with acknowledgement from the IRB.

Documents Filed in OnCore[®]:

- Package Insert (if the study drug is commercial).
- Protocol signature page(s) with PI signature(s) for all protocol versions.
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC) document.

- Screening/enrollment log.
- Data and Safety Monitoring Committee (DSMC) monitoring reports.
- DSMC dose escalation approvals with study status summary forms.
- Case Report Form (CRF) completion manual.
- Drug Destruction Standard Operating Procedure (SOP).
- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature.
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, and Staff Training Documents (i.e., Collaborative Institute Training Initiative (CITI), etc.).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center.
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor.
- Drug Destruction Standard Operating Procedure (SOP).
- For all laboratories listed on the FDA 1572, will need CUA certifications, CAP certifications, lab licenses, CV(s) and Medical License(s) of Lab Director(s), and laboratory reference ranges.

Documents Filed in Regulatory Binder:

- Delegation of Authority Log with signatures (to be scanned in OnCore once the trial is complete).

2. Additional Essential Documents for Therapeutic Multicenter Trials for the

Coordinating Center (filed in OnCore or Zip Drive):

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act {HIPAA} Consent Form for the Participating Site(s).
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s), will need Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for investigational New Drug Application).
- Site Initiation Visit (SIV) minutes and correspondence with the Participating Site(s).

- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s).
- Protocol Violations (PV) Reports to IRB with acknowledgement from IRB for Participating Site(s).
- Single Patient Exception (SPE) Reports to IRB with IRB Approval Letters for Participating Site(s).
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s).
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s).
- For all laboratories listed on FDA 1572, will need CUA certifications, CAP certifications, lab licenses, CVs and Medical License(s) of Lab Director(s), and laboratory reference ranges for the Participating Site(s).
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study).
- Serious Adverse Event (SAE) forms submitted to the IRB for the Participating Site(s).

3. Required Multicenter Essential Regulatory Document Checklist for Therapeutic and Non-Therapeutic Trials (For Start-Up Only):

- See attached checklist(s).

4. Required Essential Regulatory Documents for Single Site and Multicenter Therapeutic IND-Exempt Studies (filed in OnCore):

- For IND Exempt studies, the Essential Regulatory Documents for UCSF would include all documents in Section #1 of this policy. The Essential Regulatory Documents from the participating site(s) for Multicenter Trials when UCSF is the Coordinating Center would only include the signed protocol signature page, CV of the PI, and the IRB approval letters. All other documents in Section #2 of this policy would be the responsibility of the Participating Site(s).

5. Required Essential Regulatory Documents for Single Site Non-Therapeutic Studies (filed in OnCore):

- For Single Site non-therapeutic trials, all Regulatory Documents in Section #1 of this policy are required except for: current and prior versions of the Investigator Brochure (IB), package insert (if the study drug is commercial), DSMC dose escalation approvals with study status summary forms, approvals for Biosafety Committee, Radiation Committee, and Infusion Center, and drug destruction SOPs.

6. Required Essential Regulatory Documents for Multicenter Non-Therapeutic

Studies (filed in OnCore):

- For Multicenter non-therapeutic trials with UCSF as the Coordinating Site, all required Regulatory Documents listed above in Section #5 for Single Site non-therapeutic trials are required for the Coordinating Site. The only required Regulatory Documents from the Participating Site(s) will be: IRB approval letters, IRB roster, and ICF and HIPAA consent forms, the Delegation of Authority Log (with NIH or CITI human subject protection training certificates or GCP training certification), Protocol Violations and Single Patient Exception (SPE) reports to the IRB with supporting fax documentation (if applicable), Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor, and the Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s). If applicable, a copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study) will be required.

Alternate Procedures

There are no alternate procedures to the HDFCCC policy for requirements for Essential Regulatory Documents for Multicenter Investigator-Initiated Oncology Clinical Trials.

References

- ICH Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance (current version).
- International Conference on Harmonization: Good Clinical Practice: Consolidated Guideline (current version).
- International Conference on Harmonization: Essential Documents for the Conduct of a Clinical Trial (current version).
- 21CFR50

- 21 CFR56.11
- 45CFR46
- 21 CFR312

Required Regulatory Documents for Sub-sites Participating in Therapeutic UCSF Investigator Initiated Multicenter trial

Directions: Scan the documents in a zip drive and upload to OnCore.

1572

PI and Sub investigators:

- CV and Medical license
- Financial disclosure form
- NIH or CITI human subject protection training certification

Laboratories:

- CLIA &CAP and Lab Licenses
- CV and Medical License of Lab Director
- Laboratory reference ranges

Local Institutional Review Board

- IRB Approval letter
- Reviewed/Approved documents
 - Protocol version date: _____
 - Informed consent version date: _____
 - Investigator Brochure version date: _____
 - HIPAA
- Current IRB Roster

Other

- Delegation of Authority Log
 - Include NIH or CITI human subject protection training certificates or GCP training certification
- Pharmacy
 - Drug destruction SOP and Policy
- Protocol signature page
- Executed sub contract