CLINICAL STUDY PROTOCOL

Title:	**A Phase 2, Randomized, Multicenter Study of PEGPH20 (PEGylated Recombinant Human Hyaluronidase) Combined with nab-Paclitaxel Plus Gemcitabine Compared With nab-Paclitaxel Plus Gemcitabine in Subjects With Stage IV Previously Untreated Pancreatic Cancer**
Protocol Number:	**HALO-109-202**
IND:	**102770**
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Previous Version date:	**06 April 2015**
Sponsor:	**Halozyme, Inc.** **11388 Sorrento Valley Road** **San Diego, CA 92121** [redacted]

1. SYNOPSIS

Sponsor/Company

Halozyme, Inc.

11388 Sorrento Valley Road

San Diego, CA 92121

Protocol Number

HALO-109-202

Study Title

A Phase 2, Randomized, Multicenter Study of PEGPH20 (PEGylated Recombinant Human Hyaluronidase) Combined With nab-Paclitaxel Plus Gemcitabine Compared With nab-Paclitaxel Plus Gemcitabine in Subjects with Stage IV Previously Untreated Pancreatic Cancer

NOTE: The purpose of this Protocol Amendment 6 (Version 7) is to introduce study closeout procedures. These include a reduction of study procedures for the 1 subject still on treatment and discontinuation of study procedures for subjects in long-term follow-up. The closeout procedures are effective as of the date of this protocol amendment and supersede all study procedures required per previous Protocol Amendment 5 (Version 6) dated 06 April 2015. See Synopsis section titled "Study Closeout Procedures" and Section 6.1.4 for details.

Study Objectives

Primary:

- To estimate the progression-free survival (PFS) duration of PEGPH20 combined with nab-paclitaxel (NAB) plus gemcitabine (GEM) (PAG treatment).
- To evaluate the thromboembolic events in subjects treated in the PAG arm in Stage 2 of the study as of this protocol amendment.

Secondary:

- To estimate the relative benefit of PAG treatment versus NAB plus GEM (AG treatment), as assessed by the PFS hazard ratio.
- To estimate the relative benefit of PAG treatment versus AG treatment, as assessed by the PFS hazard ratio based on subject tumor-associated hyaluronan (HA) levels.
- To estimate the objective response rate (ORR), as defined by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), of PAG treatment and the relative benefit of PAG treatment versus AG treatment.
- To estimate the overall survival (OS) duration of PAG treatment and the relative benefit of PAG treatment versus AG treatment, as assessed by the OS hazard ratio.
- To evaluate the safety and tolerability profile of the PAG and AG treatment groups.
- To characterize the plasma pharmacokinetics (PK) of PEGPH20 when given in combination with NAB plus GEM.

Exploratory:

- To estimate the OS benefit of PAG treatment versus AG treatment based on HA levels from tumor biopsies.
- To estimate the duration of response (DR) of responders (complete response [CR] and partial response [PR]) of PAG and AG treatment.
- To compare the disease control rate (DCR; CR, PR and stable disease [SD]) between the PAG and AG treatment groups.
- To compare CA19-9 changes between the PAG and AG treatment groups.
- To assess treatment effect of PAG with regard to hyaluronan (HA) levels in plasma and in tumor biopsies.

Study Design

This is a Phase 2, multicenter, open-label, randomized study of PEGylated recombinant human hyaluronidase (PEGPH20) combined with nab-paclitaxel (NAB) plus gemcitabine (GEM) (PAG treatment) compared with NAB plus GEM (AG treatment) in subjects with Stage IV previously untreated pancreatic cancer. The study has two run-in phases and 2 stages, as described below.

A dose of 3.0 µg/kg was identified as the maximum-tolerated dose for PEGPH20 as either a single agent or in combination with GEM in two separate Phase 1 clinical studies. In both studies, PEGPH20 was administered twice weekly for the first 4 weeks, then once weekly for 3 out of every 4 weeks for the duration of participation.

Since PEGPH20 has not been evaluated in clinical studies in combination with NAB and GEM, this study will have a run-in phase to evaluate the safety and tolerability of PAG treatment (original PEGPH20 formulation) compared with AG treatment before initiating Phase 2. The Phase 2 portion is an open-label randomized study. With Amendment 1.0, an additional run-in phase will be conducted to incorporate a new formulation of PEGPH20 during the Phase 2 enrollment.

The dosing schedule for subjects randomized to the PAG and AG treatment groups will be the same in the run-in phases and Phase 2 (see Table S-1). The treatment period will consist of 4-week treatment cycles (28 days) with Week 4 of every cycle as a washout week (i.e., no treatment will be given). Treatment will continue until disease progression or unacceptable toxicity is documented.

Run-in Phases

In the first run-in phase, approximately 8 subjects will be randomized in a 3:1 ratio to receive PEGPH20 (3.0 µg/kg; original formulation) in combination with standard dosing of NAB+GEM (PAG treatment) or NAB+GEM (AG treatment). No stratification factors will be used. Additional subjects may be enrolled to further assess the tolerability of PEGPH20 in order to establish the acceptable safety profile prior to the randomization of the Phase 2 study.

The Sponsor, the participating Investigators, and the independent safety physician will determine if the dose and regimen for Phase 2 is acceptable after reviewing all available safety data from Cycle 1 from all subjects in the run-in phase.

With Amendment 1.0, a second run-in phase will be conducted to evaluate a new formulation of PEGPH20. Approximately 8 subjects will be randomized in a 3:1 ratio to receive the new formulation of PEGPH20 at 3.0 µg/kg in combination with standard dosing of NAB+GEM (PAG treatment) or NAB+GEM (AG treatment).

The Sponsor, the participating Investigators, and the independent safety physician will determine if the dose and regimen for the new formulation of PEGPH20 is acceptable after reviewing available safety data from Cycle 1 from all subjects in the second run-in phase. If the safety profile and the PK profile of the new formulation are deemed acceptable, the new formulation of PEGPH20 will be available to all subjects on the study.

Phase 2

In Phase 2, approximately 237 subjects will be randomized to receive PEGPH20 (3.0 µg/kg, pending outcome of run-in phase safety assessment) in combination with standard dosing of NAB+GEM (PAG treatment) or NAB+GEM (AG treatment). Randomization will be stratified by Karnofsky Performance Status (70% to 80% and 90% to 100%).

Phase 2 will have 2 stages due to a partial clinical hold that occurred from April through July 2014 (see Section 6.1.2.1 for additional details). The first stage will randomize subjects in a 1:1 ratio. The second stage will randomize subjects in a 2:1 ratio (PAG:AG). The second stage of the study will start as of Amendment 3.0, in which the inclusion and exclusion criteria were modified, re-start procedures were added, and low molecular weight heparin prophylaxis use was added.

Table S-1: Overview of Study Medication Schedule by Treatment Group

Timepoint	PAG Treatment Group	AG Treatment Group
Cycle 1		
Day 1	PEGPH20	NAB and GEM
Day 2	NAB and GEM (24 ± 4 hours after Day 1 dose of PEGPH20)	No visit
Day 4	PEGPH20	No visit
Day 8	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 11	PEGPH20	No visit
Day 15	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 18	PEGPH20	No visit
Day 22	No treatment (i.e., washout)	No treatment (i.e., washout)
Cycle 2 onwards		
Day 1	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 8	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 15	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 22	No treatment (i.e., washout)	No treatment (i.e., washout)

Abbreviations: AG = nab-paclitaxel plus gemcitabine; GEM = gemcitabine; PAG = PEGPH20 in combination with nab-paclitaxel plus gemcitabine; NAB = nab-paclitaxel.
Note: Each treatment cycle is 28 days. Dose interruption and modifications are permitted; refer to Section 8.3 for further guidance.

Dexamethasone 8 mg will also be given to each treatment group as follows:

- PAG treatment group: Within 2 hours prior to the beginning of each PEGPH20 infusion and 8 to 12 hours after the completion of the PEGPH20 infusion.
- AG treatment group: Within 2 hours prior to the beginning of each NAB infusion and 8 to 12 hours after the completion of the GEM infusion.

Effective with amendment 4.0 (protocol version 5.0), all subjects on both arms will be treated with enoxaparin at a dose of 1 mg/kg/day. Enoxaparin should be started immediately following consent for amendment 4.0 for ongoing subjects and on Day 1 for new subjects entered into the trial.

Study Re-starting Procedures Overview Following Temporary Hold

The following thromboembolic event risk factors will be assessed for all subjects (both treatment groups) after signing the updated ICF (protocol amendment 3.0) and prior to the next scheduled treatment:

- Prior history of cerebrovascular accident or transient ischemic attack
- Pre-existing carotid artery disease
- Concomitant use of megestrol acetate (subjects on the PAG arm must discontinue use >10 days before re-starting PEGPH20 treatment and subjects on the AG arm should discontinue use immediately)
- DVT on Doppler ultrasound or pulmonary embolism (PE) on chest CT prior to re-initiating therapy after study hold

Subjects who were randomized to the PAG treatment arm and answer yes to one or more of the questions above cannot re-start PEGPH20 therapy. Subjects who were randomized to the AG arm who answer yes to one or more questions may continue. All subjects (in both treatment arms) will continue receiving Gemcitabine and Nab Paclitaxel regardless of how the above questions were answered. Subjects re-starting PEGPH20 should re-start on the next scheduled visit day of the cycle they are currently in (i.e., do not "make up" visits).

Additionally, all subjects will begin enoxaparin therapy. Subjects who are contraindicated to receive enoxaparin (see the exclusion criteria) will be discontinued from study treatment (PAG and AG).

Study Closeout Procedures

With this protocol amendment 6 (Version 7), the Sponsor is implementing study closeout procedures as described below. These include a reduction of study procedures for the 1 subject still on treatment (PAG group) and discontinuation of study procedures for subjects in long-term follow-up.

The closeout procedures are effective as of the date of this Protocol Amendment 6, 09 February 2018, and supersede all study procedures required per previous Protocol Amendment 5 (Version 6) dated 06 April 2015.

Study closeout procedures for subjects that are either on treatment or in long-term follow-up are described below:

- The remaining subject on treatment will continue to receive study medication (PAG) until disease progression or other protocol-specified reasons for treatment discontinuation (see Section 7.3.1) or study discontinuation (see Section 7.3.2). For this subject, all procedures required per Protocol Amendment 5 will be immediately discontinued except for the following (see Table 10):
  - Administration of PEGPH20 on Days 1, 8, and 15 (as in Protocol Amendment 5); and NAB and GEM every 2 weeks (Days 1 and 15) or at the Investigator's

discretion and per standard of care (vs. on Days 1, 8, and 15 in Protocol Amendment 5)

  - Administration of dexamethasone and enoxaparin (see Section 6.1.3.1 and Section 6.1.2.3 for additional details)
  - Imaging assessments performed locally (vs. sent to a CIR in Protocol Amendment 5) at a reduced frequency (every 4 cycles or less frequently, at the Investigator's discretion and per standard of care [vs. every 2 cycles in Protocol Amendment 5]) to minimize radiation exposure
  - Clinical laboratory assessments (blood chemistry, hematology, and coagulation) by a local laboratory, all at a reduced frequency (Days 1, 8, and 15 [vs. Days 1, 8, 15, and 22 in Protocol Amendment5]) and at the End of Treatment visit. The clinical laboratory tests on Days 1, 8, and 15 will also be reduced in scope with fewer assessments (details in Table 10) to ensure the subject's well-being and monitor key safety parameters through the remainder of study treatment.
  - Collection/reporting of serious adverse events (SAEs) and adverse events of special interest (TE events) for 30 days after the last dose of study treatment (additional details on SAE and TE event reporting in Section 10.3 and Section 10.4, respectively) (no other adverse events [AEs] will be collected).
  - Collection/reporting of pregnancy information as specified in Section 8.2.13 and Section 10.7

- For subjects in long-term follow-up, the long-term follow-up will be discontinued immediately. For the 1 subject still on treatment, long-term follow-up will not be implemented when this subject discontinues treatment and completes the End of Treatment Visit (Section 8.1.3.2). This subject's End of Treatment Visit will correspond to the end of the study.

The end of the study is defined by the time when all subjects have discontinued treatment.

Study Population

Subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer will be enrolled. See below for a list of all inclusion and exclusion criteria.

Planned Total Sample Size

This study is planned to randomize approximately 253 subjects.

Run-in phases: Approximately eight subjects will be randomized in a 3:1 ratio to receive PAG (original formulation of PEGPH20) or AG treatment. With Amendment 1.0, an additional 8 subjects will be randomized 3:1 to receive PAG (new formulation of PEGPH20) or AG treatment.

Phase 2: Approximately 237 subjects will be randomized to receive PAG or AG treatment. Stage 1 enrolled 123 subjects (1:1 ratio), Stage 2 planned to enroll 114 subjects (2:1 ratio, PAG:AG).

Inclusion Criteria

- Signed, written Institutional Review Board/Ethics Committee-approved Informed Consent Form.
- Histologically confirmed Stage IV pancreatic ductal adenocarcinoma (PDA) with documented disseminated neoplasm to the liver and/or the lung. Prior to enrollment, confirmation of the following must be obtained:
  - Available tumor tissue block or a minimum of five unstained core biopsy slides that meet specific tissue sample requirements (see Study Laboratory Manual).
    Note: Fine needle aspirates or brushing biopsies will not be acceptable. If an archived sample is not available, a pre-dose core tumor biopsy will be required in order to enter the study (i.e., an archived or fresh pre-dose core biopsy is required).
- One or more metastatic tumors measurable on computed tomography (CT) scan per RECIST v1.1 criteria, excluding the primary pancreatic lesion.
- Subject must have received no previous radiotherapy, surgery, chemotherapy, or investigational therapy for the treatment of metastatic disease.
  - Prior treatment with 5-FU or GEM administered as a radiation sensitizer during and up to 4 weeks after radiation therapy is allowed (if there is lingering toxicity, then the Sponsor should be consulted).
  - If a subject received therapy in the adjuvant setting, tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of the adjuvant therapy.
- Karnofsky Performance Status ≥70%.
- Life expectancy ≥3 months.
- Age ≥18 years.
- A negative pregnancy test, if female subject is of reproductive potential.
- Screening clinical laboratory values as follows:
  - Total bilirubin ≤1.5 times upper limit of normal (ULN).
  - Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (serum glutamic pyruvate transaminase) ≤2.5 times ULN, (if liver metastases are present, then ≤5 times ULN is allowed).
  - Serum creatinine ≤2.0 mg/dL or calculated creatinine clearance ≥60 mL/min.
  - Serum albumin ≥3.0 g/dL.
  - Prothrombin time/international normalized ratio within normal limits (±15%) or within therapeutic range if on warfarin.
  - Partial thromboplastin time within normal limits (±15%).
  - Hemoglobin ≥ 10 g/dL.

- Absolute neutrophil count ≥1,500 cells/mm^3.
- Platelet count ≥100,000 /mm^3

- For men and women of reproductive potential, agreement to use an effective contraceptive method from the time of screening and throughout their time on study. Effective contraceptive methods consist of prior sterilization, intra-uterine device, oral or injectable contraceptives, and/or barrier methods. Abstinence alone is not considered an adequate contraceptive measure for the purposes of this study.

Exclusion Criteria

- Non-metastatic PDA.
- Evidence of deep vein thrombosis (DVT) or pulmonary embolism (PE) or other known thromboembolic event present during the screening period.
- Previous neoadjuvant treatment for pancreatic cancer
- Known central nervous system involvement or brain metastases.
- New York Heart Association Class III or IV cardiac disease or myocardial infarction within the past 12 months.
- Prior history of cerebrovascular accident or transient ischemic attack
- Pre-existing carotid artery disease
- Active, uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
- Known infection with human immunodeficiency virus, hepatitis B, or hepatitis C.
- Known allergy to hyaluronidase.
- Current use of megestrol acetate (use within 10 days of Day 1).
- Contraindication to heparin as per NCCN guidelines:
  - Recent central nervous system bleed, intracranial or spinal lesion at high risk for bleeding
  - Active bleeding (major): more than 2 units transfused in 24 hours
  - Spinal anesthesia/lumbar puncture
  - Chronic, clinically significant measurable bleeding >48 hours
  - Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)
  - Recent major operation at high risk for bleeding
  - Underlying hemorrhagic coagulopathy
  - High risk for falls (head trauma)

- Previous major bleed (bleeding requiring transfusion of red blood cells) on low molecular weight heparin (LMWH)
- Women currently pregnant or breastfeeding.
- Intolerant of dexamethasone.
- History of another primary cancer within the last 3 years with the exception of non-melanoma skin cancer, early stage prostate cancer, or curatively-treated cervical carcinoma in-situ.
- Any other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding that leads to reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that may render the subject at high risk for treatment complications.
- Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the subject unsuitable for the study.
- Inability to comply with study and follow-up procedures as judged by the Investigator.

Study Medication

For the purposes of this study, study medication is defined as PEGPH20, NAB, and/or GEM.

PEGPH20: PEGPH20 drug product (original formulation) is supplied as an aqueous solution containing 3.5 mg/mL PEGPH20 with 10 mM histidine and 130 mM NaCl at pH 6.5. Each vial contains 1.2 mL (4.2 mg) or 0.6 mL (2.1 mg) of PEGPH20 drug product. This PEGPH20 drug product is provided as a frozen formulation. It should be stored at or below -20°C before use.

PEGPH20 drug product (new formulation) is supplied as an aqueous solution containing 0.30 mg/mL PEGPH20 with 10 mM succinic acid, 130 mM NaCl, and 10 mM L-methionine at pH 6.2. Each vial contains 1.2 mL (0.36 mg, current investigational material) or 1.0 mL (0.30 mg, commercial-scale material) of PEGPH20 drug product. This PEGPH20 drug product is provided as a refrigerated formulation and should be stored at 2°C to 8°C before use.

PEGPH20 mixing instructions will be provided for both formulations. PEGPH20 will be administered as an intravenous (IV) infusion over 10 minutes, approximately 1 mL/minute (a window of +2 minutes is allowed, i.e., infusion can be 10 to 12 minutes).

Nab-paclitaxel: NAB is an albumin-bound form of paclitaxel and is an approved anti-cancer therapy. It is supplied as a lyophilized powder in single-use vials containing 100 mg of paclitaxel. NAB will be given as an IV infusion at 125 mg/m^2 over 30 minutes and prior to the GEM infusion. For subjects in the PAG treatment group, NAB will be given after the PEGPH20 infusion is completed.

Gemcitabine: GEM is an approved chemotherapy. It is supplied as a solid lyophilized powder in single-use vials: 200 mg in 10-mL vials or 1 g in 50-mL vials. GEM will be given as an IV infusion at 1000 mg/m^2 over 30 minutes after the NAB infusion is complete.

Study Duration

Subjects will be allowed to continue treatment on study until disease progression or unacceptable toxicity is documented. Disease progression will be defined by presence of one or both of the following:

- Disease progression documented by CT scan based on RECIST v1.1, as determined by the Central Imaging Reader (CIR).
- Clinical tumor-related progression that is well documented in the absence of radiologic disease progression.

Disease progression is based on the assessment of the CIR. Investigators should continue study treatment until the CIR's progressive disease determination. Investigators may discontinue study treatment if there is documented clinical disease progression and/or study treatment is no longer in the best interest of the subject. Subjects who discontinue treatment should remain in the study for long-term follow-up assessments unless they withdraw consent, die, or become lost to follow-up.

Criteria for Evaluation

Primary Endpoint

- PFS (measured from the date of randomization until disease progression or death from any cause).
- Proportion of subjects in the PAG arm who experience any thromboembolic event in Stage 2 of the study, as of Amendment 3.0.

Secondary Efficacy Endpoints

- PFS in relation to HA levels.
- ORR (defined as the percentage of subjects with a RECIST v1.1 PR or CR).
- OS (measured from the date of randomization until death from any cause).

Exploratory Efficacy Endpoints

- OS in relation to HA levels.
- DR (measured from the date of the first CR/PR until disease progression).
- DCR (defined as the percentage of subjects with SD, PR, or CR).
- Serum CA 19-9 response rate between the PAG and AG treatment groups.
- PEGPH20 anti-tumor activities based on HA levels in plasma and in tumor biopsies.

Statistical Methods

Analysis Populations

Intent-to-treat (ITT) Population: All subjects who are randomized, including the run-in phase, will be included in the ITT Population. The ITT Population will be used for subject disposition, demographics, and overall efficacy analyses.

Overall Evaluable Population: All randomized subjects, including the run-in phase, who have a post-baseline response assessment, or have clinical disease progression without a post-baseline CT scan, or have died on study, while they are on randomized treatment after randomization, will be included in the Evaluable Population for Efficacy. The Overall Evaluable Population will be used as the primary analysis population for overall efficacy analyses.

Overall Safety Population: All subjects who received any part of a dose of study medication will be included in the Safety Population. Subjects in the Safety Population will be grouped according to the treatment they received. The Safety Population will be used for all safety analyses.

Safety Population of Stage 2: Subjects in the Overall Safety Population at Stage 2 of the study. The Safety Population of Stage 2 will be used for analyses of safety data of Stage 2 of the study. This is the analysis population for the primary safety endpoint.

PK Analysis Population: All subjects who received any part of a dose of PEGPH20 and had measurable PEGPH20 concentrations in at least one sample collected for PK analysis will be included in the PK Analysis Population.

Efficacy

Median PFS, OS, and DR will be estimated using the Kaplan-Meier method. The median and its 95% confidence intervals, and quartiles, will be presented by treatment group. The PFS and OS comparisons of the two treatment groups will be based on stratified log-rank tests, where the stratum is the Karnofsky Performance Status (70% to 80% and 90% to 100%). The estimated hazard ratio (and 95% confidence interval) for the treatment effect will be prepared using a stratified Cox regression model. ORR (CR+PR) will be descriptively summarized. The ORR and DCR for each treatment group will be estimated and a comparison between the two treatment groups will be analyzed using the Cochran-Mantel-Haenszel test.

All efficacy analyses will be conducted based on tumor HA status (HA high and HA low). Tumor samples will be analyzed in a prospective-retrospective fashion using an affinity histochemistry diagnostic assay, the VENTANA HA RxDx assay (see Section 8.2.20 for additional details).

Safety

The primary safety endpoint is the proportion of subjects in the PAG arm who experience any thromboembolic event in Stage 2 of the study (P). Subjects with multiple events will be counted only once for the primary safety analysis.

The hypothesis test will be conducted using the one-sided exact binomial test against the null hypothesis test of $P \leq 12\%$.

For 76 newly enrolled subjects in the PAG arm in Stage 2, four safety analyses, three interim and one final analyses as shown in Table 1 will be conducted when the last subject in each analysis has

been treated for one PAG treatment cycle or has discontinued from PAG treatment during the first treatment cycle as follows:

- Interim #1: enoxaparin dose: 40 mg/day (12 PAG patients).
- Interim #2: enoxaparin dose: 1 mg/kg/day (12 PAG patients).
- Interim #3: enoxaparin dose: 1 mg/kg/day (29 PAG patients).
- Final analysis: enoxaparin dose: 1 mg/kg/day (58 PAG patients)..

Table S-2: Stopping Boundaries for Subjects in the PAG Arm of Study 202, Stage 2

Safety Analyses	1st Interim (IA#1)	Cumulative IA#1 Follow-up	2nd Interim (IA#2)	3rd Interim (IA#3)	Final
Prophylactic enoxaparin dose level	40 mg/day	40 mg/day OR 40 mg/day and 1 mg/kg/day	1 mg/kg/day	1 mg/kg/day	1 mg/kg/day
No. of Subjects in PAG Arm	12	18	12	29	58 (last subject)
Stopping boundary: TE** Rate	>25%	n/a	>25%	>24%	>22%
Stopping boundary: Subjects with TE**	>3	n/a	>3	>7	>12
Stopping boundary: p-value	<0.05*	n/a	<0.05*	<0.035	<0.035

The shaded columns indicate PAG patients who have received the 40 mg/day enoxaparin dose only (IA#1) or have received the 40 mg/day OR the 40 mg/day and the 1 mg/kg/day enoxaparin doses after IA#1.
* The p-value boundary for the 1st and 2nd safety analyses was increased to 0.05 from the Pocock boundary of 0.035 to increase the chance of early stop.
** Thromboembolic event

For subjects in Stage 1 who are eligible to re-initiate PEGPH20 treatment, an interim analysis will be conducted after the last re-entry subject has had one cycle of PAG treatment or has discontinued from treatment during the first treatment cycle after re-entry. If the thromboembolic event rate exceeds 25%, all re-entry subjects will be discontinued from PEGPH20 treatment.

All AEs will be presented in incidence tables coded by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. Additionally, separate AE incidence tables, coded by MedDRA type, will be presented for each treatment group and overall by: 1) toxicity grade (severity) graded by the Common Terminology Criteria for Adverse Events v4.03 or the current version (CTCAE), and 2) relationship to study mediation (PEGPH20, NAB, and/or GEM), as determined by the Investigator.

All AEs, SAEs, treatment discontinuations due to AEs, and deaths occurring during the course of the study will be summarized.

Laboratory toxicity will be summarized for all post-baseline data. Shift tables will be presented for selected laboratory parameters: liver function tests (ALT, AST, alkaline phosphatase, total bilirubin), WBC, ANC, hemoglobin, platelet count, PT, PTT, INR, and creatinine. Shift tables will use CTCAE grades, v4.03 (or current version). Selected laboratory parameters and vital signs (blood pressure, pulse, respiratory rate temperature) and the corresponding change from baseline over time will be summarized using descriptive statistics and data listings.

Pharmacokinetics

For PEGPH20, noncompartmental and population PK modeling will be performed. The area-under-the-concentration time curve, the maximum-observed concentration, and time-to-maximum concentration will be summarized along with descriptive statistics. Other PK/pharmacodynamic analyses will be performed, and estimation of PK parameters including terminal half-life, volume of distribution, and clearance will be evaluated and reported if the data are sufficient. For HA, descriptive statistics will be used to summarize the measured plasma concentrations.

Interim Analysis

No formal interim analyses of efficacy were initially planned for this study. However, 2 interim analyses of efficacy data from Stage 1 were performed to develop the HA algorithm and determine the cut--point to define HA-high subjects using a prototype HA assay and the investigational VENTANA HA RxDx assay, respectively. The 50% HA cut-point identified based on the Stage 1 data was defined based on the VENTANA HA RxDx assay prior to the analysis of Stage 2 data. Stage 2 data were used to validate the HA algorithm and 50% cut-point. A third, comprehensive interim analysis of efficacy and safety data was performed to validate the VENTANA HA RxDx assay algorithm and cut-point of 50% and enable a thorough benefit/risk assessment based on HA status.

Sample Size Considerations

Approximately 16 subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer will be randomized in 3:1 ratio to receive PAG and AG treatment in the run-in Phase.

123 subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer were randomized in a 1:1 ratio to either the PAG or AG treatment group in the Phase 2 portion of the study in stage 1.

In Stage 2 of this study, 114 subjects were planned to be randomized in a 2:1 ratio to receive PAG or AG treatment: 76 subjects in the PAG arm and 38 subjects in the AG arm. To ensure adequate assessment of the primary safety endpoint of TE event incidence and a meaningful number of HA-high subjects in Stage 2, 133 subjects were actually randomized.

The primary safety endpoint is the proportion of subjects who experience any thromboembolic event in Stage 2 of the study (P).

The hypothesis test will be conducted using the one-sided exact binomial test against the null hypothesis test of $P \leq 12\%$.

Four safety analyses will be conducted using the stopping boundary of the one-sided p-value of 0.05 for the first two analyses and 0.035 for the remaining two analyses based on the Pocock method.

It is expected that a total of 237 subjects in Phase 2 will be enrolled in approximately 20 months and these subjects will be followed up for additional 15 months. There will be approximately 200 subjects, including subjects from the run-in phase, in the Overall Efficacy Evaluable Population for the primary comparisons. The study planned to provide approximately 80% statistical power to detect a 45% treatment effect in median PFS (5.5 months for AG versus 8 months for PAG) with 182 PFS events based on the two-sided log-rank test at the significance level of 0.1. However, the interim data showed a low likelihood of achieving 182 PFS events from a total of 256 subjects actually randomized in Phase 2, and therefore the final analysis will be conducted when at least 95% of the enrolled subjects and 95% of HA-high subjects have discontinued study treatment.

In addition, the study will provide 80% statistical power to detect 40% benefit in median OS (8.5 months for AG versus 11.9 months for PAG) at one-sided alpha level of 0.1. Assuming 35% subjects with high HA, the study has 80% statistical power for the high HA subgroup to detect 90% benefit in median PFS (5.5 months for AG versus 10.5 months for PAG) at two-sided alpha level of 0.1 and 80% benefit in median OS (8.5 months for AG versus 15.3 months for PAG) at one-sided alpha level of 0.1.

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3. STUDY SCHEDULES OF EVENTS

With Protocol Amendment 6, the procedures listed in Section 6.1.4 will supersede all the procedures listed in Table 1 through Table 5.

Table 1: Study Schedule of Events: Screening (PAG and AG Treatment Groups)

Tests and Assessments[a]	Screening		
	≤20 Days Prior to D1	≤14 Days Prior to D1	≤7 Days Prior to D1
Sign and Date ICF	X		
Confirm Availability of Tumor Tissue[b]	X[b]		
Subject Registration/Randomization		X	
Medical History	X		
Physical Examination		X[c]	
Vital Signs		X[c]	
Karnofsky Performance Status		X	
Height		X[c]	
Weight/BSA		X[c]	
Disease Assessment (CT)[d]	X[c]		
Doppler Ultrasound of lower extremities			X
Local Laboratory Tests			
Urine/Serum Pregnancy Test (female subjects of reproductive potential)		X	

Table 1: Study Schedule of Events: Screening (PAG and AG Treatment Groups) (Continued)

Tests and Assessments[a]	Screening		
	≤20 Days Prior to D1	≤14 Days Prior to D1	≤7 Days Prior to D1
Central Laboratory Tests			
Hematology		X	
Blood Chemistry		X	
Urinalysis		X	
Coagulation Tests (PT, PTT, INR)		X	
CA19-9		X	
Plasma HA levels		X	
Prior Medication History	X		

[a] See Section 8.2 for details on individual assessments.

Abbreviations: AG = nab-paclitaxel+gemcitabine; BSA = body surface area; CT = computed tomography; D1 = Study Day 1; HA = hyaluronan; ICF = Informed Consent Form; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine.

[b] Archived or fresh tissue from the primary or a metastatic lesion is required. Availability of a minimum of five unstained core biopsy slides or a block are required to send to central laboratory.

[c] If these procedures are performed as part of standard of care prior to signing the ICF, the results may be used for screening purposes providing they were performed within the screening window.

[d] Chest CT should also be read locally to evaluate for the presence of PE. This can be the same scan that is sent to the central lab. If a subject shows signs or symptoms of a PE after the initial scan was done, the scan should be repeated prior to randomization to verify whether the subject has a PE. If a PE is present the subject may not enter the trial.

Table 2: Study Schedule of Events: PEGPH20+nab-Paclitaxel+Gemcitabine (PAG Treatment Group)

Tests and Assessments[a]	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2+ (Repeats every 4 weeks)				End of Treatment[b]	Long-term Follow-up
	Week 1			Week 2		Week 3		Week 4	Week 1	Week 2	Week 3	Week 4		
	D1	D2	D4	D8	D11	D15	D18	D22	D1	D8	D15	D22		
Physical Examination	X								X				X	
Vital Signs	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X[c]	X[c]	X[c]	X	X	
Karnofsky Performance Status	X								X				X	
Weight/BSA	X								X				X	
12-lead ECG[d]	X					X								
Disease Assessment (CT)												X[e]	X[f]	
Central Laboratory Tests														
Hematology	X			X		X		X	X	X	X	X	X	
Blood Chemistry	X			X		X		X	X	X	X	X	X	
Immunogenicity	X[g]								X[g]				X	
CA19-9								X				X	X	
PK & HA levels	Refer to Table 4 and Table 5 for schedule for PK & HA sampling timepoints													
PEGPH20 Administration	X		X	X	X	X	X		X	X	X			
Coagulation Testing (PT, PTT, INR- Local Lab)	X			X		X		X	X	X	X	X	X	
Dexamethasone Administration[h]	X		X	X	X	X	X		X	X	X			

Table 2: Study Schedule of Events: PEGPH20+nab-Paclitaxel+Gemcitabine (PAG Treatment Group) (Continued)

Tests and Assessments[a]	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2+ (Repeats every 4 weeks)				End of Treatment[b]	Long-term Follow-up
	Week 1			Week 2		Week 3		Week 4	Week 1	Week 2	Week 3	Week 4		
	D1	D2	D4	D8	D11	D15	D18	D22	D1	D8	D15	D22		
Nab-paclitaxel Administration		X[i]		X[j]		X[j]			X[j]	X[j]	X[j]			
Gemcitabine Administration		X[i]		X[j]		X[j]			X[j]	X[j]	X[j]			
Optional Post-dose Tumor Biopsy[k]								X				X		
Concomitant Therapy and Procedure Recording	X												X	
Adverse Event Recording	X												X	
Long-term Follow-up[l]														X

Abbreviations: BSA = body surface area; CT = computed tomography; D = day; ECG = electrocardiogram; HA = hyaluronan; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine; PK = pharmacokinetics

[a] See Section 8.2 for details on individual assessments.

[b] Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after determination of progressive disease or within 7 days after treatment discontinuation for other reasons.

[c] Vital signs will be done pre-dose.

[d] 12-lead ECG, done in triplicate, will be done pre dose and between 1 and 4 hours after PEGPH20 dosing but before the nab-paclitaxel dose.

[e] CT scans will be obtained and sent to the Central Imaging Reader at the end of Cycle 2 and at the end of every second treatment cycle thereafter (i.e., Week 4 of Cycles 4, 6, 8, etc.) Scans may be obtained any time after dosing on Day 15 to allow for enough time for the scan to be sent to and reviewed by the central reader prior to the subject's next scheduled dosing visit. The results should be interpreted and sent to the site before dosing in the next cycle begins. For subjects who are withdrawn from the study due to clinical disease progression, a CT scan should be requested as soon as possible after clinical progression is determined. A Chest CT should also be done after PEGPH20 study hold (both treatment groups), after signing updated ICF (Amendment 3.0) to evaluate for the presence of pulmonary embolism.

[f] CT should only be done if radiologic progressive disease was not documented in the previous CT scan.

[g] Plasma PEGPH20 immunogenicity will be drawn prior to PEGPH20 dosing.

[h] Dexamethasone should be given within 2 hours prior to the start of each PEGPH20 dose and 8-12 hours after each PEGPH20 dose.
[i] Nab- paclitaxel and gemcitabine will be given 24 hours (±4 hours) after the dose of PEGPH20. Nab-paclitaxel will be given first.
[j] Nab-paclitaxel and gemcitabine will be given 2 to 4 hours after the PEGPH20 dose. Nab-paclitaxel will be given first.
[k] Optional post-dose tumor biopsy may be done anytime in Week 4 of any Cycle. See Section 8.2.10 for tissue requirements.
[l] After the End of Treatment Visit, subjects will enter long-term follow-up during which information on the subject's survival will be obtained by the site on a monthly basis. In addition, efforts should be made to collect data on the subject's next anti cancer therapy on a monthly basis. Long term follow-up will continue until the subject dies, is lost to follow-up, or withdraws consent.

Table 3: Study Schedule of Events: nab-Paclitaxel+Gemcitabine (AG Treatment Group)

Tests and Assessments[a]	All Treatment Cycles (Repeats every 4 weeks)				End of Treatment[b]	Long-term Follow-up
	Week 1	Week 2	Week 3	Week 4		
	D1	D8	D15	D22		
Physical Examination	X				X	
Vital Signs	X[c]	X[c]	X[c]	X	X	
Karnofsky Performance Status	X				X	
Weight/BSA	X				X	
12-lead ECG[d]	X		X			
Disease Assessment (CT)				X[e]	X[f]	
Central Laboratory Tests						
Hematology	X	X	X	X	X	
Blood Chemistry	X	X	X	X	X	
CA19-9				X	X	
Plasma HA Levels	X[g]					
Coagulation Testing (PT, PTT, INR - local Lab)	X	X	X	X	X	
Dexamethasone Administration[h]	X	X	X			
Nab-paclitaxel Administration[i]	X	X	X			
Gemcitabine Administration[i]	X	X	X			
Optional Post-dose Tumor Biopsy[j]				X		

Table 3: Study Schedule of Events: nab-Paclitaxel+Gemcitabine (AG Treatment Group) (Continued)

Tests and Assessments[a]	All Treatment Cycles (Repeats every 4 weeks)				End of Treatment[b]	Long-term Follow-up
	Week 1	Week 2	Week 3	Week 4		
	D1	D8	D15	D22		
Concomitant Therapy and Procedure Recording	X					
Adverse Event Recording	X					
Long-term Follow-up[k]						X

Abbreviations: AG = nab-paclitaxel+gemcitabine; BSA = body surface area; CT = computed tomography; D = day; ECG = electrocardiogram; HA = hyaluronan.

[a] See Section 8.2 for details on individual assessments.

[b] Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after determination of progressive disease or within 7 days after treatment discontinuation for other reasons.

[c] Vital signs will be done before nab-paclitaxel dosing.

[d] 12-lead ECG, done in triplicate, will be done before nab-paclitaxel dose and within 1 to 4 hours after the gemcitabine dose in Cycle 1 only.

[e] CT scans will be obtained and sent to the Central Imaging Reader at the end of Cycle 2 and at the end of every second treatment cycle thereafter (i.e., Week 4 of Cycles 4, 6, 8, etc.) Scans may be obtained any time after dosing on Day 15 to allow for enough time for the scan to be sent to and reviewed by the central reader prior to the subject's next scheduled dosing visit. The results should be interpreted and sent to the site before dosing in the next cycle begins. For subjects who are withdrawn from the study due to clinical disease progression, a CT scan should be requested as soon as possible after clinical progression is determined. A Chest CT should also be done after PEGPH20 study hold (both treatment groups), after signing updated ICF (Amendment 3.0) to evaluate for the presence of pulmonary embolism.

[f] CT should only be done if radiologic progressive disease was not documented in the previous CT scan.

[g] HA level plasma sample should be drawn prior to the first nab-paclitaxel dose in each cycle.

[h] Dexamethasone should be given within 2 hours prior to each nab-paclitaxel dose and 8-12 hours post each gemcitabine dose.

[i] Nab-paclitaxel will be given first, followed by gemcitabine.

[j] Optional post-dose tumor biopsy may be done anytime in Week 4 of any Cycle. See Section 8.2.10 for tissue requirements.

[k] After the End of Treatment Visit, subjects will enter long-term follow up during which information on the subject's survival will be obtained by the site on a monthly basis. In addition, efforts should be made to collect data on the subject's next anti cancer therapy on a monthly basis. Long term follow-up will continue until the subject dies, is lost to follow-up, or withdraws consent.

Table 4: Study Schedule of Events: Pharmacokinetic and HA Sample Collection (Run-in Phases PAG Treatment Groups)

Treatment Group	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2+ (Repeats every 4 weeks)			
	Week 1			Week 2		Week 3		Week 4	Week 1	Week 2	Week 3	Week 4
	D1	D2	D4	D8	D11	D15	D18	D22	D1	D8	D15	D22
PK and HA Sample Collection[a]	X[b]	X[c]	X[d]	X[e]	X[d]	X[b]	X[d]		X[f]	X[d]		

Abbreviations: D = day; HA = hyaluronan; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine; PK = pharmacokinetics.

[a] Windows for blood draws: Pre-dose: within 2 hours of dosing. Post-dose: 15 minutes ±5 minutes, 1 hr (±15 minutes), 2 hour (±15 minutes), 4 hour (±30 minutes), Post gemcitabine= within 2 hours of completion of gemcitabine administration.

[b] **PK**: Pre-PEGPH20 dosing, and 15 minutes, 1 hour, 2 hours, and 4 hours post-PEGPH20 dosing. A Cycle 1 Day 15, 24 hour post-dose sample is optional. **HA:** Pre-PEGPH20 dose (Day 1 only).

[c] **PK and HA:** 24 hours post-PEGPH20 dose (±4 hours) and prior to nab-paclitaxel dose.

[d] **PK**: Pre-PEGPH20 dose and 1 hour post-PEGPH20 dose.

[e] **PK**: Pre-PEGPH20 dose and 1 hour post-PEGPH20 dose, and immediately after gemcitabine dose.

[f] **HA**: Collect 1 HA sample pre-PEGPH20 and a second HA sample after gemcitabine administration.

Table 5: Study Schedule of Events: Pharmacokinetic and HA Sample Collection (Phase 2; PAG Treatment Group)

Treatment Group	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2+ (Repeats every 4 weeks)			
	Week 1			Week 2		Week 3		Week 4	Week 1	Week 2	Week 3	Week 4
	D1	D2	D4	D8	D11	D15	D18	D22	D1	D8	D15	D22
PK and HA Sample Collection[a]	X[b]	X[c]				X[d]			X[e]	X[f]		

Abbreviations: D = day; HA = hyaluronan; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine; PK = pharmacokinetics. Post gemcitabine= within 2 hours of completion of gemcitabine administration.

[a] Windows for blood draws: Pre-dose: within 2 hours of dosing. Post-dose: 1 hour (± 15 minutes).

[b] **PK:** Pre-PEGPH20 dose and 1 hour post-PEGPH20 dose. **HA**: Pre-PEGPH20 dose.

[c] **PK and HA**: 24 hours post-PEGPH20 dose (±4 hours) and prior to nab-paclitaxel dose.

[d] **PK**: Pre-PEGPH20 dose and 1 hour post-PEGPH20 dose.

[e] **HA**: Collect 1 HA sample pre-PEGPH20 and a second HA sample after gemcitabine administration.

[f] **PK**: Pre-PEGPH20 dose and 1 hour post PEGPH20 dose.

4. BACKGROUND AND RATIONALE

Halozyme, Inc. (Halozyme) has developed an investigational new molecular entity, PEGylated recombinant human hyaluronidase PH20 (PEGPH20), which uses a novel mechanism of action to systemically target tumors that accumulate the substrate for this enzyme, hyaluronan (HA). In preclinical models, depletion of HA in the tumor microenvironment has been shown to inhibit the growth of tumors characterized by accumulation of HA (Thompson 2010). A detailed background rationale for HA as a target in cancer therapy is described in Kultti et al. (Kultti 2012).

Tumor accumulation of HA has been shown to occur in the most aggressive forms of several malignancies (Sironen 2011). Enzymatic HA depletion from the extracellular matrix (ECM) microenvironment, with PEGPH20 either alone or in combination with chemotherapy, represents an innovative potential treatment that may provide improved therapeutic outcomes for patients.

HA is a linear, repeating polysaccharide comprised of N-acetylglucosamine and glucuronic acid disaccharide units. The metabolism of HA is a dynamic process, with normal turnover in tissues ranging from several weeks to less than a day in skin (Fraser 1997). HA is synthesized at the plasma membrane by three conserved HA synthases (HAS) and degraded by cell associated or acid-active hyaluronidases and exoglycosidase enzymes (Tammi 2011).

Local aberrations of HA metabolism have been reported in many solid tumor malignancies, where elevated levels of HA frequently correlate with poor prognosis in tumors such as pancreatic, breast, gastric, colorectal, ovarian, prostate and lung carcinoma.

Approximately 87% of all pancreatic cancers express high levels of HA (Figure 1; Kultti 2012). As discussed below, log-rank analysis of HA levels in tumor tissue revealed that the survival rate was significantly lower among patients with high HA levels than patients with low HA levels (738 days versus 229 days, respectively; $p<0.05$; Figure 2). These data suggest that HA levels in pancreatic adenocarcinoma patients may be predicative of survival(Whatcott 2011).

In breast carcinoma, the five-year survival rate deteriorated with increasing stromal HA levels; the five-year overall survival (OS) for low, moderate, and high HA levels, was 45%, 39%, and 26%, respectively ($p = 0.002$) and the recurrence-free survival was 66%, 56%, and 40%, respectively ($p = 0.008$). The presence of HA-positive carcinoma cells correlated significantly with axillary lymph node positivity and poor differentiation. The five-year OS of patients exhibiting HA-positive carcinoma cells was significantly lower compared with patients without HA-positive carcinoma cells (54% versus 81%, respectively, $p = 0.01$) (Auvinen 2000).

Gastrointestinal cancers are among those diseases with a significant proportion of cases characterized by HA accumulation. In gastric carcinoma, Setälä et al. examined the HA profile of 215 Stage I-IV gastric carcinoma patients. A high proportion of HA-positive cells were found and were significantly associated with deep tumor invasion, nodal metastasis, positive lymphatic invasion, poor differentiation grade, as well as with inferior prognosis in univariate survival analysis. Forty-four percent of the tumors evaluated had a HA labeling index of 30 to100% HA-positive cells (Setälä 1999).

In colorectal carcinomas, Ropponen et al. examined the cellular association of HA to survival and recurrence-free survival in colorectal carcinoma samples from 202 patients followed for a

mean of 14 years. Both high HA intensity and labeling indices were frequently found and significantly associated with poorer OS, shorter recurrence-free survival, and elevated Dukes classification for 187 evaluable patients (Ropponen 1998). Halozyme has shown that 87% of all pancreatic cancers are characterized by significant accumulation of HA (Figure 1; Kultti 2012)

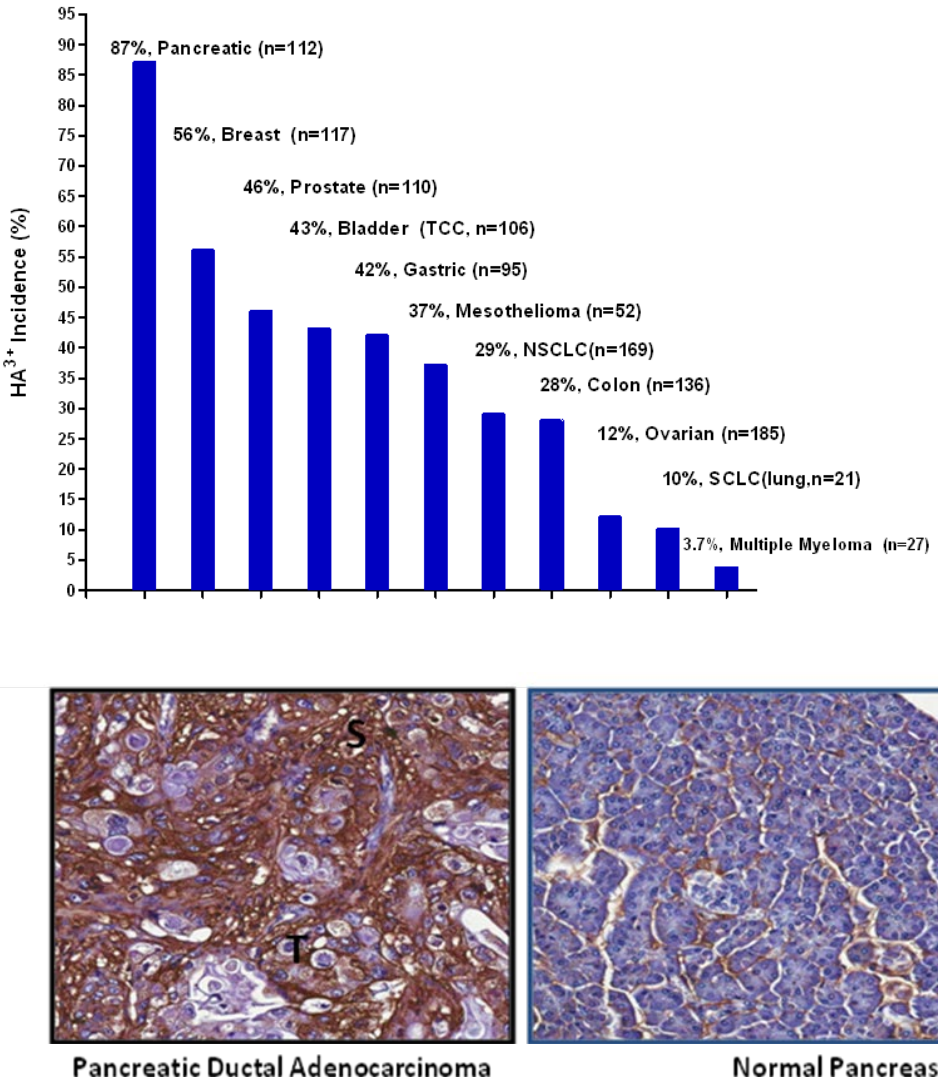
Anttila et al. studied HA levels in 309 epithelial ovarian cancers and 45 matched metastatic lesions. While in 73% (227 of 309) of the cases, the fraction of HA-positive cancer cells was <10%, high stromal HA levels were significantly correlated with poor differentiation, serous histologic type, advanced stage, and large primary residual tumor (Anttila 2000).

Profiles of HA deposition in solid tumors have generally been categorized as pericellular or stromal. Elevated plasma levels of HA have been observed most notably in patients with Wilms' tumor, mesothelioma, and liver metastases (Wu 1984, Dahl 1989, Thylen 1999, Rosenthal 2005). The underlying cause for local HA accumulation in solid tumors has not been well characterized. HA synthase overexpression, poor lymphatic drainage or unbalanced synthesis and degradation have been proposed as potential mechanisms. Nevertheless, studies that have investigated HA levels in tumors have shown that aberrant accumulation of HA occurs in many solid tumor malignancies, and HA is an indicator of poor prognosis when associated with stromal or cellular compartments (Sironen 2011).

Substantial human data exist for non-PEGylated, animal-derived hyaluronidase products for multiple therapeutic applications (Dunn 2010, Frost 2007). Intravenously administered hyaluronidase from animal sources has shown potential for improving the clinical efficacy of chemotherapy in doses up to 200,000 U/day (Pillwein 1998, Baumgartner 1998, Klocker 1998). In addition, previous preclinical studies have attributed chemopotentiation by hyaluronidase to a reduction in interstitial tumor pressure that facilitates enhanced drug penetration into HA-rich tumors (Spruss 1995, Brekken 1998, Eikenes 2005). Increased production of HA in tumor cells, via ectopic expression of HA synthases, has been shown to induce microvillus structures, suppress contact inhibition, and increase tumor growth rates in vivo (Kosaki 1999, Kultti 2006, Koyama 2007). Conversely, reduction of tumor HA levels in preclinical studies, either by addition of hyaluronidase or by inhibition of HA-synthase activity, has been reported to reduce in vitro tumor cell proliferation, motility and invasion, and to reduce the growth of implanted tumors (Shuster 2002, Simpson 2002, Kim 2004, Nishida 2005, Udabage 2005, Li 2007, Thompson 2010).

While early hyaluronidase clinical investigations in cancer patients demonstrated potential therapeutic activity, these studies were curtailed because of concerns of potential anaphylactic responses to the foreign proteins that are found in hyaluronidase products from animal sources. Animal-derived hyaluronidase enzymes also have a very short half-life of enzymatic activity in blood (approximately 5 min) limiting the duration of action of intravenous (IV) doses. Halozyme has developed a recombinant human hyaluronidase enzyme, rHuPH20, derived from the human PH20 DNA sequence. The PH20 enzyme is a soluble domain of the endogenous human PH20 glycoprotein, devoid of its carboxy-terminal, lipid anchor attachment site. The enzyme has been approved by the Food and Drug Administration (FDA) in an injectable formulation and is marketed as HYLENEX® recombinant.

Figure 1: Hyaluronan is Expressed in High Levels in a Variety of Human Cancer Tissues



Over-expression of HA (HA^{high}) was demonstrated in a variety of human cancer tissue utilizing a biotinylated HA binding protein-based staining method in tissue biopsies. Columns represent tumor expression of HA and. The bottom micrographs are representative histochemically stained tissue demonstrating HA is high in pancreatic ductal adenocarcinoma (PDA) compared with normal pancreas (brown stain indicates HA and blue stain is tumor stroma detected via H&E). (Kultti 2012)

The native recombinant human PH20 enzyme has a very short plasma half-life ($t_{1/2}$ <3 minutes), making depletion of tumor HA in vivo impractical. Attempts to utilize rHuPH20 for systemic therapy in murine cancer models have shown it to be ineffective as a single agent (Jiang 2012). Therefore, to maximize the hyaluronidase activity, Halozyme developed a PEGylated version of PH20 to provide a longer half-life and enable systemic therapeutic exposure. Like rHuPH20, PEGPH20 removes HA from the ECM by depolymerizing the substrate (Thompson 2010). The PEGPH20 protein demonstrates a significantly increased plasma half-life relative to the non-PEGylated rHuPH20 protein. In many different tumor types tested in murine xenograft models, response to PEGPH20 has been shown to be more robust for tumors characterized by

higher HA expression (Jiang 2012). PEGPH20 has a terminal plasma half-life of approximately 10 hours in rodents and 50 hours in monkeys. In humans, data from two subjects dosed with 50 µg/kg PEGPH20 in Study HALO-109-101 demonstrated a plasma half-life of 2.5 to 4.8 hours for the initial phase and 26 to 49 hours (1 to 2 days) for the terminal phase. The increased plasma half-life of PEGPH20 makes sustained depletion of tumor-associated HA feasible.

4.1. Thromboembolic Events in Cancer

It has been well documented that patients with cancer are at a higher risk for thromboembolic events (TE), specifically of venous origin, venous thromboembolic event (VTE), than the general population. Based on a review by Timp and colleagues, the odds ratio of risk of a VTE for individuals with cancer versus those with no cancer ranges between 4.1 (95% CI; 1.9-8.5, Heit 2000) and 6.7 (95% CI; 5.2-8.6, Blom 2005). Multiple factors can further increase the risk, such as the type of malignancy, the stage of cancer, the time since cancer diagnosis, and the type of treatment (Timp 2013). Khorana and colleagues summarized a predictive model for chemotherapy- associated VTE (Khorana 2010). They identified the following patient characteristics as high risk for developing thromboembolic events: site of cancer (very high risk [stomach and pancreas]; high risk [lung, lymphoma, gynecologic, bladder and testicular]), prechemotherapy platelet count 350 x 10^9/L or more; hemoglobin level <10.0 g/dL or use of erythropoiesis-stimulating agents; prechemotherapy leukocyte count > 11 x 10^9/L; and BMI 35 kg/m^2 or more.

Pancreatic cancer is at higher risk of VTE among various cancer types (NCCN Guideline 2013). Several studies reported the incidence rate between 5-36% in retrospective studies and between 19-67% in autopsy cases series (Epstein and O'Reilly 2012). In a meta-analysis of 38 papers in cancer patients, pancreas cancer had approximately 102 VTE in 1000 person-years, as compared to brain (116/1000 PY), lung (52/1000 PY), and hematologic cancer (35/1000 PY) (Horsted 2012). Epstein and O'Reilly studied selected factors relevant to pancreas cancer and thrombosis in the molecular associations and clinical and treatment variables, they found that factors associated with coagulation included fibrin, plasminogen, thrombin, etc. The associated clinical and treatment variables included hospitalization/sedentary status, surgery, venous access/catheterization, weight extremes, anemia, medications (erythropoietin-stimulating agents, chemotherapy, and megestrol), and other co-morbidities (e.g., heart, liver, and kidney disease; diabetes) (Epstein and O'Reilly 2012).

Epstein and colleagues conducted a comprehensive analysis of the incidence and clinical outcomes in patients with thromboembolic events and pancreatic cancer at Memorial Sloan-Kettering Cancer Center. They identified 1,915 patients who had a diagnosis of pancreatic cancer between 1 Jan 2000 and 31 Dec 2009, of which 36% (N=690 patients) had at least one documented TE. Of the 690 subjects, venous events predominated in 614 of patients presenting with a noncatheter-related deep vein thromboembolic event and/or a pulmonary embolism (89%, 614/690) (Epstein 2012). This equates to a 32% incidence amongst all subjects in the sample cohort (614/1,915). In this study, arterial events were rare and were reported in 30 patients (4.4%). The majority of patients (n = 638, 92.5%) had locally advanced or metastatic disease at the time of first TE. Of those, 78% had Stage IV disease.

Two clinical studies were conducted to specifically assess the rate of symptomatic VTEs with or without the use of prophylactic low molecular weight heparin (LMWH) in patients receiving standard chemotherapy agents.

The CONKO-004 (Riess 2010) was a prospective, open-label, randomized, multicenter and group-sequential phase IIb study in patients with locally advanced or metastasized pancreatic cancer who are treated with a palliative chemotherapy (stratified for risk) using either gemcitabine alone or in combination with cisplatin, 5-fluorouracil (5-FU) and folinic acid, both with or without enoxaparin at 1 mg/kg once daily. The primary endpoint was the incidence of clinically relevant VTE (symptomatic deep venous thrombosis (DVT) of the leg and/or pelvic and/or pulmonary embolism (PE)) within the first 3 months. Secondary endpoints included the incidence of symptomatic and asymptomatic VTE after 6, 9 and 12 months as well as remission at 3, 6, 9 and 12 months, overall survival and bleeding. A total of 312 subjects were recruited. The event rate of all-type TE events (venous and arterial) in patients not receiving LMWH prophylaxis was 10% at 3 months and 15% at 12 months as compared to 1.3% and 5% at 3 and 12 months, respectively, with LMWH. Since the data are presented in abstract form, the breakdowns of arterial versus venous TE rates are not presented.

The FRAGEM study (Maraveyas 2012) was a randomized controlled phase IIb trial to assess the effectiveness of LMWH in reducing VTE events in the selected population. Patients were eligible if they had histopathological or cytological diagnosis of non-resectable, recurrent or metastatic pancreatic adenocarcinoma with no obvious thromboembolism, not on anticoagulation, and should not have had a thromboembolic event in the 6 months before randomization. Central venous access devices and inferior vena cava filters were not allowed. Exclusion criteria included previous gemcitabine-containing treatment, comorbidities which in the opinion of the investigator would compromise informed consent or compliance, history of other advanced malignancy, ongoing anticoagulation treatment and treatment with antiplatelet agents for vascular disease (i.e., aspirin at a dose >75 mg, clopidogrel, etc.). Subjects were randomized to receive either gemcitabine (GEM) or gemcitabine with dalteparin (GEMWAD) for up to 12 weeks. A total of 123 patients were randomized. A total of 31% (19/62) of subjects sustained a VTE in the GEM arm as compared to 12% (7/59) on the GEMWAD arm. VTE events leading to death were reported as 8% (5/62) in the GEM arm and 0% (0/59) in GEMWAD arm.

4.2. Clinical Experience with PEGPH20 and Clinical Development Plan

PEGPH20 is being developed as an investigational, novel therapeutic agent for use in combination with chemotherapy for the treatment of patients with cancers that accumulate HA.

As of 01 April 2014, 68 subjects have been treated with PEGPH20 in two Phase 1 clinical studies (Studies HALO-109-101 and HALO-109-102) and one Phase 1b/2 study (Study HALO-109-201). Both Phase 1 studies are closed to enrollment. A total of 14 subjects were dosed in Study HALO-109-101 and 26 in Study HALO-109-102. Enrollment in the Phase 1b/2 study is complete; 28 subjects have been dosed.

4.2.1. Phase 1 Study HALO-109-101

The first Phase 1 study (Study HALO-109-101) was initiated in 2009. This study enrolled 14 subjects with advanced malignancies (including two subjects with advanced pancreatic cancer) who experienced disease progression after previous therapy. The first two subjects received one administration of PEGPH20 at 50 µg/kg and experienced severe musculoskeletal pain starting between 4 and 10 hours after the initial PEGPH20 dose. For the first subject, the

joint and muscle pain resolved over 16 days; however, residual muscle weakness remained and interfered with daily activities until death, 19 days after the first dose. The cause of death was pulmonary edema due to congestive heart failure, which was deemed not related to study drug. For the second subject, the musculoskeletal pain returned to baseline (Grade 1) within 8 days.

The protocol was amended to reduce the dose by 100-fold for the next subject. The third subject was dosed at 0.5 μg/kg dose level twice weekly. Grade 1 transient right calf cramping occurred prior to the second dose. Intermittent muscle cramping returned in the feet, calves, and thighs one day after the second dose and had increased to Grade 3; it was accompanied by Grade 3 muscle pain. The muscle spasms and pain began improving within five days and decreased to Grade 1 within 10 days and all were resolved within 30 days.

The protocol was again amended due to the severe musculoskeletal events, and the treatment cycle was reduced to one dose every 21 days. On this schedule, three subjects were dosed at 0.5 μg/kg, four were dosed at 0.75 μg/kg, three were dosed at 1 μg/kg, and one was dosed at 1.5 μg/kg. Subjects received one to three doses prior to disease progression. No dose-limiting toxicities (DLTs) occurred at these dose levels and dosing frequency. The majority of musculoskeletal events (MSEs) reported were Grade 1 or 2 and were variable in duration. One subject at the 0.75 μg/kg dose level experienced Grade 3 intermittent muscle pain, which was resolved within four days. Of the 14 subjects received PEGPH20, 1 subject had advanced NSCLC experienced grade 1 superficial phlebitis. Subject was treated as an outpatient with Lovenox and the event was resolved without sequelae.

This study was closed due to musculoskeletal toxicities and the slow dose escalation scheme. To attenuate and prophylactically manage the musculoskeletal symptoms, Study HALO-109-102 was initiated to define the maximum-tolerated dose (MTD) of PEGPH20 when used with dexamethasone. Dexamethasone is commonly used in oncology to treat symptoms associated with IV anti-cancer therapy. Premedication with dexamethasone completely prevented the development of PEGPH20-induced musculoskeletal observations in beagle dogs at doses that are approximately 60 to 200 times higher than any dose to be evaluated in this study. This was accomplished with preservation of the anti-tumor growth effect of PEGPH20 in preclinical studies in mice.

4.2.2. Phase 1 Study HALO-109-102

Study HALO-109-102 was initiated to evaluate the safety profile of PEGPH20 using the regimen of once or twice weekly PEGPH20 administration. Dexamethasone (pre- and post-PEGPH20 doses) was added to the regimen to alleviate musculoskeletal toxicities. PEGPH20 doses administered ranged from 0.5 to 5.0 μg/kg either once or twice weekly (Days 1 and 4) schedule for the first cycle (4 weeks) and once per week for subsequent cycles. In addition, subjects received 4 or 8 mg dexamethasone 1 hour prior to and 8 to 12 hours after PEGPH20 administration.

There were 3 DLTs reported. One subject at 5.0 μg/kg PEGPH20 on a twice weekly schedule with 4 mg dexamethasone treatment experienced Grade 3 muscle pain following the third dose in Cycle 1 (Cycle 1, Day 8). The event resolved within four days. Following this event, dexamethasone treatment was increased to 8 mg. One subject at 3.0 μg/kg on a once weekly schedule with the 8 mg dexamethasone experienced a DLT with generalized Grade 2 muscle spasms. The third DLT occurred at 5.0 μg/kg PEGPH20 on a once weekly schedule with 8 mg

dexamethasone treatment. The subject developed Grade 3 muscle cramps 1 day after the first dose; the muscle cramps decreased to Grade 1 within 2 days. Therefore 5.0 µg/kg either once or twice weekly was not tolerated.

In summary, of the total of 26 subjects enrolled in this study, six were treated at 3.0 µg/kg once weekly and 15 received 3.0 µg/kg twice weekly schedule. Only one subject experienced a DLT at the 3.0 µg/kg once weekly schedule. Intermittent dose interruption due to MSEs was rare and dose reduction from 3.0 µg/kg to 1.6 µg/kg occurred in one subject, in Cycle 1 Day 18. The number of PEGPH20 doses received ranged from 1 to 22 doses (median is approximately 7). Treatment duration ranged from one week up to five cycles (20 weeks). The MTD was determined to be 3.0 µg/kg once or twice weekly. PEGPH20 doses up to and including 3.0 µg/kg administered once or twice weekly with 8 mg dexamethasone treatment have been fairly well tolerated with mostly Grade 1 or 2 musculoskeletal events. These musculoskeletal symptoms include muscle cramping, muscle pain, joint pain, back pain, cramping and drawing in of hands and fingers, and muscle weakness. Subjects also received symptomatic treatment with other medications, including muscle relaxants and pain medications.

Of the 26 subjects received PEGPH20, 4 subjects had advanced pancreatic cancer. One advanced pancreatic cancer experienced a grade 2, non-serious thromboembolic event (embolism). He was treated as an outpatient with warfarin and the event was resolved without sequelae.

4.2.3. Phase 1b/2 Study HALO-109-201

The objective of the Phase 1b portion of Study HALO-109-201 study is to identify the recommended Phase 2 dose of PEGPH20 in combination with gemcitabine (GEM) in subjects with metastatic pancreatic cancer. Subjects were treated with PEGPH20 administered by IV infusion twice per week for the first 4 weeks, then weekly for three weeks, followed by one week rest. GEM was administered at 1000 mg/m^2 IV over 30 minutes once per week for 7 weeks followed by one week rest. Dexamethasone was used 1 hour pre and 8 hours post PEGPH20 dosing. From Cycle 2 onward, PEGPH20 and GEM were administered once weekly for three weeks in a 4-week cycle. As of 01 April 2013, 28 subjects were enrolled and all received study medication. Four subjects received PEGPH20 at 1 µg/kg dose level, four received PEGPH20 at 1.6 µg/kg dose level, and 20 subjects received PEGPH20 at 3.0 µg/kg dose level. Treatment duration ranges from 1 day to more than 10 months. Enrollment is ongoing. Two subjects (1 µg/kg and 3.0 µg/kg dose levels) had infusion reaction when PEGPH20 was administered as an IV push or IV slow push. The protocol has since been amended to administer PEGPH20 as an IV infusion over 10 minutes. No additional infusion reactions have been reported.

The safety profile of PEGPH20 in combination with GEM is similar to what was observed in the first 2 Phase 1 studies, with MSEs as the most common toxicities. The most common toxicities observed for GEM were myelosuppression (such as neutropenia) and GI toxicities (such as nausea and vomiting). In addition, most of the AEs related to GEM were similar in frequency and severity regardless of the PEGPH20 dose levels. Of the 24 subjects who received either 1.6 or 3.0 µg/kg, treatment duration ranged from one dose to up to 9 cycles. Two subjects experienced infusion reactions when PEGPH20 was administered as a 2 mL slow push. After this event, the protocol was amended to administer PEGPH20 as a 10 mL IV infusion over 10 minutes (1 mL/minute). Additionally, the protocol amendment clarified that hypersensitivity related reactions are not considered DLTs because hypersensitivity reactions in general are not

related to the dose level of a drug since even a small amount of exposure can lead to hypersensitivity reactions. There were no DLTs reported according to study DLT definition.

In general, the most commonly reported toxicities associated with PEGPH20 have been musculoskeletal events (e.g., muscle, joint, and bone pain; muscle cramping; and other involuntary contractions). Less commonly reported events are edema in the legs or arms, fatigue and generalized weakness, diarrhea, nausea, vomiting, and decreased appetite, rash, mild sore throat, voice hoarseness, and hiccups. Atrial fibrillation was reported in one subject (although high doses of steroids are well known to be associated with an irregular heartbeat (e.g., bradycardia, cardiac arrest, and cardiac arrhythmia), a relationship to PEGPH20 could not be ruled out). Pneumonitis was also reported in one subject (reported rarely following one or more doses of GEM, per GEM package insert; however, the relationship to PEGPH20 could not be ruled out).

Treatment emergent TE events were reported in 8 subjects. The most frequently reported thromboembolic event was pulmonary embolism, which occurred in 5 subjects (18%, 5/28 [1 at 1 µg/kg and 4 at 3.0 µg/kg]). Among the five subjects with a pulmonary embolism, one subject also had a deep vein thrombosis, which occurred one day after the reported pulmonary embolism. One other subject experienced partial thrombosis of the right gonadal vein, DVT, splenic infraction and cerebrovascular accident. One subject experienced jugular vein thrombosis and one experienced cerebrovascular accident. Since the total incidence of subjects with either a venous or arterial TE in this single arm study is 28.5% (8/28) and was within the reported range of 5-36% in patients with PDA (Epstein AS 2012), these events were not identified as increased AEs.

The on-study duration for all 28 patients ranged from 6 to 365 days, with a median duration of 92 days. Responses were assessed by an independent central radiologist. Partial responses were reported in 10 of the 24 patients who received PEGPH20 at either 1.6 or 3.0 µg/kg dose level. In addition, subjects who had high HA in tissue biopsies experienced better responses (5/6 subjects), which correlated with prolonged progression free survival (219 days) and overall survival (~529 days). Partial responses were seen in 4 of the 11 subjects who had lower HA in tissue biopsies. The PFS and OS in the low HA group was 108 days and 174 days, respectively (Hingorani 2013).

The recommended Phase 2 dose for PEGPH20 in combination with GEM is 3.0 µg/kg twice weekly in the first 4 weeks and once weekly thereafter.

Based on the emerging safety profile of PEGPH20, the proposed starting dose of 3.0 µg/kg is acceptable for the intended patient population. Considering that the subjects who will be enrolled in this study have an overall poor prognosis, with extra pancreatic disease precluding curative surgical resection, and that their Phase 3 study (Von Hoff 2013) results improved the overall survival for the primary objective, which further confirmed the published Phase 2 study results (Von Hoff 2011), it is reasonable to test the treatment effect of PEGPH20 in combination with nab-paclitaxel (NAB) plus GEM in advance pancreatic cancer patients.

4.2.4. Thromboembolic events reported in the current study

As of April 1 2014, a total of 146 subjects were enrolled in the HALO-109-202 study. Preliminary safety data suggested the possibility of an increase in TE events in the PEGPH20

plus nab-paclitaxel and gemcitabine (PAG) arm compared to the nab-paclitaxel and gemcitabine arm (AG).

Based on a comprehensive review of literature (Section 4.1 and Section 4.2) and cancer treatment guidelines, and in consultation with oncology/hematology thrombosis experts , the current protocol is amended. To reduce the rate of TE events, subjects at high risk of venous and arterial thromboembolic events will be excluded from entering the study. High risk subjects will also be excluded from continuing PEGPH20 therapy. LMWH therapy will be used in all subjects on this study (see Section 6.1.3 for details).

Subjects at higher risk of arterial events, specifically those with a prior history of cerebrovascular accident and a history of evidence of carotid artery disease will be excluded from trial participation. In Stage 2 of the study, prior to Amendment 5.0, the Khorana Risk Score factors (Khorana 2010) were utilized to identify those subjects at higher risk of venous thromboembolic events. The Khorana Risk Score is designed to stratify cancer patients into low, intermediate, and high risk for developing VTE. This risk score was originally derived from a development cohort of 2701 patients and was then validated in an independent cohort of 1365 patients from a prospective registry. Observed rates of VTE in the development and validation cohorts were 0.8% and 0.3% in the low-risk category, 1.8% and 2% in the intermediate-risk category, and 7.1% and 6.7% in the high-risk category, respectively. Among the potential risk factors for developing TE events, having pancreatic cancer, hemoglobin < 10 g/dL, BMI ≥ 35kg/m^2, WBC ≥ 11x10^9/L platelet count >350,000/L, were the key risk factors.

Prophylactic use of enoxaparin was studied in patients with either locally advanced or metastasized pancreatic cancer by Riess et al (Riess 2010). In this study 312 patients were treated with a palliative chemotherapy (stratified for risk) using either gemcitabine alone or in combination with cisplatin, 5-fluorouracil (5-FU) and folinic acid, with or without enoxaparin, initially at a dose of 1 mg/kg, then at a dose of 40 mg daily. The event rate of all-type TE events (venous and arterial) in patients not receiving LMWH prophylaxis was 10% at 3 months and 15% at 12 months as compared to 1.3% and 5% at 3 and 12 months in patients receiving LMWH, respectively (p=0.01). Other LMWHs, such as dalteparin, semuloparin, were also studied in advanced cancer patients receiving chemotherapy. In general, use of LMWH reduced the VTE events significantly, with no increase in major bleeds reported in pancreatic cancer, however some increase has been reported in other cancers (Agnelli 2009, Agnelli 2012, Maraveyas 2012, Farge 2013).

It is well documented that the use of Megestrol acetate causes thrombosis. Ruiz et al reviewed over 35 trials with 3963 patients for effectiveness and 3180 for safety with regard to appetite improvement and weight gain in cancer, AIDS and other underlying conditions (Ruiz 2013). The review shows that megestrol acetate is associated with an increased risk of blood clots (which may result in swelling, pain or redness of one extremity and not the other, sudden difficulty in breathing, severe headache or vision changes), fluid retention (resulting in swelling of the feet or hands) and death. Therefore, concomitant use of megestrol acetate is prohibited in this study.

4.2.5. Clinical Pharmacokinetics

Subjects enrolled in the Phase 1 studies received PEGPH20 at doses ranging from 0.5 to 50 µg/kg with or without dexamethasone. Blood samples were collected at scheduled timepoints, and plasma was analyzed for PEGPH20 concentrations. Pharmacokinetic (PK) analysis suggests

that a linear PK model adequately described the available PEGPH20 plasma concentration versus time profiles. The maximum plasma concentrations were estimated to be between 0.4 and 1.0 hours after dosing. Subjects dosed with 50 µg/kg PEGPH20 in Study HALO-109-101 demonstrated a plasma half-life of 2.5 to 4.8 hours for the initial phase and 26 to 49 hours (1 to 2 days) for the terminal phase. Estimates for initial distribution volume were consistent with expectations for therapeutic macromolecules. The prolonged plasma half-life of PEGPH20 makes sustained depletion of tumor-associated HA feasible.

Table 6 provides a summary of descriptive PK parameters, including the maximum-observed concentration (C_{max}), time-to-maximum plasma concentration (t_{max}) and the area-under-the-concentration time curve (AUC) estimates for 0 to 72 hours (AUC_{0-72}) following the initial dose of PEGPH20 for subjects in Study HALO-109-101. Results from this descriptive PK analysis indicate a dose-dependent increase in systemic exposure (C_{max}, AUC_{0-72}) after a single PEGPH20 dose in the 0.5 to 50 µg/kg range.

Table 6: Descriptive Pharmacokinetic Parameters (Mean ± SD) after Initial IV PEGPH20 Dosing at 0.5 to 1.5 µg/kg (Study HALO-109-101)

Dose (µg/kg)	N	t_{max} (h)	C_{max} (U/mL)	AUC_{0-72} (U·h/mL)
0.5[a]	4	0.423 ± 0.133	0.325 ± 0.221	2.23 ± 2.95
0.75	4	0.580 ± 0.244	0.558 ± 0.148	0.873 ± 0.578
1.0	3	1.01 ± 0.883	0.718 ± 0.094	8.13 ± 6.37
1.5	1	0.5	1.61	13.5
50	2	0.625 ± 0.530	30.9 ± 0.566	580 ± 84.3

Abbreviations: AUC_{0-72}= area-under-the-concentration time curve from 0 to 72 hours; C_{max} = maximum-observed concentration; h = hour; IV = intravenous; SD = standard deviation; t_{max} = time-to-maximum concentration

[a] N = 3 in statistical calculations, except for C_{max} (N = 4).

Preliminary PK data are available from the initial 18 subjects who received multiple doses of PEGPH20 with dexamethasone in Study HALO-109-102. Table 7 provides an interim summary of descriptive PK parameters, including C_{max}, t_{max}, and AUC_{0-72} following the initial dose of PEGPH20 for subjects in Study HALO-109-102. For subjects treated with 0.5 or 1.6 µg/kg PEGPH20, C_{max} values were consistent with those measured in Study HALO-109-101. Concentrations typically fell to the limit of quantification within the first day. C_{max} values from subjects treated with 5.0 µg/kg, maximum PEGPH20 concentrations were approximately one tenth of the C_{max} values detected for subjects treated with 50 µg/kg in Study HALO-109-101.

Table 7: Descriptive Pharmacokinetic Parameters (Mean ± SD) after Initial IV PEGPH20 Dosing at 0.5 to 5.0 µg/kg (Study HALO-109-102)

Dose (µg/kg)	N	t_{max} (h)	C_{max} (U/mL)	AUC_{0-72} (U·h/mL)
0.5	1	0.25	0.4	NC
1.6	3	0.667 ± 0.382	0.90 ± .015	2.27 ± 0.37
3.0	12	0.792 ± 1.04	3.76 ± 6.86	42.42 ± 60.93
5.0	2	0.875 ± 0.177	4.33 ± 1.31	98.71 ± 13.99

Abbreviations: AUC_{0-72} = area-under-the-concentration time curve from 0 to 72 hours; C_{max} = maximum-observed concentration; h = hour; IV = intravenous; SD = standard deviation; t_{max} = time-to-maximum observed plasma concentration.

Plasma samples collected approximately 1 hour after repeat PEGPH20 dosing were used to evaluate the effects of twice-weekly dosing on plasma PK. Consistent with the limited results in Study HALO-109-101, there was no evidence for significant accumulation of PEGPH20 in the plasma. This preliminary analysis suggests that the plasma PK of PEGPH20 is similar for these two Phase 1 studies.

The ongoing HALO-109-201 study is to evaluate the treatment effect of PEGPH20 in combination with GEM in subjects with advanced pancreatic cancer. Serial blood samples were drawn to characterize the pharmacokinetic profile of PEGPH20 in combination with GEM. Preliminary PK results are available in the first 18 subjects who received PEGPH20 at doses ranged from 1.0 µg/kg to 3.0 µg/kg in combination with GEM. Table 8 summarizes descriptive PK parameters, including C_{max}, t_{max}, and AUC_{0-72} following the initial dose of PEGPH20 for subjects in Study HALO-109-201

Table 8: Descriptive Pharmacokinetic Parameters (Mean ± SD) after Initial IV PEGPH20 Dosing at 1.0 to 3.0 µg/kg in Combination With Gemcitabine (Study HALO-109-201)

Dose (µg/kg)	N	t_{max} (h)	C_{max} (U/mL)	AUC_{0-72} (U·h/mL)
1.0	3	0.25 ± 0.0	1.09 ± 0.627	11.93 ± 13.09[a]
1.6	4	0.438 ± 0.375	2.89 ± 1.74	31.56 ± 22.48
3.0	10	0.25 ± 0.0	2.607 ± 1.60	33.80 ± 53.10

Abbreviations: AUC_{0-72} = area-under-the-concentration time curve from 0 to 72 hours; C_{max} = maximum-observed concentration; h = hour; IV = intravenous; SD = standard deviation; t_{max} = time-to maximum observed plasma concentration.

[a] N=2 for AUC.

Consistent with PK results of the two Phase 1 single agent studies, plasma concentrations of PEGPH20 when combined with GEM were similar to predictions from a linear PK model that has been established for PEGPH20 as a single agent.

4.2.6. Pharmacodynamic Evaluations

Measurements of plasma HA catabolites (breakdown products of HA after enzymatic depletion by PEGPH20) were used to provide an initial indicator of PEGPH20 pharmacodynamics. Prior to dosing with PEGPH20, HA plasma concentrations were typically <1 µg/mL or below the level of quantification (0.5 µg/mL). For subjects dosed with 50 µg/kg PEGPH20 plasma concentrations of HA increased slowly with maximum HA measurements observed ≥72 hours post-PEGPH20 dose, and plasma concentrations were still detectable up to 2 weeks post-PEGPH20 administration. Analysis of reported initial 24-hour data from subjects enrolled in Studies HALO-109-101 and HALO-109-102 demonstrated a dose-dependent increase in HA plasma concentrations.

A comparative evaluation of tumor biopsies was performed in two subjects treated with 1.6 µg/kg PEGPH20. Histochemical staining using a biotinylated HA binding protein demonstrated a decrease in pericellular and stromal HA in tumor specimens collected after 4-weekly doses of PEGPH20. Decreased levels of HA in tumor together with increased detection of HA in the plasma are consistent with the expected enzymatic activity of PEGPH20.

The pharmacologic activity of PEGPH20 was also assessed using magnetic resonance imaging (MRI) and FDG-PEG. MRI scans were collected prior to and 2 to 4 days after PEGPH20 dosing, and increases in apparent diffusion coefficient values in tumors were reported in 7 of 11 subjects evaluated. Dynamic contrast-enhanced MRI was conducted in a subset of subjects, and permitted estimation of K^{trans}, extracellular space volume fraction, and blood plasma volume fraction of the whole tissue. Transient increases in tumor K^{trans} values were reported two subjects within 24 hours of PEGPH20 dosing. FDG-PET was used to evaluate tumor metabolism in one subject with metastatic rectal cancer that received 3 µg/kg PEGPH20 treatment. Comparison of standardized uptake values (SUVs) before and after treatment demonstrated reductions in tumor SUVs that ranged from 19% to 42% (Infante 2012). These preliminary data are consistent with a mechanism for PEGPH20 that includes modification of the ECM and facilitation of tumor uptake of anti-tumor agents.

4.2.7. Evaluation of the New Formulation of PEGPH20

The original formulation of PEGPH20 (frozen drug product at 3.5 mg/mL) uses histidine in the formulation and has been tested in nonclinical pharmacology and toxicology studies and in clinical studies (see the Investigators Brochure for additional information).

A new formulation of PEGPH20 (liquid drug product at 0.3 mg/mL) has been developed based on drug administration needs determined in earlier clinical studies. This succinic acid formulation provides enhanced stability, allowing the drug product to be stored at 2°C to 8°C, instead of -20°C, which is required for the original PEGPH20 formulation. Comparative studies have shown that PEGPH20 histidine and succinic acid formulations have equivalent exposure (AUC and C_{max}) in rats. Based on these findings, the new succinic acid formulation is proposed for evaluation in ongoing and future studies.

As of June 2013, over 20 subjects have been treated with the original formulation of PEGPH20 at 3.0 µg/kg. The established safety and PK profile of PEGPH20 at this dose level was acceptable, with minimum toxicities in most subjects. PK and safety data from these subjects

will be compared with subjects receiving the new formation of PEGPH20 at 3.0 µg/kg in the current study.

4.3. Study Rationale

The incidence of pancreatic carcinoma has markedly increased during the past several decades and ranks as the fourth leading cause of cancer death in the United States (US). Approximately 44,000 new cases of pancreatic cancer were diagnosed in the US in 2011 with an estimated 37,600 deaths. Metastatic PDA is a lethal disease with a median survival of approximately 6 months.

GEM is the only approved single agent for the treatment of pancreatic carcinoma, with a median survival of 5.7 months versus 4.4 months for fluorouracil (5-FU), and a 1-year rate of 20% (Burris 1997). GEM is also given in combination with other therapies. Recently Conroy and colleagues reported that the median OS for treatment with FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin combination chemotherapy) was 11.1 months versus 6.5 months for treatment with GEM alone (Conroy 2011). The efficacy of GEM in combination with NAB was evaluated in a Phase 2 study of previously untreated advanced pancreatic cancer patients (Von Hoff 2011). At the MTD (the recommended dose for Phase 3), 1000 mg/m^2 of GEM plus 125 mg/m^2 of NAB were administered weekly for 3 weeks and repeated every 4 weeks. The overall response rate (ORR) was 48%, with OS at 12.2 months, and 1-year survival rate of 48%. The study reported the highest response rate with significant improvement of survival benefit in recent years. The follow-up Phase 3 study was reported to have reached statistical significance on survival benefit, though the exact benefit has not yet been published. Based on the Phase 2 study results, National Comprehensive Cancer Network guidelines recommend the combination treatment of GEM plus NAB as one of the front-line therapies for metastatic pancreatic cancer. It is reasonable to believe that NAB plus GEM may become one of the standard of care treatments for pancreatic cancer. Therefore, this Phase 2 study was designed to evaluate the treatment effect of PEGPH20 in combination with NAB plus GEM with NAB plus GEM.

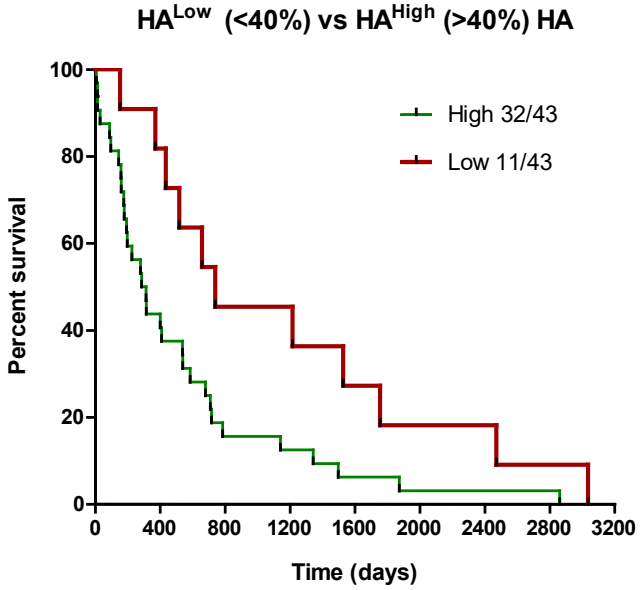
PEGPH20 is a PEGylated version of human recombinant PH20 hyaluronidase. In preclinical studies, PEGPH20 has been shown to remove HA from the ECM surrounding tumor cells by depolymerizing this substrate. In tumors that are rich in HA, such as 87% of pancreatic cancers (Figure 1) (Kultti 2012), tumor tissue may be especially sensitive to the HA-degradation properties of PEGPH20 and thus more responsive to the cytotoxic effects of a given dose of chemotherapy.

In order to understand the role of HA and survival in patients with PDA, Translational Genomics Research Institute conducted a retrospective study of HA-specific staining in tissue microarrays constructed from 43 resected PDA samples for which patient survival had been followed for more than 8 years (Whatcott 2011). One hundred percent (100%) of the patient tumors stained positive for HA in at least some fraction of the tissue area (stroma). Log-rank analysis of HA levels in tumor tissue revealed that the survival rate was significantly lower among patients with high HA levels than patients with low HA levels (738 days versus 229 days, respectively; $p<0.05$; Figure 2). These data suggest that HA levels in pancreatic adenocarcinoma patients may be predicative of survival.

PEGPH20 has demonstrated anti-tumor activity alone or in combination with GEM in a variety of preclinical tumor model systems, including xenograft and genetically engineered murine

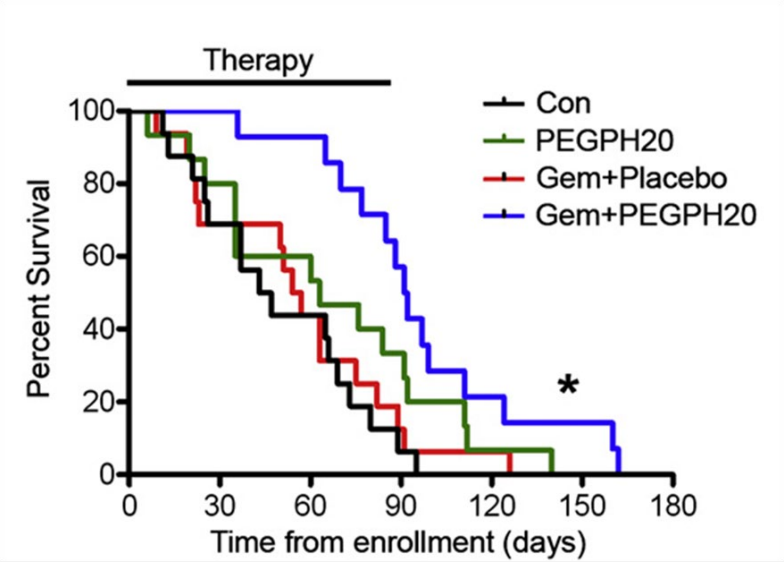
models of pancreatic cancer. In a genetically engineered mouse model of PDA, mice develop tumors with clinical, histopathologic and molecular features indistinguishable from human PDA; importantly, the murine tumors are also found to express high levels of HA (Hingorani 2005). In this *Kras*$^{LSL\text{-}G12D/+}$;*Trp53*$^{LSL\text{-}R172H/+}$; *Cre* (*KPC*) model of PDA, co-treatment of PEGPH20 with GEM significantly prolonged survival when compared with GEM treatment alone (Figure 3). Mice treated with GEM alone survived for 15 days while mice treated with GEM and PEGPH20 survived for 28.5 days (Jacobetz 2013). In a second study, both PEGPH20 and GEM were administered IV on a weekly regimen mimicking the proposed human study. In this study, median OS was increased by approximately 83%, from 55.5 days with GEM plus placebo to 91.5 days for GEM plus PEGPH20 (Provenzano 2012).

Figure 2: Survival by High and Low Hyaluronan levels in Pancreatic Ductal Adenocarcinoma Tumors



Retrospective study utilizing a biotinylated HA binding protein-based staining method in a tissue microarray constructed from 43 resected PDA samples for which patient survival had been followed for more than 8 years. HA staining was primarily observed in the peritumoral, or stromal, compartments of the tumor tissue samples. 100% of the patient tumors stained positive in at least some fraction of the tissue area (stroma) for HA. Staining with a biotinylated HA binding protein was scored according to the percentage area of HA-positivity relative to the total tissue area. (Whatcott 2011)

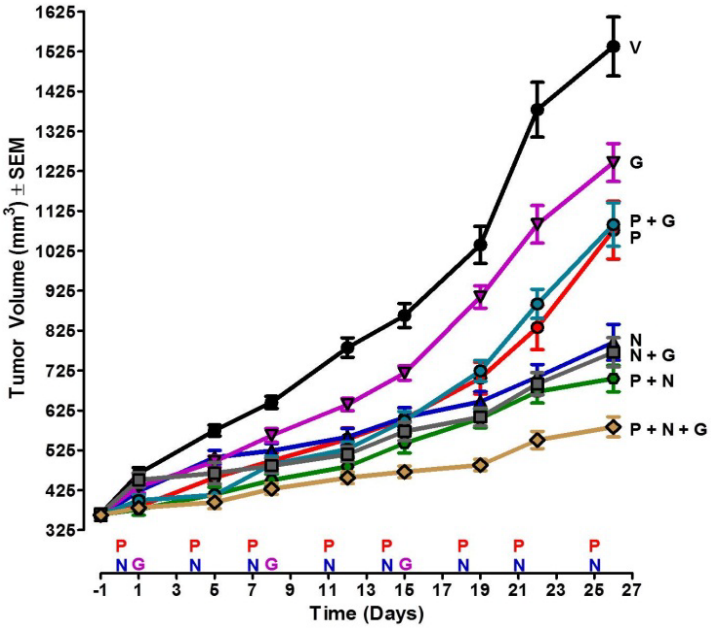
Figure 3: PEGPH20 Combined with Gemcitabine Significantly Increased Survival in the KPC Mouse Model of Pancreatic Ductal Adenocarcinoma



PEGPH20 combined with GEM significantly increased survival in the KPC mouse model of human PDA. In the first study, both PEGPH20 and GEM were administered IV and on a weekly regimen mimicking the proposed human study. In this study, median OS was increased by approximately 70%, i.e. from 55.5 days with GEM plus placebo (n=16) to 92 days for the combination of PEGPH20 + GEM (n=14) ($p<0.004$; Figure 3) (Provenzano 2012). In a second study, mice were treated twice per week with 100 mg/kg GEM intraperitoneally and/or 4.5 mg/kg PEGPH20 IV. Mice treated with vehicle or PEGPH20 survived a median of 11 days, mice treated with GEM survived for a median of 15 days and mice treated with PEGPH20 plus GEM survived a median of 28.5 days with a significant difference in survival of GEM versus GEM plus PEGH20 of 13.5 days (Jacobetz 2013).

In addition to studies in KPC mice, the combination of PEGPH20 with GEM and/or NAB was evaluated in a human PDA BxPC3 xenograft model (Figure 4). The highest tumor growth inhibition (TGI) measured (81%) was in the triple combination group (PEGPH20 plus GEM plus NAB) compared with all other combinations tested. This represented a 23% increase in TGI over GEM plus NAB without PEGPH20. Further, the addition of PEGPH20 increased the median survival time of the GEM plus NAB group by 31% (Osgood 2012).

Figure 4: PEGPH20 Combined with Gemcitabine and Nab-Paclitaxel Significantly Increased Survival in the KPC Mouse Model of Pancreatic Ductal Adenocarcinoma



Treatment *(Ranked by Efficacy)*	TGI (%)*	p-value†
GEM	25	0.0110
PEGPH20 + GEM	38	<0.0001
PEGPH20	39	0.0028
NAB	63	<0.0001
NAB + GEM	66	<0.0001
PEGPH20 + NAB	71	<0.0001
PEGPH20 + NAB + GEM	**81**	<0.0001

* *TGI relative to vehicle at Day 26*
† *Relative to vehicle at Day 26*

The addition of PEGPH20 to NAB and GEM increased TGI to 81% ($p < 0.0001$) relative to vehicle and was superior to NAB + GEM treatment (66%; $p = 0.0004$). In brief, mice were staged into eight treatment groups (n=8/group): vehicle control, PEGPH20 (4.5 mg/kg, IV, 2x/wk) ± NAB (10 mg/kg, IV, 2x/wk) ± GEM (180 mg/kg, intraperitoneal, 1x/wk, dosed 24 hours after PEGPH20 and NAB). Note: to mimic GEM dosing in the clinic, mice were given a one week GEM holiday following the third GEM dose. (Osgood 2012)

These data suggest that pancreatic adenocarcinomas express high levels of HA and that degrading tumor-associated HA may make these tumor cells more susceptible to the growth-inhibiting properties of GEM and NAB.

4.3.1. Rationale for Selection of the PEGPH20 Starting Dose

A total of 40 subjects received at least one dose of PEGPH20 as a single agent in the Studies HALO-109-101 and HALO-109-102. The MTD for PEGPH20 was 3.0 µg/kg in the once weekly or twice weekly dosing regimen, when dexamethasone was given at 8 mg 1 hour pre- and 8 hours post-PEGPH20 dosing. The most common and DLTs were MSEs. At the 3.0 µg/kg dose level, most of the MSEs reported were Grade 1 or 2, and most resolved within one week after dosing was stopped. In Study HALO-109-201, PEGPH20 was tested at 3 dose levels (1.0, 1.6, and 3.0 µg/kg) in combination with GEM (1000 mg/m^2) in 28 subjects. The MTD for PEGPH20 was determined to be 3.0 µg/kg.

In Study HALO-109-101, analysis of plasma samples demonstrated quantifiable levels of hyaluronidase activity between 15 minutes and 76 to 224 hours post-PEGPH20 dosing. Plasma concentrations declined exponentially with time and were frequently below the limit of assay sensitivity, especially after lower doses of PEGPH20. Interim PK analysis suggests that a linear PK model adequately described the concentration versus time profiles. Maximum measured plasma concentrations were 30.5 U/mL and 31.2 U/mL in subjects dosed with 50 µg/kg

PEGPH20. Estimates for initial distribution volume were consistent with expectations for therapeutic macromolecules. Plasma half-life estimates were 2.5 to 4.8 hours for the initial phase and 26 to 49 hours (1 to 2 days) for the terminal phase. This analysis predicts that twice weekly dosing with 1.6 µg/kg PEGPH20 will keep the plasma concentrations above 0.1 U/mL. The predicted plasma concentration-time profile can be expected to produce continuous enzymatic activity in vivo that acts to hydrolyze tumor HA.

Supported by data that dexamethasone can prevent musculoskeletal observations in a canine model and a decreased prevalence and severity of musculoskeletal symptoms with a pre- and post-treatment dosing regimen of dexamethasone in Studies HALO-109-102 and HALO-109-201, a premedication regimen of dexamethasone 8 mg twice a day (bid) should accompany PEGPH20 doses. The Investigator may adjust the dose of dexamethasone based on the clinical presentation of each subject.

In preclinical models, PEGPH20, either a single agent or in combination with GEM effectively inhibited tumor growth at doses as low as 0.01 to 0.1 mg/kg (data on file at Halozyme). To predict the equivalent human exposure at these doses, an interspecies scaling algorithm was used that assumes plasma clearance of PEGPH20 scales in proportion to (body weight)$^{0.67}$. The efficacious doses in mice (0.01 to 0.1 mg/kg) scale to human equivalent doses of 0.75 to 7.5 µg/kg. As mice have approximately 20 times the circulating levels of HA compared to humans, it is hypothesized that an equivalent dose of PEGPH20 may have relatively more anti-tumor activity in humans.

In Study HALO-109-102, a dose level of 1.6 µg/kg PEGPH20 administered on a twice weekly schedule increased circulating concentrations of HA catabolites and reduced tumor-associated HA (Infante 2012). The degradation of tumor-associated HA is hypothesized to increase the ability of anti-cancer agents to penetrate tumor tissue and, therefore increase cytotoxic activity in tumors. In tumors that are rich in HA, which has been documented to occur in approximately 87% of all pancreatic cancers (Figure 1), tumor tissue may be especially sensitive to the HA-degradation by PEGPH20 and thus responsive to an increase in the cytotoxic effects of a given dose of GEM. Modifying the extracellular environment to increase the penetration and efficacy of chemotherapeutics represents a novel approach to treating pancreatic cancer in a setting that has demonstrated limited therapeutic efficacy.

Preliminary anti-tumor activity has been observed in metastatic pancreatic cancer subjects at PEGPH20 dose levels of 1.6 and 3.0 µg/kg in combination with GEM in Study HALO-109-201. This Phase 2 study plans to investigate PEGPH20 at a 3.0 µg/kg dose level when combined with NAB and GEM.

4.4. Background of Nab-paclitaxel

NAB is an albumin-bound form of paclitaxel. NAB promotes the assembly of microtubules from tubulin dimmers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

NAB (ABRAXANE®) is approved by FDA and other regulatory agencies as a single agent for the treatment of metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. It is also approved as a first-line treatment in combination with carboplatin in locally advanced or metastatic non-small cell lung cancer in patients who are not candidates for curative surgery or radiation therapy.

4.5. Background of Gemcitabine

GEM 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. GEM is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of GEM is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, GEM 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, GEM 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 GEM triphosphate into DNA (self-potentiation). After the GEM 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 GEM nucleotide and repair the growing DNA strands (masked chain termination).

GEM (GEMZAR®) is approved by the FDA and other regulatory agencies as a single agent as the first-line treatment for patients with locally advanced (Stage II or Stage III when surgery is not an option) or metastatic (Stage IV) adenocarcinoma of the pancreas. GEM is also indicated for patients previously treated with 5-FU.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objective

- To estimate the progression-free survival (PFS) duration of PEGPH20 combined with NAB plus GEM (PAG treatment).
- To evaluate the thromboembolic events in subjects treated in the PAG arm in Stage 2 of the study as of this protocol amendment.

5.1.2. Secondary Objectives

- To estimate the relative benefit of PAG treatment versus NAB plus GEM (AG treatment), as assessed by the PFS hazard ratio.
- To estimate the relative benefit of PAG treatment versus AG treatment, as assessed by the PFS hazard ratio based on subject tumor-associated HA levels.
- To estimate the ORR, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), of PAG treatment and the relative benefit of PAG treatment versus AG treatment.
- To estimate the OS duration of PAG treatment and the relative benefit of PAG treatment versus AG treatment, as assessed by the OS hazard ratio.
- To evaluate the safety and tolerability profile of the PAG and AG treatment groups.
- To characterize the plasma PK of PEGPH20 when given in combination with NAB plus GEM.

5.1.3. Exploratory Objectives

- To estimate the OS benefit of PAG treatment versus AG treatment based on HA levels from tumor biopsies.
- To estimate the duration of response (DR) of responders (complete response [CR] and partial response [PR]) of PAG and AG treatment.
- To compare the disease control rate (DCR; CR, PR, and stable disease [SD]) between the PAG and AG treatment groups.
- To compare CA19-9 changes between the PAG and AG treatment groups.
- To assess treatment effect of PAG with regard to HA levels in plasma and in tumor biopsies.

5.2. Study Endpoints

5.2.1. Primary Endpoint

- PFS (measured from the date of randomization until disease progression or death from any cause).

- Proportion of subjects in the PAG arm who experience any thromboembolic event in Stage 2 of the study as of Amendment 3.0.

5.2.2. Secondary Efficacy Endpoints

- PFS in relation to HA levels.
- ORR (defined as the percentage of subjects with a RECIST v1.1 PR or CR).
- OS (measured from the date of randomization until death from any cause).

5.2.3. Exploratory Efficacy Endpoints

- OS in relation to HA levels.
- DR (measured from the date of the first CR/PR until disease progression).
- DCR (defined as the percentage of subjects with SD, PR, or CR).
- Serum CA 19-9 response rate between the PAG and AG treatment groups.
- PEGPH20 anti-tumor activities based on HA levels in plasma and in tumor biopsies.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan: Description

This is a Phase 2, multicenter, open-label, randomized study of PEGPH20+NAB+GEM (PAG treatment) compared with NAB+GEM (AG treatment) in subjects with Stage IV previously untreated pancreatic cancer. The study has two run-in phases, one for each formulation of PEGPH20 (original and new formulations). The first run-in phase will evaluate the safety and tolerability of PAG treatment (original PEGPH20 formulation) compared with AG treatment before initiating Phase 2. The Phase 2 portion is an open-label randomized study and has two stages. With Amendment 1.0, an additional run-in phase will be conducted to incorporate a new formulation of PEGPH20 during the Phase 2. Stage 2 was added in Amendment 3.0.

The dosing schedule for subjects randomized to the PAG and AG treatment groups will be the same in the run-in phases and Phase 2 (see Section 6.1.3). The treatment period will consist of 4-week treatment cycles (28 days) with Week 4 of every cycle as a washout week (i.e., no treatment will be given). Treatment will continue until disease progression or unacceptable toxicity is documented.

6.1.1. Run-in Phases

6.1.1.1. Original Formulation of PEGPH20

In the first run-in phase, approximately 8 subjects will be randomized in a 3:1 ratio to receive PEGPH20 (3.0 µg/kg; original formulation) in combination with standard dosing of NAB+GEM (PAG treatment) or NAB+GEM (AG treatment). No stratification factors will be used. Additional subjects may be enrolled to further assess the tolerability of PEGPH20 in order to establish the acceptable safety profile prior to the randomization of the Phase 2 study.

The Sponsor, the participating Investigators, and the independent safety physician will determine if the dose and regimen for Phase 2 is acceptable after reviewing all available safety data from Cycle 1 from all subjects in this run-in phase.

6.1.1.2. New Formulation of PEGPH20

With Amendment 1.0, a second run-in phase will be conducted to evaluate a new formulation of PEGPH20. Approximately 8 subjects will be randomized in a 3:1 ratio to receive the new formulation of PEGPH20 at 3.0 µg/kg in combination with standard dosing of NAB+GEM (PAG treatment) or NAB+GEM (AG treatment). All study sites will be invited to participate in this second run-in phase. Phase 2 enrollment using the original formulation of PEGPH20 will continue in parallel with this run-in phase.

The Sponsor, the participating Investigators, and the independent safety physician will determine if the dose and regimen for the new formulation of PEGPH20 is acceptable after reviewing available safety from Cycle 1 from all subjects in the second run-in phase. If the safety profile and the PK profile of the new formulation are deemed acceptable, the new formulation of PEGPH20 will be available to all subjects on the study. Subjects currently receiving the old formulation of PEGPH20, will be switched to the new formulation.

6.1.2. Phase 2

In Phase 2, approximately 237 subjects will be randomized to receive PEGPH20 (3.0 µg/kg, pending outcome of run-in phase safety assessment) in combination with standard dosing of NAB+GEM (PAG treatment) or NAB+GEM (AG treatment). Randomization will be stratified by Karnofsky Performance Status (70% to 80% and 90% to 100%).

Phase 2 will have 2 stages due to a partial clinical hold that occurred from April through July 2014 (see Section 6.1.2.1 for additional details). The first stage will randomize subjects in a 1:1 ratio. The second stage will randomize subjects in a 2:1 ratio (PAG:AG). The second stage of the study will start as of Amendment 3.0.

6.1.2.1. Clinical Hold

This study was initiated in March 2013 (first subject first visit). In April 2014, the study data monitoring committee (DMC) reported an imbalance in TE events with a higher incidence in subjects treated with PAG (28.4%) than AG (14.8%) and advised the Sponsor to stop enrollment and dosing of PEGPH20 pending further analysis. The Sponsor followed the recommendation and halted the study, after which it was placed on a partial clinical hold. All subjects in the PAG group stopped PEGPH20 therapy and remained on AG therapy alone (Stage 1 of the study; N=146 randomized, N=135 treated).

The Sponsor presented a risk management plan to mitigate the TE events. On 4 June 2014, the FDA removed the partial clinical hold and the study protocol was amended (Amendment 3) to: (1) include concomitant use of prophylactic enoxaparin (40 mg/day), (2) provide enhanced pharmacovigilance by immediate reporting of all TE events to Halozyme Drug Safety, (3) discontinue PEGPH20 after a TE, and (4) exclude subjects with evidence of a DVT and PE as well as those subjects determined to be at high risk of a TE event based on the Khorana criteria (Khorana 2008). Subjects accrued to the study per Protocol Amendment 3 (Version 4) were assigned to Stage 2.

Study enrollment reopened in June 2014 (Stage 2 of the study; N=133 randomized and enrolled from 24 July 2014 through 19 February 2016, N=125 treated) with all subjects receiving prophylactic enoxaparin (40 mg/day and then increased to 1 mg/kg/day subcutaneously [SC] [Protocol Amendment 4]).

6.1.2.2. Study Re-Starting Procedures Overview Following Temporary Hold

The following thromboembolic event risk factors will be assessed for all subjects (both treatment groups) after signing the updated ICF (protocol amendment 3.0) and prior to the next scheduled treatment:

- Prior history of cerebrovascular accident or transient ischemic attack
- Pre-existing carotid artery disease
- Concomitant use of megestrol acetate (subjects on the PAG arm must discontinue use >10 days before re-starting PEGPH20 treatment and subjects on the AG arm should discontinue use immediately)
- DVT on Doppler ultrasound or pulmonary embolism (PE) on chest CT prior to re-initiating therapy after study hold

Subjects who were randomized to the PAG treatment arm and answer yes to one or more of the questions above cannot re-start PEGPH20 therapy. Subjects who were randomized to the AG arm who answer yes to one or more questions may continue. All subjects (in both treatment arms) will continue receiving Gemcitabine and Nab Paclitaxel regardless of how the above questions were answered. Subjects re-starting PEGPH20 should re-start on the next scheduled visit day of the cycle they are currently in (i.e., do not "make up" visits).

Additionally, 1 mg/kg daily enoxaparin will be administered to or self-administered by all subjects on both study arms. Subjects who are contraindicated to receive enoxaparin (see the exclusion criteria) will be discontinued from study treatment (PAG and AG).

6.1.2.3. Treatment with Enoxaparin

A new guidance from a Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis recommends that all patients undergoing outpatient therapy for advanced pancreatic cancer should receive treatment with low molecular weight heparin (Khorana 2014). The recommended dose for enoxaparin is 1.0 mg/kg SC daily as was studied in the CONKO-004 study (Riess 2010). Thus, effective with amendment 4.0, the dose of enoxaparin is increased to 1.0 mg/kg/day SC for ongoing and newly enrolled subjects on both arms of the study. If a subject requires daily doses of enoxaparin greater than 1.0 mg/kg/day SC (e.g., a therapeutic dose), he/she may still continue in the study. Ongoing patients who have required enoxaparin dose reduction below 40 mg should continue at their current dose. Refer to Section 10.1.1 for enoxaparin management guidelines.

6.1.2.4. Use of Doppler ultrasound and Chest CT

Doppler ultrasound of both legs and chest CT will be performed during screening to exclude subjects with DVTs and PEs. For all subjects in either arm who are in treatment at the time the study is restarted, a Doppler ultrasound and chest CT will be conducted prior to the next dose of PEGPH20 or chemotherapy. If a DVT or PE is detected, the subject should not re-start with PEGPH20 treatment. The event should be noted as an adverse event (if detected after receipt of study treatment). Subjects should be treated with therapeutic doses of LMWH and should continue with chemotherapy and be monitored as per standard practice (i.e., routine Doppler ultrasound or chest CT scans and other routine laboratory testing). For newly enrolling patients, the Doppler study should be performed within 7 days of Day 1 dosing.

6.1.3. Overview of Treatment Schedule

6.1.3.1. PAG Treatment Group

In Cycle 1 Week 1, PEGPH20 will be administered alone on Day 1 and Day 4 (e.g., Monday/Thursday or Tuesday/Friday), and NAB+GEM will be given on Day 2, approximately 24 hours after the first dose of PEGPH20 (e.g., Tuesday or Wednesday). In Cycle 1 Weeks 2 and 3, PEGPH20 will be administered twice per week on Days 8, 11, 15, and 18. NAB and GEM will be administered once per week, 2 to 4 hours after PEGPH20 administration on Days 8 and 15.

In Cycle 2 onwards, PEGPH20, NAB, and GEM will be given once weekly on Days 1, 8, and 15. NAB and GEM will be given 2 to 4 hours after the dose of PEGPH20.

Dexamethasone 8 mg will be administered in each treatment cycle to alleviate musculoskeletal toxicities. Dexamethasone will be administered within 2 hours prior to the beginning of each PEGPH20 infusion and 8 to 12 hours after the completion of the PEGPH20 infusion.

See Table 9 and Figure 5 for an example of the PAG treatment schedule.

6.1.3.2. AG Treatment Group

In all cycles, NAB and GEM will be given once weekly on Days 1, 8, and 15.

Dexamethasone 8 mg will be administered in each treatment cycle. Dexamethasone will be administered within 2 hours prior to the beginning of each NAB infusion and 8 to 12 hours after the completion of the GEM infusion.

See Table 9 and Figure 6 for an example of the AG treatment schedule.

Table 9: Overview of Study Medication Schedule by Treatment Group

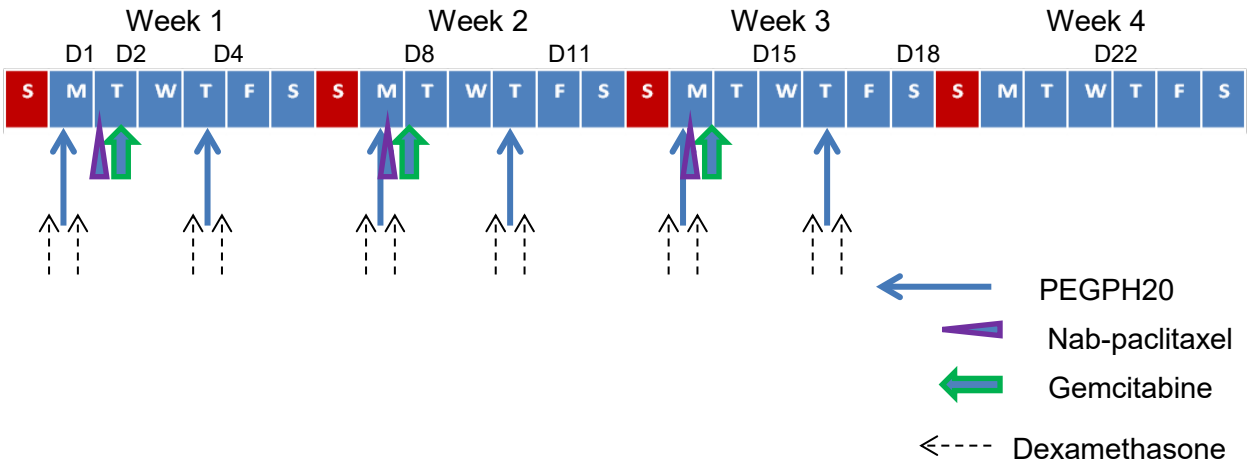
Timepoint	PAG Treatment Group	AG Treatment Group
Cycle 1		
Day 1	PEGPH20	NAB and GEM
Day 2	NAB and GEM (24 ± 4 hours after Day 1 dose of PEGPH20)	No visit
Day 4	PEGPH20	No visit
Day 8	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 11	PEGPH20	No visit
Day 15	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 18	PEGPH20	No visit
Day 22	No treatment (i.e., washout)	No treatment (i.e., washout)
Cycle 2 onwards		
Day 1	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 8	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 15	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)	NAB and GEM
Day 22	No treatment (i.e., washout)	No treatment (i.e., washout)

Abbreviations: AG = nab-paclitaxel plus gemcitabine; GEM = gemcitabine; PAG = PEGPH20 in combination with nab-paclitaxel plus gemcitabine; NAB = nab-paclitaxel.

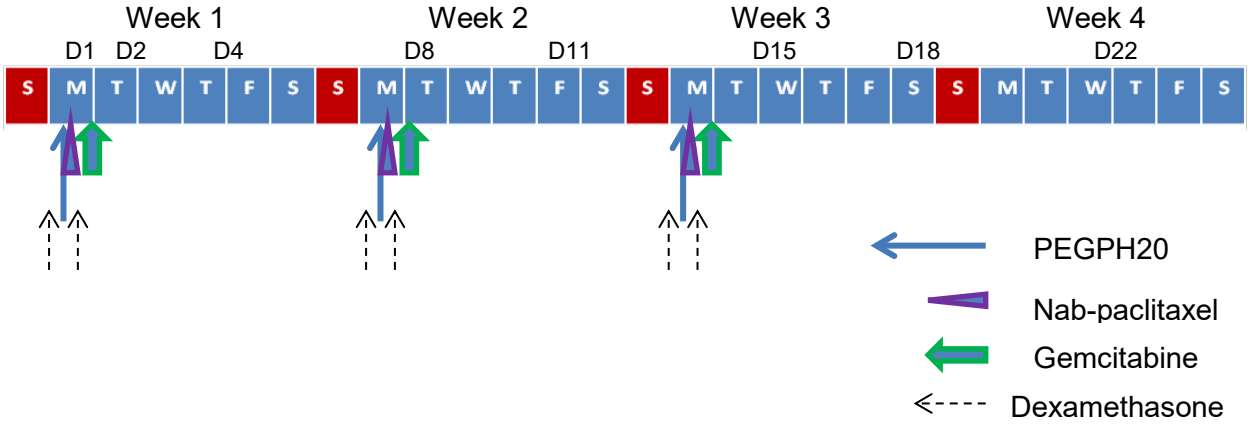
Note: Each treatment cycle is 28 days. Dose interruption and modifications are permitted; refer to Section 8.3 for further guidance.

Figure 5: Example of PEGPH20+nab-Paclitaxel+Gemcitabine (PAG) Treatment Schedule

Cycle 1



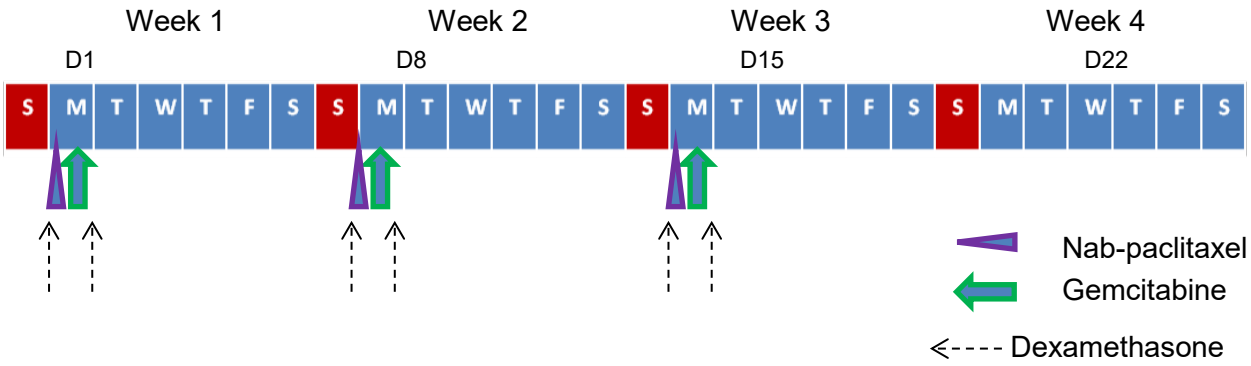
Cycle 2 onwards



Note: Day 1 of Cycle 1 may start on any day; all subsequent study days would be adjusted.

Figure 6: Example of nab-Paclitaxel+Gemcitabine (AG) Treatment Schedule

All Cycles



Note: Day 1 of Cycle 1 may start on any day; all subsequent study days would be adjusted.

6.1.4. Study Closeout Procedures

The purpose of this Protocol Amendment 6 (Version 7) is to introduce study closeout procedures as described in this section. These include a reduction of study procedures for the 1 subject still on treatment (PAG group) and discontinuation of study procedures for subjects in long-term follow-up.

The closeout procedures are effective as of the date of this Protocol Amendment 6, 09 February 2018, and supersede all study procedures required per previous Protocol Amendment 5 (Version 6) dated 06 April 2015.

Study closeout procedures for subjects that are either on treatment or in long-term follow-up are described below:

- The remaining subject on treatment will continue to receive study medication (PAG) until disease progression or other protocol-specified reasons for treatment discontinuation (see Section 7.3.1) or study discontinuation (see Section 7.3.2). For this subject, all procedures required per Protocol Amendment 5 will be immediately discontinued except for the following (details in Table 10):
  - Administration of PEGPH20 on Days 1, 8, and 15 (as in Protocol Amendment 5); and NAB and GEM every 2 weeks (Days 1 and 15) or at the Investigator's discretion and per standard of care (vs. on Days 1, 8, and 15 in Protocol Amendment 5)
  - Administration of dexamethasone and enoxaparin (see Section 6.1.3.1 and Section 6.1.2.3 for additional details)
  - Imaging assessments performed locally (vs. sent to a CIR in Protocol Amendment 5) at a reduced frequency (every 4 cycles or less frequently, at the

Investigator's discretion and per standard of care [vs. every 2 cycles in Protocol Amendment 5]) to minimize radiation exposure

- Clinical laboratory assessments (blood chemistry, hematology, and coagulation) by a local laboratory, all at a reduced frequency (Days 1, 8, and 15 [vs. Days 1, 8, 15, and 22 in Protocol Amendment5]) and at the End of Treatment visit. The clinical laboratory tests on Days 1, 8, and 15 will also be reduced in scope with fewer assessments to ensure the subject's well-being and monitor key safety parameters through the remainder of study treatment.
- Collection/reporting of serious adverse events (SAEs) and adverse events of special interest (TE events) for 30 days after the last dose of study treatment (additional details on SAE and TE event reporting in Section 10.3 and Section 10.4, respectively) (no other AEs will be collected)
- Collection/reporting of pregnancy information as specified in Section 8.2.13 and Section 10.7

- For subjects in long-term follow-up, the long-term follow-up will be discontinued immediately. For the 1 subject still on treatment, long-term follow-up will not be implemented when this subject discontinues treatment and completes the End of Treatment Visit as described in Section 8.1.3.2. This subject's End of Treatment Visit will correspond to the end of the study.

The end of the study is defined by the time when all subjects have discontinued treatment.

Table 10: Study Procedures for the Remaining Subject on Treatment (PAG Group)

Tests and Assessments[a]	Treatment Cycles 2+ (Repeats every 4 weeks)				End of Treatment[b]
	Week 1	Week 2	Week 3	Week 4	
	Day 1	Day 8	Day 15	Day 22	
Disease Assessment (CT)	X[c]				X[d]
PEGPH20 Administration	X	X	X		
Dexamethasone Administration[e]	X	X	X		
Enoxaparin Administration[f]	X				
Nab-paclitaxel Administration[g]	X		X		
Gemcitabine Administration[g]	X		X		
Local Laboratory Tests					
Hematology	X[h]	X[h]	X[h]		X[i]
Blood Chemistry	X[h]	X[h]	X[h]		X[i]
Coagulation Parameters (PT, PTT, INR)	X	X	X		X
Collection/Recording of SAEs and AEs of Special Interest (TE events)[j]	X				X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = International normalized ratio; PAG = PEGPH20 in combination with nab-paclitaxel+gemcitabine; PEGPH20 = Pegylated Recombinant Hyaluronidase; PT = Prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; SC = subcutaneously; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase; TE = thromboembolic.

[a] See Section 8 for details on individual assessments.

[b] The subject should return to the study site for an End of Treatment Visit within approximately 7 days after determination of progressive disease or within 7 days after treatment discontinuation for other reasons. This subject's End of Treatment Visit will correspond to the end of the study.

[c] CT scan assessment will be performed locally at the end of every fourth treatment cycle or less frequently, at the Investigator's discretion and per standard of care. If the subject is withdrawn from the study due to clinical disease progression, a CT scan should be requested as soon as possible after clinical progression is determined.

[d] A CT scan should only be done if radiologic progressive disease was not documented in the previous CT scan.

[e] Dexamethasone should be given within 2 hours prior to the start of each PEGPH20 dose and 8-12 hours after each PEGPH20 dose (additional details in Section 6.1.3.1).

[f] Enoxaparin 1 mg/kg will be given SC once a day during the Treatment Period (additional details in Section 6.1.2.3).

[g] Nab-paclitaxel and gemcitabine will be given every 2 weeks or at the Investigator's discretion and per standard of care, 2 to 4 hours after the PEGPH20 dose. Nab-paclitaxel will be given first.

[h] Assessments will include the following for blood chemistry: glucose, BUN, total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), and electrolytes (potassium and calcium); and hematology: hemoglobin, white blood cell count, and platelet count.

[i] Assessments will include the full panel for blood chemistry and hematology as specified in Section 8.2.12.

[j] SAEs and TE events will be collected for 30 days after the last dose of study treatment (additional details on SAE and TE event reporting in Section 10.3 and Section 10.4, respectively).

7. SELECTION AND WITHDRAWAL OF SUBJECTS AND STUDY TERMINATION

The study plans to randomize approximately 253 subjects with previously untreated pancreatic cancer at study sites in the US.

Run-in phases: Approximately eight subjects will be randomized in a 3:1 ratio to receive PAG (original formulation of PEGPH20) or AG treatment. With Amendment 1.0, an additional 8 subjects will be randomized 3:1 to receive PAG (new formulation of PEGPH20) or AG treatment.

Phase 2: Approximately 237 subjects will be randomized to receive PAG or AG treatment.

7.1. Inclusion Criteria

Subjects must satisfy **all** of the following inclusion criteria to be enrolled in the study.

- Signed, written Institutional Review Board (IRB)/Ethics Committee (EC)-approved Informed Consent Form (ICF).
- Histologically confirmed Stage IV PDA with documented disseminated neoplasm to the liver and/or the lung. Prior to enrollment, confirmation of the following must be obtained:
  - Available tumor tissue block or a minimum of five unstained core biopsy slides that meet specific tissue sample requirements (see Study Laboratory Manual). Note: Fine needle aspirates (FNA) or brushing biopsies will not be acceptable. If an archived sample is not available, a pre-dose core tumor biopsy will be required in order to enter the study (i.e., an archived or fresh pre-dose core biopsy is required).
- One or more metastatic tumors measurable on computed tomography (CT) scan per RECIST v1.1, excluding the primary pancreatic lesion.
- Subject must have received no previous radiotherapy, surgery, chemotherapy, or investigational therapy for the treatment of metastatic disease.
  - Prior treatment with 5-FU or GEM administered as a radiation sensitizer during and up to 4 weeks after radiation therapy is allowed (if there is lingering toxicity, then the Sponsor should be consulted).
  - If a subject received therapy in the adjuvant setting, tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of adjuvant therapy.
- Karnofsky Performance Status ≥70%.
- Life expectancy ≥3 months.
- Age ≥18 years.
- A negative pregnancy test, if female of reproductive potential.

- Screening clinical laboratory values as follows:
  - Total bilirubin ≤1.5 times upper limit of normal (ULN).
  - Aspartate aminotransferase ([AST]; serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase ([ALT]; serum glutamic pyruvate transaminase [SGPT]) ≤2.5 times ULN, (if liver metastases are present, then ≤5 times ULN is allowed).
  - Serum creatinine ≤2.0 mg/dL or calculated creatinine clearance ≥60 mL/min.
  - Serum albumin ≥3.0 g/dL.
  - Prothrombin time (PT)/international normalized ratio (INR) within normal limits (±15%) or within therapeutic range if on warfarin.
  - Partial thromboplastin time (PTT) within normal limits (±15%).
  - Hemoglobin ≥10 g/dL.
  - Absolute neutrophil count (ANC) ≥1,500 cells/mm^3.
  - Platelet count ≥100,000 /mm^3
- For men and women of reproductive potential, agreement to use an effective contraceptive method from the time of screening and throughout their time on study. Effective contraceptive methods consist of prior sterilization, intra-uterine device, oral or injectable contraceptives, and/or barrier methods. Abstinence alone is not considered an adequate contraceptive measure for the purposes of this study.

7.2. Exclusion Criteria

Subjects satisfying any of the following exclusion criteria **are not** allowed in the study.

- Non-metastatic PDA.
- Evidence of deep vein thrombosis (DVT) or pulmonary embolism (PE) or other known thromboembolic event present during the screening period.
- Previous neoadjuvant treatment for pancreatic cancer
- Known central nervous system involvement or brain metastases.
- New York Heart Association Class III or IV cardiac disease or myocardial infarction within the past 12 months.
- Prior history of cerebrovascular accident or transient ischemic attack
- Pre-existing carotid artery disease
- Active, uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
- Known infection with human immunodeficiency virus, hepatitis B, or hepatitis C.
- Known allergy to hyaluronidase.
- Current use of megestrol acetate (use within 10 Days of Day 1).

- Contraindication to heparin as per NCCN guidelines:
  - Recent central nervous system bleed, intracranial or spinal lesion at high risk for bleeding
  - Active bleeding (major): more than 2 units transfused in 24 hours
  - Spinal anesthesia/lumbar puncture
  - Chronic, clinically significant measurable bleeding >48 hours
  - Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)
  - Recent major operation at high risk for bleeding
  - Underlying hemorrhagic coagulopathy
  - High risk for falls (head trauma)
- Previous major bleed (bleeding requiring transfusion of red blood cells) on LMWH
- Women currently pregnant or breastfeeding.
- Intolerant of dexamethasone.
- History of another primary cancer within the last 3 years with the exception of non-melanoma skin cancer, early state prostate cancer, or curatively-treated cervical carcinoma in-situ.
- Any other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding that leads to reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that may render the subject at high risk for treatment complications.
- Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the subject unsuitable for the study.
- Inability to comply with study and follow-up procedures as judged by the Investigator.

7.3. Subject Withdrawal Criteria

7.3.1. Discontinuation of Treatment

The Investigator must guard the subject's welfare and may discontinue study drug treatment at any time when this action appears to be in the subject's best interest. The reason for the subject's withdrawal must be recorded in the subject's electronic case report form (eCRF). Possible reasons for such actions may include, but are not limited to, the following:

- Disease progression defined by either of the following:
  - Disease progression documented by CT scan based on RECIST v1.1, as determined by the Central Imaging Reader (CIR).
  - Clinical tumor-related progression that is well documented in the absence of radiologic disease progression.

- Adverse event (AE).
- Any significant protocol violation (e.g., demonstrated lack of treatment compliance, subject starts taking any concomitant anti-cancer therapy).
- Withdrawal of consent by an enrolled subject.
- Other reasons as determined by the Investigator or Sponsor: a subject may have study treatment discontinued if, in the opinion of the Investigator or Sponsor, it is not in the subject's best interest to continue. This includes subjects who permanently discontinued the LMWH treatment for any reason.
- The subject becomes pregnant (treatment must be discontinued immediately).

Subjects who discontinue treatment should remain in the study for long-term follow-up assessments unless they withdraw consent, die, or become lost to follow-up.

7.3.2. Study Discontinuation

After the subject discontinues study treatment, the subject will be followed in long-term follow-up for assessment of survival and subsequent anti-cancer therapies (Section 8.1.4). Long-term follow-up will continue until the subject discontinues from the study. The reason for the subject's discontinuation from the study should be documented in the subject's eCRF. Possible reasons for study discontinuation include the following:

- Death
- Withdrawal of Consent
- Lost to Follow Up
- Sponsor Termination of the Study
- Other

7.4. Sponsor Study Stopping Rules

Halozyme may terminate this study after informing Investigators at any time. Investigators will be notified by Halozyme (or designee) if the study is placed on hold, completed, or closed. Conditions that may warrant termination of the study include, but are not limited to the following:

- The discovery of unexpected, serious, or unacceptable risk to the subjects in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

8. STUDY PROCEDURES AND ASSESSMENTS

With Protocol Amendment 6, the procedures listed in Section 6.1.4 will supersede the procedures described in this section and subsections unless noted otherwise.

The Study Schedule of Events (Table 1, Table 2, Table 3, Table 4, and Table 5) is given as an aid to subject management. This section describes evaluations to be done before, during, and after treatment. Section 8.2 provides information on individual study assessments.

When duplicate evaluations are performed before study commencement, the data from the evaluation closest in time to study entry will be recorded. When duplicate evaluations are performed in a given time window, the worst case value will be recorded for safety evaluations, unless otherwise stipulated. Unless otherwise specified, clinical laboratory tests may be performed one day earlier than specified in the Study Schedule of Events. Scheduled clinic attendance should occur within ±2 days of the specified dates, as long as doses are separated by the appropriate amount of time (e.g., a minimum of two days when visits are biweekly). Where this is not possible because of extenuating circumstances (e.g., holidays), the reason should be noted.

During Weeks 1 through 3 of Cycle 1, PEGPH20 should be administered twice per week. The twice weekly doses should be separated by a minimum of two days (e.g., Monday and Thursday or Tuesday and Friday schedule). Where this is not possible because of extenuating circumstances (e.g., holidays), the doses should be separated by at least 45 hours.

8.1. Study Procedures by Visit

8.1.1. Screening Visits (PAG and AG Treatment Groups)

If the following procedures were done as per the standard of care prior to the subject signing the ICF, the results may be used for this study providing they were within the screening window: physical examination, vital sign measurements, height, weight/body surface area (BSA), and CT scan.

8.1.1.1. Within 20 Days Prior to Day 1

- Sign and date ICF
- Confirm availability of tumor tissue
- Medical history
- Obtain CT scan and send to Central Imaging for eligibility review (chest CT should be read locally to evaluate for the presence of PE. If subject has signs or symptoms of PE after the initial scan was completed, the chest scan should be repeated prior to randomization)
- Prior medication history

8.1.1.2. Within 14 Days Prior to Day 1

- Physical examination
- Vital sign measurements

- Karnofsky Performance Status
- Height
- Weight/BSA
- Obtain samples for the following tests and send to local laboratory
  - Urine/serum pregnancy test (females of reproductive potential)
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Urinalysis
  - Coagulation tests
  - CA19-9
  - Plasma HA levels
- Subject registration and randomization

8.1.1.3. Within 7 Days Prior to Day 1

- Doppler ultrasound of lower extremities

8.1.2. Treatment Period (PAG Treatment Group)

AEs and concomitant medications will be obtained throughout every visit. Unless otherwise specified, the procedures listed below will be done for all PAG subjects in the run-in phases and Phase 2. Standard of care blood samples for local laboratories should be drawn before NAB and GEM dosing to confirm the subject meets the required criteria for dosing (see Section 8.3.2.3).

8.1.2.1. Treatment Cycle 1

8.1.2.1.1. Cycle 1 Day 1

Pre-PEGPH20 Infusion

- Physical examination
- Vital signs
- Karnofsky Performance Status
- Weight/BSA
- 12-lead electrocardiogram (ECG) (3 times within 5-minute period)
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry

  - Coagulation tests
  - Immunogenicity
  - PEGPH20 concentration (PK) (within 2 hours prior to PEGPH20 infusion)
  - Plasma HA levels
- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)

PEGPH20 Infusion

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min)

Post-PEGPH20 Infusion

- 12-lead ECG (3 times within 5-minute period between 1 to 4 hours after completion of PEGPH20 infusion)
- Obtain samples for the following tests (actual collection times to be recorded):
  - PEGPH20 concentration (PK)
    - Run-in phases: 15 minutes (±5 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), and 4 hours (±30 minutes) after completion of PEGPH20 infusion
    - Phase 2 subjects: 1 hour (±15 minutes) after completion of PEGPH20 infusion
- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.1.2. Cycle 1 Day 2

Pre-NAB and GEM Infusions

- PEGPH20 concentration (PK) and HA sample collection (24 hours ±4 hours after completion of Day 1 PEGPH20 infusion and prior to beginning NAB infusion)
- Vital signs

NAB and GEM Infusions

NAB and GEM will be administered 24 hours (±4 hours) after completion of Day 1 PEGPH20 infusion.

- NAB IV infusion over 30 minutes
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

8.1.2.1.3. Cycle 1 Day 4

Pre-PEGPH20 Infusion

- Vital signs
- PEGPH20 concentration (PK): **Run-in phases only**

- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)

PEGPH20 Infusion

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min)

Post-PEGPH20 Infusion

- PEGPH20 concentration (PK) (1 hour ±15 minutes after completion of PEGPH20 infusion): **Run-in phases only**
- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.1.4. Cycle 1 Day 8

Pre-PEGPH20, NAB, and GEM Infusions

- Vital signs
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation tests
  - PEGPH20 concentration (PK): **Run-in phases only**
- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)

PEGPH20, NAB, GEM Infusions

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min)
- NAB IV infusion over 30 minutes (2 to 4 hours after completion of Day 8 PEGPH20 infusion)
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

Post-PEGPH20, NAB, and GEM Infusions

- PEGPH20 concentration (PK) (1 hour ±15 minutes after completion of PEGPH20 infusion and immediately after completion of GEM infusion): **Run-in phases only**
- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.1.5. Cycle 1 Day 11

Pre-PEGPH20 Infusion

- Vital signs
- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)
- PEGPH20 concentration (PK): **Run in phases only**

PEGPH20 Infusion

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min)

Post-PEGPH20 Infusion

- PEGPH20 concentration (PK) (1 hour ±15 minutes after completion of PEGPH20 infusion): **Run-in phases only**
- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.1.6. Cycle 1 Day 15

Pre-PEGPH20, NAB, and GEM Infusions

- Vital signs
- 12-lead ECG (3 times within 5-minute period)
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation tests
  - PEGPH20 concentration (PK)
- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)

PEGPH20, NAB, and GEM Infusions

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min)
- NAB IV infusion over 30 minutes (2 to 4 hours after completion of PEGPH20 infusion)
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

Post-PEGPH20, NAB, and GEM Infusions

- 12-lead ECG (3 times within 5-minute period between 1 to 4 hours after completion of PEGPH20 infusion, and before the NAB dose)
- Obtain samples for the following tests:
  - PEGPH20 concentration (PK)
    - Run-in phases: 15 minutes (±5 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), and 4 hours (±30 minutes) after completion of PEGPH20 infusion. A PK sample collected 24 hours (±4 hours) after completion of PEGPH20 infusion is optional
    - Phase 2: 1 hour (±15 minutes) after completion of PEGPH20 infusion
- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.1.7. Cycle 1 Day 18

Pre-PEGPH20 Procedures

- Vital signs
- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)
- PEGPH20 concentration (PK): **Run-in phases only**

PEGPH20 Infusion procedures

- Infusion of PEGPH20 IV over 10 to 12 minutes (approximately 1 mL/min)

Post-PEGPH20 Infusion

- PEGPH20 concentration (PK) (1 hour ±15 minutes after completion of PEGPH20 infusion): **Run-in phases only**
- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.1.8. Cycle 1 Day 22

No treatments given. The following assessments should be completed:

- Vital signs
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
  - CA19-9
- Optional tumor biopsy (anytime in Week 4 of Cycle 1)

8.1.2.2. Treatment Cycle 2 Onwards (repeats every 4 weeks)

8.1.2.2.1. Cycle 2+, Day 1

Pre-PEGPH20, NAB, and GEM Infusions

- Physical examination
- Vital signs
- Karnofsky Performance Status
- Weight/BSA
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry

  - Coagulation Tests
  - Plasma HA sample
  - Immunogenicity
- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)

PEGPH20, NAB, and GEM Infusions

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/minute)
- NAB IV infusion over 30 minutes (2 to 4 hours after PEGPH20 infusion)
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

Post-PEGPH20, NAB, and GEM Infusions

- HA sample collection after the administration of GEM (no more than 2 hours after GEM administration has been completed)
- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.2.2. Cycles 2+, Day 8

Pre-PEGPH20, NAB, and GEM Infusions

- Vital signs
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
  - PEGPH20 concentration (PK)
- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)

PEGPH20, NAB, and GEM Infusions

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min)
- NAB IV infusion over 30 minutes (2 to 4 hours after PEGPH20 infusion)
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

Post-PEGPH20, NAB, and GEM Infusions

- Obtain samples for the following tests:
  - PEGPH20 concentration (PK) (1 hour ±15 minutes after completion of PEGPH20 infusion)
- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.2.3. Cycles 2+ Day 15

Pre-PEGPH20, NAB, and GEM Infusions

- Vital signs
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
- Dexamethasone administration (within 2 hours prior to PEGPH20 infusion)

PEGPH20, NAB, and GEM Infusions

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min)
- NAB IV infusion over 30 minutes (2 to 4 hours after completion of PEGPH20 infusion)
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

Post-PEGPH20, NAB, and GEM Infusions

- Dexamethasone administration (within 8 to 12 hours after completion of PEGPH20 infusion)

8.1.2.2.4. Cycles 2+ Day 22

No treatments given for PAG or AG groups. The following assessments should be completed:

- Vital signs
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
  - CA19-9
- Obtain CT scan and send to CIR for assessment of disease **every other cycle (i.e., Week 4 of Cycles 2, 4, 6, 8 etc.)** Scans may be obtained any time after dosing on Day 15 to allow for enough time for the scan to be sent to and reviewed by the central reader prior to the subject's next scheduled dosing visit. The results should be interpreted and sent to the site before dosing in the next cycle begins.
- Optional post-dose biopsy (anytime in Week 4 of any cycle)

8.1.2.3. End of Treatment Visit

Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after determination of progressive disease or within 7 days after treatment discontinuation

for other reasons. AEs and concomitant medications will be obtained throughout the visit, and the following assessments should be completed:

- Physical examination
- Vital signs
- Karnofsky Performance Status
- Weight/BSA
- Obtain CT scan and send to CIR **(**CT should only be done if radiologic progressive disease was not documented in the previous CT scan)
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
  - Immunogenicity
  - CA19-9

8.1.3. Treatment Period (AG Treatment Group)

AEs and concomitant medications will be obtained throughout every visit. The procedures listed below will be done for all AG subjects in the run-in phases and Phase 2. Standard of care blood samples for local laboratories should be drawn before NAB and GEM dosing to confirm the subject meets the required criteria for dosing (see Section 8.3.2.3).

8.1.3.1. All Treatment Cycles

8.1.3.1.1. All Cycles Day 1

Pre-NAB and GEM Infusions

- Physical examination
- Vital signs
- Karnofsky Performance Status
- Weight/BSA
- 12-lead electrocardiogram (ECG) (3 times within 5-minute period) **Cycle 1 only**
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
  - Plasma HA levels

- Dexamethasone administration (within 2 hours prior to NAB infusion)

NAB and GEM Infusions

- NAB IV infusion over 30 minutes
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

Post-NAB and GEM Infusions

- 12-lead ECG (3 times within 5-minute period between 1 to 4 hours after completion of GEM infusion): **Cycle 1 only**
- Dexamethasone administration (within 8 to 12 hours after completion of GEM infusion)

8.1.3.1.2. All Cycles Day 8

Pre-NAB and GEM Infusions

- Vital signs
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
- Dexamethasone administration (within 2 hours prior to NAB infusion)

NAB GEM Infusions

- NAB IV infusion over 30 minutes
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

Post-NAB and GEM Infusions

- Dexamethasone administration (within 8 to 12 hours after completion of GEM infusion)

8.1.3.1.3. All Cycles Day 15

Pre- NAB and GEM Infusions

- Vital signs
- 12-lead ECG (3 times within 5-minute period): **Cycle 1 only**
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
- Dexamethasone administration (within 2 hours prior to NAB infusion)

NAB and GEM Infusions

- NAB IV infusion over 30 minutes
- GEM IV infusion over 30 minutes (immediately after completion of NAB infusion)

Post-NAB and GEM Infusions

- 12-lead ECG (3 times within 5-minute period between 1 to 4 hours after completion of GEM infusion): **Cycle 1 only**
- Dexamethasone administration (within 8 to 12 hours after completion of GEM infusion)

8.1.3.1.4. All Cycles Day 22

No treatments given. The following assessments should be completed:

- Vital signs
- Obtain samples for the following tests:
  - Hematology
  - Blood chemistry
  - Coagulation Tests
  - CA19-9
- Optional tumor biopsy (anytime in Week 4)
- Obtain CT scan and send to CIR for assessment of disease **every other cycle (i.e., Week 4 of Cycles 2, 4, 6, 8 etc.)** Scans may be obtained any time after dosing on Day 15 to allow for enough time for the scan to be sent to and reviewed by the central reader prior to the subject's next scheduled dosing visit. The results should be interpreted and sent to the site before dosing in the next cycle begins.

8.1.3.2. End of Treatment Visit

Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after determination of progressive disease or within 7 days after treatment discontinuation for other reasons. AEs and concomitant medications will be obtained throughout the visit, and the following assessments should be completed:

- Physical examination
- Vital signs
- Karnofsky Performance Status
- Weight/BSA
- Obtain CT scan and send to CIR (CT should only be done if radiologic progressive disease was not documented in the previous CT scan)
- Obtain samples for the following tests:

- Hematology
- Blood chemistry
- Coagulation Tests
- CA19-9

8.1.4. Long-term Follow-up (PAG and AG Treatment Groups)

After the End of Treatment Visit, all subjects will enter long-term follow-up during which information on the subject's survival status will be obtained by the site on a monthly basis. In addition, efforts should be made to collect data on all the subject's next anti-cancer therapies (i.e., therapies received, responses) on a monthly basis. Information may be collected by chart review, phone calls, clinic visits, or by other means as appropriate. Long-term follow-up will continue until the subject dies, is lost to follow-up, or withdraws consent.

8.1.5. Procedures for Study Treatment Discontinuation

In the event of study treatment discontinuation, the subject should be instructed to report to the clinic as early as possible after the decision to discontinue study treatment has been made or for the next scheduled clinic visit. When the subject returns to the clinic, all End of Treatment procedures should be conducted (see Sections 8.1.2.3 and 8.1.3.2). The Investigator will make his or her best efforts to perform these procedures.

8.2. Study Assessments

8.2.1. Informed Consent

The Investigator or designee must present and explain the study protocol to prospective study subjects before Screening. The ICF must be in a language that the subject can read and understand. Once the subject has had an opportunity to read the ICF, the Investigator or designee must be available to answer any questions the subject may have regarding the study protocol and procedures. The Investigator or designee must explain that the subject is not obliged to enter the study and is free to withdraw from it at any time for any reason. If new safety information becomes available and results in significant changes in risk/benefit assessment, the ICF should be reviewed and updated if necessary. Under this circumstance, all subjects, including those already being treated, should be given the new information, given a copy of the revised ICF, and allowed to re-evaluate their consent to continue in the study.

A copy of the signed and dated ICF will be provided to the subject. The original ICF will be retained by the Investigator.

8.2.2. Inclusion/Exclusion Criteria

The inclusion/exclusion criteria (Sections 7.1 and 7.2) must be reviewed at Screening to ensure that the subject qualifies for the study. Subjects may be enrolled into the study if all criteria are met.

8.2.3. Medical History

A complete medical history (significant past and ongoing conditions including tobacco/nicotine history) and demographic information will be obtained at Screening. Previous history of allergies/allergic reactions (e.g., allergy to bee stings, anaphylaxis, etc.) should also be captured on the Medical History eCRF page.

8.2.4. Concomitant Medications

Information regarding how to collect concomitant medications is defined in Section 10.12.

8.2.5. Adverse Events

AEs will be collected as defined in Section 10.

8.2.6. Physical Examination

Physical examination including ears/eyes/nose/throat/neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, central and peripheral nervous system, and dermatologic assessments will be performed when required by protocol.

8.2.7. Height and Weight/Body Surface area

Height will be recorded in cm, and weight should be recorded in kg. BSA will be calculated from the height and weight.

8.2.8. Karnofsky Performance Status

The subject's Karnofsky Performance Status will be assessed (see Appendix B).

8.2.9. Vital Signs

Assessment of vital signs includes the measurement of blood pressure (systolic and diastolic), pulse, respiratory rate, and body temperature. Blood pressure and pulse will be measured with the subject at rest and in a sitting position for at least 5 minutes.

8.2.10. Tumor Biopsy Tissue Samples

Tumor biopsies will be used to assess the pharmacodynamic (PD) effects of PEGPH20 within the tumor/stroma. A tumor tissue block or a minimum of five unstained core biopsy slides (ten are requested) that meet specific tissue sample requirements will be required for this study. FNA or brushing biopsy is not acceptable for this study. The pathology report must be provided. If an archived sample is not available, a pre-dose core tumor biopsy will be required in order to enter the study (i.e., a pre-dose core biopsy is required; it may be archived or fresh). Specific sampling processing instructions will be outlined in a separate laboratory manual. The tumor biopsy, whether a block or unstained slides, must be sent to the appropriate laboratory as soon as possible after it is obtained; however, it should not be sent prior to the subject signing the ICF. Tumor biopsy samples will be utilized for analysis of HA and other exploratory biomarkers. The biopsy samples will be analyzed during the study, however some of these samples will be stored and may be analyzed at a later date for other potential biomarkers.

Subjects may consent to an optional post-dose biopsy at the end of Cycle 1.

8.2.11. 12-lead ECG

All ECGs will be done in triplicate within a 5-minute period. The Investigator's evaluation of the ECGs as normal or as abnormal without or with clinical significance will be recorded in the eCRF.

8.2.12. Blood Chemistry, Hematology, Coagulation Parameters, and Urinalysis

Blood chemistry, hematology, coagulation parameters, and urinalysis will all be analyzed by the central laboratory. Coagulation tests done after screening will be done at a local laboratory, results should be entered into the CRF. If anti-Xa testing is completed (Section 10.1), it should be done at a local laboratory. Standard of care blood samples for local laboratories should also be drawn before NAB and GEM dosing to confirm the subject meets the criteria for dosing (see Section 8.3.2.3). The Investigator must evaluate all results outside the reference range and determine the clinical significance (clinically significant or not clinically significant). If local laboratory data need to be used instead of central laboratory data, the local laboratory data must be entered in the appropriate eCRF.

- Blood chemistry: glucose, blood urea nitrogen (BUN), albumin, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), electrolytes (including sodium, potassium, calcium, magnesium, chloride, and bicarbonate), and creatinine.
- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count, neutrophils (absolute), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophil (absolute), granulocyte (absolute), mean corpuscular hemoglobin, mean corpuscular volume, and platelet count.
- Coagulation: INR, PT, and PTT.
- Urinalysis: protein, glucose, ketones, blood, specific gravity, nitrite, pH, leukocytes.

8.2.13. Pregnancy Test

A serum or urine human chorionic gonadotropin test to determine whether a female subject is pregnant should be collected for all women of reproductive potential. This assessment will be done by the local laboratory.

8.2.14. Immunogenicity

A blood sample will be collected from PAG subjects and analyzed to determine if PEGPH20 is provoking a humoral immune response. Initial testing will be done during the study; however, samples will be stored for possible re-analysis if deemed necessary.

8.2.15. CA19-9

CA19-9 (carbohydrate antigen 19-9 or sialylated Lewis(a) antigen) is a blood test from the tumor marker category. Blood samples will be collected and sent to the central laboratory for analysis.

8.2.16. Imaging/Radiologic Evaluation

CT with contrast evaluations will be performed in accordance with each site's Standard of Care Pancreatic CT imaging protocol (must include venous phase chest, abdomen and pelvis contrast enhanced CT). In the event that the subject is intolerant to the CT contrast agent, a non-contrast chest

CT and iodinated contrast enhanced MRI of the abdomen and pelvis is acceptable (please refer to the imaging manual for full directives).

All scans should be sent to the CIR for disease assessment using RECIST v1.1. For study eligibility, the CIR must determine the presence of one or more metastatic tumors based on CT scans performed within 20 days of Day 1. During the study, CT scans for objective tumor assessment will occur at the end of Cycle 2, and at the end of every second treatment cycle thereafter (Week 4 of Cycle 4, 6, 8, etc.) CT scans should be performed post-last dose or the following week in each cycle (e.g. post-dose Cycle 2 Day 15 or early in Week 4 in Cycle 2) to allow time for reading of the scans by the CIR prior to starting subsequent cycles. The results of these scans should be interpreted by the CIR and sent to the site before dosing in the next cycle begins. For subjects who are withdrawn from the study due to clinical disease progression, a CT scan should be requested as soon as possible. At the End of Treatment Visit, a CT should only be done if radiologic progressive disease was not documented in the previous CT scan.

8.2.16.1. Chest CT To Exclude Pulmonary Embolism

The chest CT obtained during the screening period should be read locally to assess for the presence of PE (central read will only confirm RECIST 1.1 criteria, (refer to Section 8.2.16) and will not assess for PE). If a subject has signs and symptoms of PE after the initial screening scan was obtained, the scan should be repeated prior to randomization. A chest CT should also be done after PEGPH20 study hold is removed (both treatment groups), after signing the updated ICF (Amendment 3.0), and before the next chemotherapy dose or restart of PEGPH20 to evaluate for the presence of pulmonary embolism. This should be done per local practice and should not be sent to the central lab for analysis (refer to Section 6.1.2.4 for additional details).

8.2.17. Doppler Ultrasound

Doppler ultrasound should be performed as per Section 6.1.2.4. Bilateral Doppler ultrasound scanning of the proximal and distal veins is the current standard for routine clinical assessment of possible lower extremity DVT.

8.2.18. Pharmacokinetic Assessments

Plasma samples to assess the potential effects of NAB+GEM on PEGH20 PK will be collected in the PAG treatment group in the run-in phases and Phase 2. Post-dose PK timepoints should be relative to the stop time of the PEGPH20 infusion. If samples are collected from a central line, the line should be flushed with saline prior to collecting the PK samples. Samples should not be collected from the same line used to administer PEGPH20. Actual sampling times must be recorded. Initial testing will be done during the study; however, samples will be stored for possible re-analysis if deemed necessary. Additional testing to assess the potential effects of PEGPH20 on GEM and NAB PK may be done in the future utilizing the plasma samples collected in this study.

8.2.19. Pharmacodynamic Endpoints

Plasma HA is a potential biomarker indicator of tumor burden and tumor biology. Baseline and post-dose HA levels in plasma and in tumor biopsy samples will be analyzed to evaluate the PEGPH20 treatment effect on tumor response. Initial testing will be done during the study,

however, samples will be stored for possible re-analysis if deemed necessary.
Note: Post-dose plasma HA sample collection will begin once central laboratory kits are available.

8.2.20. Tumor-Associated Hyaluronan Investigational VENTANA HA RxDx Assay

Tumor-associated HA may be a potential biomarker indicator of tumor burden and tumor biology.

During the PEGPH20 clinical development, the Sponsor partnered with Ventana Medical Systems, Inc. (VMSI) to develop an investigational affinity histochemistry diagnostic assay (VENTANA HA RxDx assay) to detect HA in tumor biopsies. After the development of the scoring algorithm and determination of the cut-point (≥50% for PDA), the investigational diagnostic HA assay is used to evaluate any correlation between HA accumulation and the potential PEGPH20 treatment effect.

Tumor samples will be collected and analyzed in a prospective-retrospective fashion using the VENTANA HA RxDx assay. Tumor samples and clinical outcome data from HALO-109-202 Stage 1 served as the Training Set for HA algorithm and cut-point development, while tumor samples and clinical outcome data from Stage 2 served as the Validation Set. Additional details of the VENTANA HA RxDx assay are given in the PEGPH20 Investigator's Brochure.

8.3. Study Drug Administration

Each treatment cycle is 4 weeks (28 days) and consists of 3 weeks of treatment followed by 1 week of rest (i.e., washout week).

Day 1 of Cycle 1 is based on the administration of PEGPH20 (PAG treatment group) or either NAB or GEM (AG treatment group). Day 1 of subsequent cycles is based on the administration of chemotherapy (for both treatment groups). If both the NAB and GEM doses are missed or held on Day 1 of treatment cycles 2+, the cycle will not start until the day the first dose of either NAB or GEM is administered to the subject (i.e., for the PAG treatment group, PEGPH20 should be held if both NAB and GEM are held). If one of the chemotherapy drugs (NAB or GEM) is held, the other study drugs may be given; if PEGPH20 is held, NAB and GEM may be given.

If any dose (PEGPH20, NAB, or GEM) is missed on Day 8 or Day 15 of a cycle, the cycle will continue as scheduled with just that missed dose or all doses skipped if medically necessary.

8.3.1. PEGPH20

The PEGPH20 dose will be individually calculated for all dosing visits according to the subject's screening weight. In calculating the dose, there will be no downward adjustment to "ideal" body weight. Doses should be re-adjusted if the subject's weight changes by >10%. If the subject's weight changes by ≤10%, no adjustment is necessary unless the site has a standard procedure to adjust doses based upon current weight. The dispensing pharmacist will verify the dose accuracy with a qualified study staff member. The appropriate dose will be diluted as per the instructions provided in a separate pharmacy manual.

After completion of pre-dose activities, PEGPH20 will be administered as an IV infusion over 10 minutes, approximately 1 mL/minute (a window of +2 minutes is allowed, i.e., infusion can be 10 to 12 minutes), under observation by qualified clinic staff. The volume and/or duration of

PEGPH20 administration may change at the discretion of the Sponsor, based upon safety information. The study nurse or alternate designee by the Investigator will record the time the infusion was started and stopped. A saline flush should follow IV delivery of the complete PEGPH20 dose as per standard of care for flushing IV lines. Only a peripheral line should be used for the administration of PEGPH20 (heparin flushes should not be used on the same line as PEGPH20), but heparin flushes may be used for central lines as per standard of care. In the event that peripheral venous access cannot be obtained, the central line may be used. If this happens, ensure the line is flushed with saline (minimum of 10 cc) prior to administering PEGPH20 and after administering PEGPH20. Ensure the PEGPH20 administration is not done immediately before or after the central line has been flushed with a heparin flush (e.g., ensure the line is flushed with a heparin flush no earlier than 1 hour before or after the PEGPH20 administration).

8.3.1.1. Hypersensitivity to PEGPH20

In the event of a hypersensitivity reaction, the PEGPH20 infusion should be stopped and the symptoms should be treated as necessary. If a hypersensitivity reaction is suspected, PEGPH20 administration should be immediately stopped, and blood should be drawn and analyzed at a local laboratory to confirm the reaction (e.g., IgE, IgG, and serum tryptase levels). Halozyme should be contacted immediately (see study manual for contact information) so that current knowledge of laboratory testing could be provided to the site. Results should be documented in the eCRF.

At the Investigator's discretion and after discussion with the Sponsor, a re-challenge for the next visit may be done if the reaction is not considered anaphylaxis and is ≤ Grade 2. Any subject with anaphylaxis or a ≥ Grade 3 hypersensitivity reaction/infusion reaction should be discontinued from the study. In the event of a ≤ Grade 2 hypersensitivity/infusion reaction, the Sponsor and Investigator will agree on how subsequent injections will be administered. In general, a re-challenge should be done after pre-medication with a combination of IV diphenhydramine, IV H2 blockers (such as famotidine), and IV dexamethasone. If the hypersensitivity reactions are experienced at the re-challenge, the subject should be discontinued from the study.

8.3.1.2. PEGPH20 Dose Modification Guidelines

PEGPH20 dose adjustments are allowed based on toxicities that are deemed related, possibly related, or probably related to PEGPH20. See Table 11 for guidelines.

Table 11: PEGPH20 Dose Adjustment and Toxicity Management Guidelines

Event	Management/Action
Musculoskeletal	
Any Grade 1 MSEs	No change in dose. May give additional dexamethasone, muscle relaxer, or pain medication.
Any Grade 2 intermittent muscle cramps or other types of MSEs	No change in dose or frequency required, but may reduce the dose to 1.6 µg/kg or decrease the frequency of PEGPH20 with mutual agreement with the Sponsor if the MSEs are persistent and resolved to baseline or Grade 1 with additional dexamethasone, muscle relaxer, or pain medication.
Any Grade 3 or 4 MSEs that resolve to Grade ≤ 2 within 14 days	Hold treatment. If resolved to ≤ Grade 2 within 14 days, may resume treatment at 1.6 µg/kg and/or decrease the frequency to once weekly (in the first cycle) of PEGPH20 with mutual agreement with the Sponsor. For Grade 4 events, continuation of treatment must be discussed with the Sponsor's Medical Monitor prior to restarting treatment at 1.6 µg/kg once weekly.
Any Grade 3 or 4 MSEs	Hold treatment if the events do not resolve (as noted above) and remain as Grade 3 or 4 events for >14 days. Treatment may resume at 1.6 µg/kg with mutual agreement with the Sponsor if the MSEs are resolved to ≤ Grade 2.
All non-MSE Events (except TE events) potentially related to PEGPH20	
Grade 1 or 2	No change.
Grade 3	Hold treatment. Treatment may resume at the same dose level if toxicity is resolved to baseline within 14 days. Treatment may resume but at 1.6 µg/kg or decrease the frequency with mutual agreement from the Sponsor if toxicity is reduced to ≤ Grade 2 within 14 days.
Grade 4	Hold treatment. Treatment may resume if toxicity is resolved to ≤ Grade 2 or baseline and should be at 1 dose level below or at a reduced frequency, at the discretion of the Investigator after discussion with the Sponsor.
Thromboembolic Events (Regardless of relatedness to PEGPH20)	
Any Grade TE	Discontinue PEGPH20 treatment permanently and treat event per NCCN guidelines until documented resolution of event. Nab-paclitaxel and gemcitabine treatment may continue in accordance with the chemotherapy dose modification guidelines listed in Table 13 and Table 15.

Abbreviation: MSEs = musculoskeletal events.

Only one re-challenge at the same dose level is allowed, and only one dose reduction and/or decrease in dosing frequency is allowed. The lower dose level for dose reduction will be 1.6 µg/kg. PEGPH20 re-escalations are allowed at the Investigator's discretion.

If both NAB and GEM are held on Day 1 of treatment cycles 2+, PEGPH20 must also be held; however, PEGPH20 may be given alone or in combination with either or both chemotherapy drugs on Days 8 and 15 of any cycle. If PEGPH20 is held during a treatment cycle, NAB and GEM may still be given if the subject meets all criteria for dosing.

If PEGPH20 is permanently discontinued, PAG subjects should continue with all other visits and procedures as outlined in Table 2. Pre-PEGPH20 laboratory samples should be obtained as per protocol but should be collected before nab-paclitaxel administration (instead of the PEGPH20). This includes pre-dose PK, immunogenicity, and HA samples. Post-dose PEGPH20 PK samples will not be collected. Samples collected after chemotherapy should continue to be collected (e.g., HA). Dexamethasone should be given within 2 hours prior to each nab-paclitaxel dose and 8-12 hours post each gemcitabine dose. ECGs should be collected pre-nab-paclitaxel and 1-4 hours after gemcitabine administration.

8.3.2. Nab-paclitaxel and Gemcitabine

8.3.2.1. Nab-paclitaxel Administration

NAB will be administered by IV infusion at a dose of 125 mg/m^2 over 30 minutes (study sites may follow standard of care dosing windows) once weekly for 3 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment.

The NAB dose will be individually calculated for all infusion visits according to the subject's screening BSA. In calculating the dose, there will be no downward adjustment to "ideal" body weight unless institution policy requires it. Doses should be re-adjusted if the subject's BSA changes by >10%. If the subject's BSA changes by ≤10%, no adjustment is necessary unless the site has a standard procedure to adjust doses based upon current BSA.

NAB will be administered after PEGPH20 (for PAG treatment group) and before GEM (both PAG and AG treatment groups).

For the PAG subjects, in Cycle 1 the first administration of NAB should occur 24 hours (±4 hours) after PEGPH20 administration and 2 to 4 hours after PEGPH20 administration on Days 8 and 15. In Cycle 2 onwards, NAB should be administered 2 to 4 hours after PEGPH20 administration on Days 1, 8, and 15.

If NAB is withheld, PEG and GEM may still be given if the subject meets all criteria for dosing.

8.3.2.2. Gemcitabine Administration

GEM should be administered after NAB by IV infusion at a dose of 1000 mg/m^2 over 30 minutes (study sites may follow standard of care dosing windows) once weekly for 3 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Note: Prolongation of the infusion time >60 minutes has been shown to increase toxicity.

The GEM dose will be individually calculated for all infusion visits according to the subject's screening BSA. In calculating the dose, there will be no downward adjustment to "ideal" body weight unless institution policy requires it. Doses should be re-adjusted if the subject's BSA changes by >10%. If the subject's BSA changes by ≤10%, no adjustment is necessary unless the site has a standard procedure to adjust doses based upon current BSA.

The administration of GEM should occur immediately after NAB (all subjects all visit where chemotherapy is administered). If NAB is held on Day 2 for PAG subjects, GEM should be administered 24 hours (±4 hours) after PEGPH20. If NAB is held on Day 1 of Cycles 2+ or Days 8 and 15 of any cycle, GEM should be administered 2 to 4 hours after PEGPH20 (PAG subjects).

If GEM is held, PEGPH20 and NAB may still be given if the subject meets all criteria for dosing.

8.3.2.3. Nab-paclitaxel and Gemcitabine Dose Adjustment and Toxicity Management

Subjects should be monitored using standard of care local laboratory results prior to each NAB and GEM dose. Subjects must not begin a new treatment cycle with NAB and GEM if any hepatic or hematologic parameter is outside of what is listed in Table 13 and Table 14 (Day 1 dose modification guidelines). Dose reductions are permitted as outlined in Table 12; however these may be superseded by updates in the GEM or NAB package inserts. Study treatment should be discontinued if a subject experiences toxicity that requires more than 2 dose reductions. Study treatment should be modified according to the dose modification guidelines outlined in Sections 8.3.2.3.1 and 8.3.2.3.2; however, the guidelines below may be superseded by updates in the GEM or NAB package inserts. For additional guidance, refer to the current NAB and GEM package inserts for current prescribing information and toxicity profiles.

Table 12: Nab-paclitaxel and Gemcitabine Dose Level Reductions

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Starting Dose	125	1000
Dose -1	100	800
Dose -2	75	600

8.3.2.3.1. Day 1 Dose Modification Guidelines for Nab-paclitaxel and Gemcitabine

Day 1 dose modifications are outlined in Table 13 for non-hematologic toxicity and in Table 14 for hematologic toxicity.

Table 13: Day 1 Dose Modification Guidelines for Non-Hematologic Toxicity

Non-Hematologic Toxicity	NAB and GEM Dose Modification
Grade ≤2	Same as Day 1 of previous cycle
Grade 3	Decrease NAB and/or GEM to next lower dose level depending on whether the toxicity is related to NAB or GEM
Grade 4	Discontinue all study treatment. Subjects may only continue treatment for transient Grade 4 toxicity after discussion with Sponsor.

Abbreviations: GEM = gemcitabine; NAB = nab-paclitaxel

Notes: Dose modifications apply to Day 1 of any treatment cycle. NAB and GEM should be immediately discontinued if interstitial pneumonitis (any grade) occurs.

Table 14: Day 1 Dose Modification Guidelines for Hematologic Toxicity

Hematologic Toxicity			NAB and GEM Dose Modification
ANC		**Platelets**	
≥1,500 cells/mm^3	and	≥100,000 plt/mm^3	Treat as scheduled
<1,500 cells/mm^3	and/or	<100,000 plt/mm^3	Delay 1 week until ANC ≥1,500 cells/mm^3 and platelets ≥100,000 plt/mm^3

Abbreviations: ANC = absolute neutrophil count; GEM = gemcitabine; NAB = nab-paclitaxel; plt = platelets.
Note: Dose modifications apply to Day 1 of any treatment cycle.

8.3.2.3.2. Day 8 and Day 15 Dose Modification Guidelines for Nab-paclitaxel and Gemcitabine

Day 8 and Day 15 dose modifications for non-hematologic toxicity are outlined in Table 15.

Day 8 and Day 15 dose modifications for hematologic toxicity are outlined in Table 16. Day 15 dose modifications are based on the hematology results of Day 8 of that cycle as well as the hematologic results of Day 15.

Table 15: Day 8 and Day 15 Dose Modification Guidelines for Non-Hematologic Toxicity

Non-Hematologic Toxicity	NAB and GEM Dose Modification
Grade ≤2	Treat as scheduled or at next lower dose level
Grade 3 peripheral neuropathy	Hold NAB dose until toxicity resolves to Grade ≤2, then resume treatment at same dose or next lower dose level, but GEM dosing may continue as scheduled
All other Grade 3 (except nausea or vomiting if not treated with maximum prophylaxis)	Hold both NAB and GEM dose until toxicity resolves to Grade ≤2, then resume treatment at next lower dose level
Grade 4	Discontinue all study treatment. Subjects may only continue treatment for transient Grade 4 toxicity after discussion with Sponsor.

Abbreviations: GEM = gemcitabine; NAB = nab-paclitaxel.
Notes: Dose modifications apply to Day 8 and Day 15 of any treatment cycle. NAB and GEM should be immediately discontinued if interstitial pneumonitis (any grade) occurs.

Table 16: Day 8 and Day 15 Dose Modification Guidelines for Hematologic Toxicity

Day 8		Day 15	
ANC and Platelet Counts	**NAB and GEM Dose Modification**	**ANC and Platelet Counts**	**NAB and GEM Dose Modification**
ANC ≥1,000 cells/mm^3 and Platelets ≥75,000 plt/mm^3	Treat as scheduled	ANC ≥1,000 cells/mm^3 and Platelets ≥75,000 plt/mm^3	Treat as scheduled
		ANC 500 - <1,000 cells/mm^3 or Platelets 50,000 - <75,000 plt/mm^3	Treat as scheduled plus treat with G-CSF
		ANC <500 cells/mm^3 or Platelets <50,000 plt/mm^3	Hold both drugs plus treat with G-CSF
ANC 500 – <1,000 cells/mm^3 or Platelets 50,000 – <75,000 plt/mm^3	Decrease by 1 dose level, treat on time with both drugs	ANC ≥1,000 cells/mm^3 and Platelets ≥75,000 plt/mm^3	Treat with same dose as Day 8, treat on time plus with G-CSF
		ANC 500 – <1,000 cells/mm^3 or Platelets 50,000 - <75,000 plt/mm^3	Treat with same dose as Day 8, treat on time plus with G-CSF
		ANC <500 cells/mm^3 or Platelets <50,000 plt/mm^3	Hold both drugs plus treat with G-CSF
ANC <500 cells/mm^3 or Platelets <50,000 plt/mm^3	Hold both drugs	ANC ≥1,000 cells/mm^3 and Platelets ≥75,000 plt/mm^3	Decrease planned Day 8 dose (not given) by 1 dose level plus treat with G-CSF
		ANC 500 – <1,000 cells/mm^3 or Platelets 50,000 – <75,000 plt/mm^3	Decrease planned Day 8 dose (not given) by 1 dose level plus treat with G-CSF
		ANC <500 cells/mm^3 or Platelets <50,000 plt/mm^3	Hold both drugs plus treat with G-CSF

Abbreviations: ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor; GEM = gemcitabine; NAB = nab-paclitaxel; plt = platelets.
Note: Dose modifications apply to any treatment cycle.

8.3.2.3.3. Toxicity Management Guidelines

- Prophylaxis against sepsis: At the occurrence of fever ≥38.5 C (regardless of neutrophil count) the subject should contact their physician and ciprofloxacin 500 mg orally twice per day or levofloxacin 500 mg orally once a day should be started. If the subject has a history of allergy to fluoroquinolone, then amoxicillin/clavulanate (AUGMENTIN®) 500 mg orally 2 to 3 times a day should be started. It is advised that all subjects should be given a prescription for either of the appropriate antibiotics so the subject can immediately begin either one with the first appearance of the fever.
- Colony stimulation factors: These should be given according to institutional guidelines and as outlined in Table 16.
- Interstitial pneumonitis: This can be seen with either NAB or GEM or the combination. Study drugs should be immediately discontinued. If an infection etiology is ruled out, corticosteroids should be initiated.

8.4. Excluded Concomitant Medications and Study Restrictions

Concurrent chronic use of IV heparin is prohibited; however, for acute thromboembolic events, IV heparin may be used. PEGPH20 administration must be permanently discontinued if a thrombosis or embolic event occurs. Use of megestrol acetate is prohibited.

Any other anti-cancer agents or investigational agents are prohibited while subject is on study. After treatment is discontinued, the subjects will not have any restrictions (i.e., when being followed on a monthly basis to collect survival/anti-cancer therapy data).

8.5. Treatment Compliance

Trained medical personnel are to administer the IV study treatments. Treatment compliance will be monitored by the review of drug accountability records and study treatment administration data will be recorded in the subject's medical record and eCRFs.

8.6. Randomization and Blinding

8.6.1. Run-in Phase Randomization

The run-in phases of this study is open-label. Subjects will be enrolled and randomized after all baseline assessments have been completed and the Investigator has verified that they are eligible per criteria in Sections 7.1 and 7.2. Subjects will be randomized in a 3:1 ratio to PAG or AG treatment. No stratification factors will be in place for the run-in period. Additional subjects may be enrolled to further assess the tolerability of PEGPH20 in order to establish the acceptable safety profile prior to the randomization of the Phase 2 study.

At randomization, the subject will be assigned a unique 6-digit subject identification number (the first segment of the number represents the study site and the second segment represents the subject at the study site). The subject's identification number will be used on all of that subject's eCRFs and SAE forms. **No subject may begin study treatment prior to registration and assignment of a unique subject identification number.** Any subject identification numbers that

are assigned will not be reused even if the subject does not receive treatment. Confirmation of subject enrollment and randomization status will be provided after registration.

8.6.2. Phase 2 Randomization

The Phase 2 portion of this study is open-label. Subjects will be enrolled and randomized after all screening assessments have been completed and the Investigator has verified that they are eligible per criteria in Sections 7.1 and 7.2. In stage 1, subjects will be randomized in a 1:1 ratio to PAG or AG treatment groups. In Stage 2 of the study subjects will be randomized in a 2:1 ratio to receive PAG or AG treatment. Subjects will be stratified based upon Screening Karnofsky Performance Status (70% to 80% and 90% to 100%).

Randomization will take place using a centralized Interactive Web Response System (IWRS). At registration, the IWRS will assign a unique 6-digit subject identification number (the first segment of the number represents the study site and the second segment represents the subject at the study site). The subject's identification number will be used on all of that subject's eCRFs and SAE forms. **No subject may begin study treatment prior to registration and assignment of a unique subject identification number.** Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Confirmation of subject enrollment and randomization status will be provided after registration.

9. STUDY DRUG AND MATERIALS

9.1. Study Drug Description

9.1.1. 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. rHuPH20 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 rHuPH20.

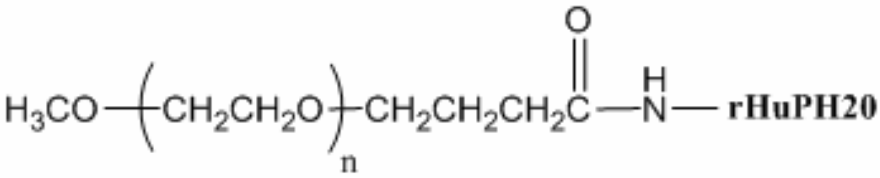
Chemical Name

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

Structural Formula

The structure of PEGPH20 is represented in Figure 7.

Figure 7: Structure of PEGPH20



PEGylated rHuPH20

The empirical formula for P is rHuPH20: $C_{2327}H_{3565}N_{589}O_{667}S_{20}$ (based on amino acid sequence) and PEG: $C_{1371}H_{2737}NO_{686}$ (based on PEG with n = 681). The average molecular weight of PEGPH20 is approximately 220,000 Da (range of approximately 90,000 to 320,000 Da).

9.1.2. Nab-paclitaxel

NAB is a microtubule inhibitor indicated for the treatment of metastatic breast cancer and locally advanced or metastatic non-small cell lung cancer. It is an albumin-bound form of paclitaxel.

Refer to the package insert for a thorough description and diagram of the structure of NAB.

9.1.3. Gemcitabine

GEM is a nucleoside analogue that exhibits anti-tumor activity. It is indicated as first-line treatment for subjects with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas.

Refer to the package insert for a thorough description and diagram of the structure of GEM.

9.2. Study Drug Packaging and Labeling

9.2.1. PEGPH20

PEGPH20 drug product (original formulation) is supplied as a frozen, sterile, single-use, injectable liquid. PEGPH20 drug product (clinical test article) is an aqueous solution containing 3.5 mg/mL PEGPH20 with 10 mM histidine and 130 mM NaCl at a pH of 6.5. Each vial contains 1.2 mL (4.2 mg) or 0.6 mL (2.1 mg) of PEGPH20 drug product. PEGPH20 drug product will be packaged in clear, Type I borosilicate 2 mL glass vials with a siliconized bromobutyl rubber stopper and aluminum 20 mm flip-off crimped cap. PEGPH20 drug product is provided as a frozen formulation. It should be stored at or below -20°C before use.

PEGPH20 drug product (new formulation) is supplied as a refrigerated, sterile, single-use, injectable liquid. This PEGPH20 drug product is also an aqueous solution containing 0.30 mg/mL PEGPH20 with 10 mM succinic acid, 130 mM NaCl, and 10 mM L-methionine at a pH of 6.2. Each vial contains 1.2 mL (0.36 mg, current investigational material) or 1.0 mL (0.30 mg, commercial-scale material) of PEGPH20 drug product. PEGPH20 drug product will be packaged in clear, Type 1 borosilicate glass vials with a 13 mm Flurotec® coated chlorobutyl rubber stopper and a 13 mm aluminum overseal with plastic flip off cap. This drug product is provided as a refrigerated formulation and should be stored at 2°C to 8°C before use.

PEGPH20 mixing instructions will be provided for both formulations.

9.2.2. Nab-paclitaxel

NAB is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP, prior to IV infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter of reconstituted suspension contains 5 mg paclitaxel and is free of solvents. The NDC number is 68817-134-50.

9.2.3. Gemcitabine

GEM is a white to off-white solid lyophilized powder. GEM is supplied in sterile single-use vials as follows:

- 200 mg white to off-white, lyophilized powder in 10-mL vials (No. 7501) NDC 0002-7501-01.
- 1 g white to off-white, lyophilized powder in 50-mL vials (No. 7502) NDC 0002-7502-01.

9.3. Study Drug Storage

9.3.1. PEGPH20

PEGPH20 drug product (original formulation), supplied at a concentration of 3.5 mg/mL, is a frozen formulation and should be stored at or below -20°C before use. This drug product may be thawed either at room temperature or at 2°C to 8°C and should be used within 24 hours after thawing. Stability testing of this PEGPH20 drug product was initiated following general International Conference on Harmonisation (ICH) guidelines at -20°C ± 5°C, and concurrent stability evaluation is ongoing. The Sponsor will monitor drug stability and provide updates on an ongoing basis.

PEGPH20 drug product (new formulation), supplied at a concentration of 0.30 mg/mL, is a liquid formulation and should be stored at 2°C to 8°C before use. Stability testing of this PEGPH20 drug product was initiated following general 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.

9.3.2. Nab-paclitaxel

The drug should be stored in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.

9.3.3. Gemcitabine

The drug should be stored at controlled room temperature from 20°C to 25°C (68°F to 77°F).

9.4. Study Drug Preparation

9.4.1. PEGPH20

PEGPH20 (original formulation), supplied at a concentration of 3.5 mg/mL, should be stored at or below -20°C prior to use. Each vial is intended for single use and should be thawed and used within 24 hours after thawing.

PEGPH20 (new formulation), supplied at a concentration of 0.30 mg/mL, should be stored at 2°C to 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 for both formulations can be found in the pharmacy manual.

9.4.2. Nab-paclitaxel

Refer to the NAB package insert for the most current drug preparation and handling guidelines.

9.4.3. Gemcitabine

Refer to the GEM package insert for the most current drug preparation and handling guidelines.

9.5. Study Drug Accountability

The Investigator, pharmacist or qualified designee is responsible for making an inventory of study drug(s) upon their receipt. All used and unused study drug supplies should be retained until final reconciliation or as indicated by Halozyme, or as per Institution policy. The study drug is to be administered/prescribed by the Principal Investigator or appropriately qualified site personnel named on the delegation of authority log. Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Although appropriate personnel may be designated to administer/dispense drug and maintain drug accountability records, the Principal Investigator is ultimately responsible for all drug accountability.

The Investigator or designee must maintain accurate records of the receipt and disposition of study drug supplies. Documentation of drug disposition should identify the subject receiving the drug, the amount and date of the dose, and any unused drug. This documentation is required in addition to drug accountability information recorded on eCRFs. A copy of the reconciled drug inventory record will be provided to Halozyme or its designee, and the study site will retain the original record.

After study drug is reconciled by the study monitor, drug may be destroyed as per Institutional Policy, or returned to the country specific drug depot as per country regulations. If used study medications cannot be stored until drug accountability has been performed as per clinic/institution policy, the Sponsor should be notified in advance, and reconciliation procedures will be agreed upon.

10. SAFETY ASSESSMENTS

Safety parameters monitored and recorded during this study include AEs; medical history; concomitant medications; immunogenicity, hematology, blood chemistry, coagulation, and urinalysis results; physical examination findings; vital signs; ECG results; pregnancy test results; and Karnofsky Performance Status.

10.1. Management of Thromboembolic Events

Thromboembolic disease is a common complication of pancreatic cancer and is associated with the generation of an intrinsic hypercoagulable state. The increase in incidence rate of clinical manifestations of thromboembolic disease in pancreatic cancer include deep venous thrombosis, pulmonary embolism, disseminated intravascular coagulation, portal vein thrombosis, and arterial thromboembolism has been well documented (Heit 2000, Epstein and O'Reilly 2012, Timp 2013). Subjects should be managed proactively to minimize the occurrence of thromboembolic events. With amendment 4.0, low-molecular-weight heparin (LMWH), specifically enoxaparin, at a dose of 1 mg/kg/day will be used in all subjects while receiving study treatment. If a subject is on a different LMWH prior to study entry, the subject should be switched over to enoxaparin. In the event the Investigator feels that an alternative anticoagulant is beneficial to the subject, the Investigator should obtain written pre-approval from the Sponsor or its designee. If pre-approval is granted, this will not be considered a deviation from the protocol.

Anti-Xa testing may be done at a local lab pre-and post-dose to verify the dose of enoxaparin is correct as per Investigator discretion under the institution guideline (Section 10.1.1).

Other tests may be done as per institutional policy if anti-Xa is not available locally. In addition, IV heparin may be used for acute management of thromboembolic events. PEGPH20 administration should be stopped during the IV heparin treatment period.

Any anti-coagulation therapy received by the subjects must be documented in the concomitant medication eCRF pages and any anti-Xa tests performed must be entered into the eCRFs as well.

10.1.1. Enoxaparin Management

All subjects should begin daily treatment with 1 mg/kg of enoxaparin. Dosage of enoxaparin should be based on the subject's screening weight and should be modified if the subject's weight changes by 10%, or per Insitution policy. Institution's rounding practices may be used when calculating the dose of enoxaparin. If pre-filled syringes of enoxaparin are used, rounding may be performed. Note that all efforts should be made to administer the dose as close to 1.0 mg/kg as possible.

Hematology and coagulation testing should be done on a weekly basis (Section 8.1). Enoxaparin should be held if the platelet count is <50,000 plt/mm^3; however, therapy should be resumed once the platelet count is above 50,000 plt/mm^3. Enoxaparin dose should be reduced to 0.5 mg/kg for Grade 2 thrombocytopenia (platelet count 50,000 – 75,000 plt/mm^3) until an increase in platelets > 75,000 plt/mm^3, at which time the dose should be increased to 1 mg/kg. Sponsor should be consulted if the Investigator does not feel the dose of enoxaparin should be re-started at a dose of 1.0 mg/kg.

Should a subject experience a thromboembolic event while on study, the dose of enoxaparin should be increased to a therapeutic dose based on standard clinical practice (i.e., standard of care/current NCCN guidelines). Administration of PEGPH20 will be stopped during the period when enoxaparin dose is held. Abraxane and gemcitabine therapy may continue according to the dose modification sections for the respective therapy. See Section 8.3.2.3. Subjects from either group who permanently discontinue LMWH therapy for any reason (refer to enoxaparin package insert) will be withdrawn from study treatment (See Section 7.3.1).

10.2. Adverse Event Definitions

An AE is any unfavorable or unintended sign, symptom, or disease temporally associated with the use of a pharmaceutical product (i.e., study drug), whether or not considered related to the pharmaceutical product.

The recording of AEs will begin at the start of the administration of the first dose of a study drug. AEs should record the development or increased severity of an undesirable medical condition or the worsening of a pre-existing medical condition during or following exposure to study drug, regardless of relationship to study drug. Additionally, changes in severity (increase or decrease) of a previously recorded AE will be recorded. See Section 10.5 for additional information.

A serious adverse event (SAE) is any AE that:

- Results in death.
- Is life-threatening.

  A life-threatening SAE is any AE that places the subject at immediate risk of death from the reaction as it occurred, as assessed by the Investigator. This definition does not include a reaction that might have caused death if it occurred in a more severe form.
- Requires inpatient hospitalization or prolongs existing hospitalization.
- For the purposes of this protocol, any hospital admission will be considered inpatient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will cases of elective hospitalization for administration of chemotherapy, hospitalization for social admissions, or hospitalization for a procedure scheduled before study enrollment. However, unexpected complications that occur during elective surgery should be recorded as AEs and assessed for seriousness.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly or birth defect.
- Is any other important medical event,

  Other medical events may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes in the SAE definition. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or

at home, blood dyscrasias or convulsions that do not result in hospitalization of the subject, or the development of drug dependency or drug abuse.

10.3. Reporting Serious Adverse Events

Report all SAEs to the designated safety contact **IMMEDIATELY AND NO LATER THAN 24 HOURS OF AWARENESS**, i.e., knowledge, discovery, or notification of the SAE. Complete the study-specific SAE Report Form and submit the completed form with any other available pertinent information (e.g., hospital records, laboratory results, etc.) to the designated safety contact (contact information is provided in the study reference binder).

If additional follow-up information is required or becomes available for a previously reported SAE, a follow-up SAE Report Form with the new information should be prepared and submitted **IMMEDIATELY AND NO LATER THAN 24 HOURS OF AWARENESS**. For hospitalizations, all attempts to obtain the hospital record should be documented in the study file.

10.4. Reporting Adverse Events of Special Interest

Thromboembolic events (TE events) are considered AEs of special interest in the current trial. All TE events, regardless of type of event, severity, or seriousness must be reported. Study sites will report any TE event to the Sponsor **IMMEDIATELY AND NO LATER THAN 24 HOURS OF AWARENESS**. Sites will complete the study-specific AE of Special Interest form (guidance regarding completion of this form will be provided to the sites) and send it to the designated safety contact (contact information is provided in the study reference binder).

10.4.1. Thromboembolic Event Grading

The current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) should be utilized when grading TE Events. Table 17 denotes the most commonly reported TE events and the associated grading scale per CTCAE Version 4.03 (14 June 2010). If the CTCAE is updated during the study, the current version of the CTCAE should be used.

Table 17: CTCAE Version 4.03 Grading for Thromboembolic Events

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death
Definition: A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction.					
Ischemia cerebrovascular	Asymptomatic; clinical or	Moderate symptoms	-	-	-

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
	diagnostic observations only; intervention not indicated				
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.					
Portal Vein Thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein.					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities.					
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.					
Vascular access complication	-	Device dislodgement, blockage, leak, or malposition; device	Deep vein or cardiac thrombosis; intervention indicated (e.g.,	Embolic event including pulmonary embolism or life	Death

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
		replacement indicated	anticoagulation, lysis, filter, invasive procedure)	threatening thrombus	
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Source: NCI CTCAE 4.03 June 14, 2010.

10.4.2. Disease-Related Events That Are Endpoints

For the purposes of this study in subjects with Stage IV pancreatic cancer, progression of the subject's underlying disease ("disease progression") is an efficacy assessment and should generally not be reported as an AE or SAE. However, if the Investigator determines that there is evidence suggesting a causal relationship between the event and the study medication, immediately report the event to the safety contact and record as an AE or SAE.

Death resulting from disease progression is a study endpoint, and generally should not be reported as a SAE. This event must be recorded in the eCRF and will be reviewed by the Sponsor and DMC periodically for increased frequency in the treatment group. However, if the Investigator determines that there is evidence suggesting a causal relationship between the event and the study medication, immediately report the event as an SAE.

10.5. Adverse Events

Events that occur before the first administration of study drug are not considered AEs, by definition (Section 10.2); record these events on the Medical History eCRF.

The Investigator or a qualified designee will question and examine subjects for evidence of AEs. Subjects should not be asked about specific AEs. Instead, they should be asked general questions (e.g., "How have you been feeling since your last visit?"). Record all AEs in the eCRF. Any changes of AEs in grade must also be recorded in the eCRF.

For an event to be recorded as an AE, the onset must occur during or after the subject's first exposure to study drug and no later than 30 days after the last study drug dose. However, there is no limit on reporting SAEs considered reasonably related to PEGPH20 (i.e., assessed as "Yes, Related," "Probably Related," or "Possibly Related," Section 10.5.2); these should be submitted as SAEs per Section 10.3, even if they are first identified during the long-term follow-up period. The Investigator should follow all AEs that are considered reasonably related to study drug until resolution or stabilization. All other AEs should be followed until resolution or stabilization or until the End of Treatment Visit, whichever occurs first.

Wherever possible, record syndromes rather than individual signs or symptoms to avoid duplication and to facilitate meaningful interpretation of data. For example, a subject presenting with rhinitis, fever, and headache should be reported as having "flu-like symptoms," without independently recording each accompanying sign. When no clearly recognizable clinical syndrome can be described, record individual clinical signs and symptoms.

All AEs that occur during the study should be treated appropriately to protect and ensure the subject's well-being. If such treatment constitutes a deviation from this protocol, Halozyme must be notified and the Investigator should comply with applicable IRB/EC reporting requirements.

The Investigator is responsible for determining whether or not an AE is severe enough to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment because of an AE. If either occurs, the subject must receive appropriate medical care, and the Investigator must strongly encourage the subject to return to the study site for the final protocol-specified visit and assessments, and to continue returning to the study site for follow-up evaluations until the AE resolves or stabilizes. All AEs, serious or not, that result in permanent withdrawal from study treatment should be immediately reported to Halozyme (Section 10.3).

Halozyme will conduct reviews of all available AEs at the end of the run-in phases and at a minimum of once every three months during Phase 2.

10.5.1. Classification of Adverse Events by Severity

The Investigator must categorize the severity of each AE using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.03 (CTCAE) or the current version.

It's important to distinguish between AE seriousness and severity; these terms are not interchangeable. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.2.

10.5.2. Classification of Adverse Events by Relationship to Study Drug

For each AE, the Investigator must document whether there is a reasonable possibility that the event was caused by administration of PEGPH20, NAB, and/or GEM. The Investigator should make this decision after careful consideration of the following questions:

- Does the AE follow a reasonable temporal sequence from administration of study drug?
- Can the AE be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy?
- Do the AE symptoms disappear or decrease on cessation of study drug or reduction in study drug dose? (There are exceptions when an AE does not disappear on discontinuation of the drug, yet drug relatedness clearly exists [e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.])
- Does the AE reappear or worsen when the study drug is re-administered?
- Does the AE follow an expected response pattern based on the established pharmacologic and toxicologic effects of the study drug?
- Does the AE follow an expected response pattern based on the known effects of other products in the same class?

For this assessment, the Investigator will classify each AE as one of the following:

- **Yes, Related:** The AE is definitely related to study drug administration.

- **Probably Related:** There is a high degree of certainty that the AE is related to study drug administration.
- **Possibly Related:** The AE could be related either to study drug administration or to concurrent disease/medication.
- **Unlikely Related:** There is a high degree of certainty that the AE is NOT related to study drug administration.
- **Not Related:** The AE is clearly due to other causes (e.g. concurrent medication, underlying disease, etc.).

For the purposes of expedited reporting to regulatory authorities, AEs assessed as "Yes, Related," "Probably Related," or "Possibly Related" will be considered suspected adverse reactions.

10.6. Abnormal Laboratory Results

Abnormal laboratory results may occur in the context of an AE that is a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of renal failure, or elevated AST/ALT in the setting of an AE of hepatitis). In these cases, do not record the abnormality itself as an AE.

However, in the absence of an AE that encompasses an observed abnormal laboratory result, report the abnormality as an AE if the Investigator judges it to be clinically significant for the subject.

10.7. Pregnancy

Pregnancy itself is not regarded as an AE unless there is suspicion that the study drug may have interfered with the effectiveness of the contraceptive medication. Pregnancy within 30 days of study drug discontinuation in a subject must be reported to the designated safety contact (contact information is provided in the study reference binder) **IMMEDIATELY AND NO LATER THAN 24 HOURS OF AWARENESS**. Complete the study-specific Pregnancy Report Form with all available information and submit the form with pregnancy test results and any other pertinent information. Also, within 24 hours, complete the eCRF with all available AE, demographic, medical history, concomitant medication, and study drug administration information available. As additional information on a previously reported pregnancy becomes available, a follow-up Pregnancy Report Form should be prepared with the new information and submitted to the safety contact.

Subjects who become pregnant during the study will not receive any additional study drug and will be withdrawn from the study. The Investigator must strongly encourage these subjects to return to the study site for the final protocol-specified visit and assessments. In addition, the Investigator will monitor the pregnancies of subjects exposed to study drug until final resolution (delivery, miscarriage, or early termination). Follow-up should occur monthly and should be documented in the study file. A follow-up Pregnancy Report Form must be completed following each follow-up contact with the subject and submitted to the Sponsor's designated safety contact. Report a spontaneous miscarriage, therapeutic abortion, stillbirth, or congenital anomaly as an SAE (Section 10.3).

10.8. Overdose

PEGPH20, NAB, and GEM will be administered by IV infusion at a qualified and experienced clinical study site. The potential for drug overdose is therefore minimal. However, should an overdose occur, the infusion should be stopped immediately. A blood PK plasma sample should be taken as soon as possible, with a notation of the time of sampling relative to the time of completion of the infusion. Investigator should also monitor the subject with appropriate blood counts and blood chemistry tests, and should also provide supportive therapy, as necessary. C**ontact the Halozyme Medical Monitor, or designee, WITHIN 24 HOURS.**

There are no data regarding PEGPH20 overdose in humans. However, the likelihood of significant MSEs (such as pain, spasms, and weakness) increases with increasing PEGPH20 dose. An overdose and AEs should be treated as per standard medical practice. There is no known antidote for PEGPH20.

Overdose of NAB or GEM should be managed per the relevant package insert.

Dosing details should be captured in the eCRF. If the subject receives a dose of a study drug that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as AEs in the eCRF and, if serious, submitted to the Sponsor's designated safety contact on an SAE Report Form. Do not record the overdose as an AE if the subject is not symptomatic.

10.9. Data Monitoring Committee

An independent DMC will be constituted and responsible for periodically reviewing safety and efficacy data of the Phase 2 study. Operational and logistical details will be provided in a separate DMC charter.

10.10. Unblinding

This study is not blinded; however, to avoid the introduction of operational bias into study conduct and to increase the interpretability and reliability of the data, a blinding plan was implemented. No interim analyses of efficacy were initially planned. However, for the purpose of tumor HA assay development, 2 interim analyses of Stage 1 efficacy data were performed to develop the HA algorithm and determine the cut-point to define HA-high subjects using a prototype HA assay and the VENTANA HA RxDx assay, respectively (additional details in Section 11.1.11). The blinding plan was updated accordingly to minimize the potential impact. For example, the Sponsor was blinded to the primary efficacy data and HA data of Stage 2, which is the validation set for HA algorithm and cut-point. A third comprehensive interim analysis of efficacy and safety data was performed to validate the VENTANA HA RxDx assay algorithm and cut-point of 50% and to enable a thorough benefit/risk assessment based on HA status. After the third interim analysis, the Sponsor became unblinded to all data.

Efficacy data (ORR) were also reviewed by the DMC during the clinical hold for a preliminary risk versus benefit assessment.

10.11. Reporting Safety Information to the Institutional Review Board

The Sponsor and/or a designated agent may provide written safety reports or other safety-related communications to the Investigator. The Investigator will ensure that these reports are reviewed and processed in accordance with regulatory and IRB/EC requirements and archived in the site's study file.

At the completion or early termination of the study, the Investigator will submit a final report to the IRB/EC within the applicable time frame.

10.12. Concomitant Medications

Any medication received during the study, other than a designated study drug (PEGPH20, NAB, or GEM), is regarded as concomitant medication. Record concomitant medications taken after the subject signs the ICF during the screening period (≤20 days prior to Study Day 1) through 30 days after the End of Treatment Visit on the Concomitant Medications eCRF.

Update information on concomitant medications, including medication used to treat an AE, at each visit according to the study schedule of events. At each visit, ask subjects if there have been any changes in their prescription or non-prescription medications since their last visit.

Subjects may receive medications during the study including, but not limited to, antibiotics, analgesics, antipyretics, etc., when clinically indicated. Prohibited medications are identified in Section 8.4.

Dexamethasone, nonsteroidal anti-inflammatory drugs, and/or cyclobenzaprine may be used for musculoskeletal symptoms and should be documented as a concomitant medication.

10.12.1. Dexamethasone

Refer to a current dexamethasone package insert for prescribing information and toxicity profile.

Dexamethasone may be used to attenuate musculoskeletal symptoms. For the PAG group, dexamethasone 8 mg should be administered within 2 hours prior to beginning each PEGPH20 infusion and 8 to 12 hours post the PEGPH20 infusion. For the AG group, dexamethasone 8 mg should be administered within 2 hours prior to the NAB infusion and 8 to 12 hours post each the GEM infusion. Additional doses of dexamethasone may be given 24 hours prior to PEGPH20 or NAB infusions or at any other time at the discretion of the Investigator based on the tolerability. Dexamethasone may be given PO, IM, or IV. 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 PEGPH20).

10.12.2. Enoxaparin

Refer to the current enoxaparin package insert for prescribing information and toxicity profile. Refer to Section 6.1.2.3 and Section 10.1.1 for additional details.

11. STATISTICS

11.1. Statistical Methods

In general, continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, maximum, quartiles). Categorical variables will be presented using frequencies and percentages. Results will be displayed for the two treatment groups as well as the two groups combined (total). All statistical analyses and data listings will be performed using SAS (Cary, NC). The SAS version will be noted in the Statistical Analysis Plan.

11.1.1. Randomization and Blinding

This is a multicenter, open-label, randomized study. To minimize bias to the PFS endpoint, disease progression is based on the assessment of the CIR. Determination of clinical progression by the Investigator without corresponding CIR confirmation must be documented with the relevant signs and symptoms.

11.1.2. Sample Size

Approximately 16 subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer will be randomized in 3:1 ratio to receive PAG and AG treatment in the run-in Phase.

Approximately 237 subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer will be randomized to either the PAG or AG treatment group in the Phase 2 portion of the study.

123 subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer were randomized in a 1:1 ratio to either the PAG or AG treatment group in the Phase 2 portion of the study in stage 1.

In Stage 2 of this study, 114 subjects were planned to be randomized in a 2:1 ratio to receive PAG or AG treatment: 76 subjects in the PAG arm and 38 subjects in the AG arm. To ensure adequate assessment of the primary safety endpoint of TE event incidence and a meaningful number of HA-high subjects in Stage 2, 133 subjects were actually randomized.

The primary safety endpoint is the proportion of subjects who have any thromboembolic event in the Safety Population of Stage 2 (P).

The hypothesis test will be conducted using the one-sided exact binomial test against the null hypothesis of $P \leq 12\%$.

Four safety analyses will be conducted using the stopping boundary of the one-sided p-value of 0.05 for the first two analyses and 0.035 for the remaining two analyses based on the Pocock method.

It is expected that 237 subjects in Phase 2 will be enrolled in approximately 20 months and these subjects will be followed up for additional 15 months. There will be approximately 200 subjects, including subjects from both run-in phase, in the Overall Efficacy Evaluable Population for the primary comparisons. It is estimated that the median PFS time is 5.5 months for AG treatment (Von Hoff 2013). A sample size of 100 evaluable subjects per treatment group with a total of 182 PFS events (disease progression or death) would provide 80% statistical power to detect a

45% treatment effect in median PFS (5.5 months for AG versus 8 months for PAG) based on the two-sided log-rank test at the significance level of 0.1. However, the interim data showed a low likelihood of achieving 182 PFS events from a total of 256 subjects actually randomized in Phase 2, and therefore the final analysis will be conducted when at least 95% of the enrolled subjects and 95% of HA-high subjects have discontinued study treatment.

In addition, a total of 200 subjects with 160 deaths will provide 80% statistical power to detect 40% benefit in median OS (8.5 months for AG versus 11.9 months for PAG) at one-sided alpha level of 0.1. Assuming 35% subjects with high HA, the study has 80% statistical power for the high HA subgroup to detect 90% benefit in median PFS (5.5 months for AG versus 10.5 months for PAG) at two-sided alpha level of 0.1 and 80% benefit in median OS (8.5 months for AG versus 15.3 months for PAG) at one-sided alpha level of 0.1. Statistical powers for different PAG treatment effects are presented in Table 18.

Table 18: Statistical Power Calculation Based on Log-rank Test

Assuming 35 months study duration with 20 months for enrollment, 5.5 months median PFS and 8.5 months median OS for AG Treatment

Statistical Power for All 200 Evaluable Subjects (10% dropout)					
Endpoint	**Alpha Level**	**PAG Treatment Effect in Median Duration**	**Median Duration for PAG Treatment**	**Statistical Power**	**No. of Events**
PFS	0.1 (two-sided)	40%	7.7 months	73%	183
		45%	8 months	80%	182
		50%	8.3 months	86%	181
OS	0.1 (two-sided)	40%	11.9 months	68%	160
		45%	12.3 months	76%	159
		50%	12.8 months	81%	158
OS	0.1 (one-sided)	40%	11.9 months	80%	160
		45%	12.3 months	85%	159
		50%	12.8 months	90%	158
Statistical Power for 70 Evaluable Subjects with High HA (35% HA high)					
Endpoint	**Alpha Level**	**PAG Treatment Effect in Median Duration**	**Median Duration for PAG Treatment**	**Statistical Power**	**No. of Events**
PFS	0.1 (two-sided)	80%	9.9 months	74%	61
		90%	10.5 months	80%	61
		100%	11 months	84%	60
OS	0.1 (two-sided)	80%	15.3 months	69%	53
		90%	16.2 months	75%	52
		100%	17 months	80%	52
OS	0.1 (one-sided)	80%	15.3 months	80%	53
		90%	16.2 months	85%	52
		100%	17 months	88%	52

Abbreviations: AG = nab-paclitaxel plus gemcitabine; PAG = PEGPH20 plus nab-paclitaxel and gemcitabine; PFS = progression-free survival; OS = overall survival; HA = hyaluronan.

11.1.3. Analysis Populations

This amendment is intended to decrease thromboembolic risk. Efficacy is not expected to change by enoxaparin treatment and exclusion of subjects with high risk of thromboembolic events. Thus, efficacy data are expected to be combinable for analyses.

11.1.3.1. Intent-to-Treat Population (ITT)

All subjects who are randomized, including the run-in phase, will be included in the ITT Population. Subjects will be grouped as randomized in the ITT population. The ITT Population will be used for subject disposition, demographic, and overall efficacy analyses.

11.1.3.2. Overall Evaluable Population

All randomized subjects, including the run-in phase, who have a post-baseline response assessment, or have clinical disease progression without a post-baseline CT scan, or have died on study, while they are on randomized treatment after randomization, will be included in the Overall Evaluable Population. The Overall Evaluable Population will be used as the primary analysis population for overall efficacy analyses.

11.1.3.3. Overall Safety Population

All subjects who received any part of a dose of study medication will be included in the Safety Population. Subjects in the Safety Population will be grouped according to the treatment they received. The Safety Population will be used for overall safety analyses.

11.1.3.4. Safety Population of Stage 2

Subjects in the Overall Safety Population at Stage 2 of the study. The Safety Population of Stage 2 will be used for analyses of safety data of Stage 2 of the study. This is the analysis population for the primary safety endpoint.

11.1.3.5. PK Analysis Population

All subjects who received any part of a dose of PEGPH20 and had measurable PEGPH20 concentrations in at least one sample collected for PK analysis will be included in the PK Analysis Population.

11.1.4. Efficacy Analyses

All efficacy analyses will be conducted based on tumor HA status (HA high and HA low). Tumor samples will be analyzed in a prospective-retrospective fashion using an affinity histochemistry diagnostic assay, the VENTANA HA RxDx assay (see Section 8.2.20 for additional details).

11.1.4.1. Analyses of the PFS Efficacy Endpoint

The primary efficacy endpoint is PFS. PFS is defined as the time from randomization until the first occurrence of disease progression, either by central radiologic determination or by clinical progression determined by the Investigator, or death from any cause. PFS data for surviving subjects without disease progression will be censored at the date of the last available

post-baseline tumor assessment. Surviving subjects without any post-baseline disease assessment will be censored on Day 1. Sensitivity analyses will be conducted to count for the impact of treatment switch.

In Stage 2 of the study, subjects in PAG arm who experience any thromboembolic event will be discontinued from PEGPH20 treatment. In order to minimize the potential bias due to PEGPH20 discontinuation, all subjects in PAG and AG arms who experience any thromboembolic event in Stage 2 will be censored at the start date of first thromboembolic event unless a PFS event occurs before first thromboembolic event. Other sensitivity analysis will be conducted to assess the impact of discontinuation due to thromboembolic event.

The presentation of results will include the Kaplan-Meier estimates of the medians (with 95% confidence intervals) and quartiles and the estimated proportion of subjects who are progression free at 1 year by treatment group (with 95% confidence intervals).

The primary PFS comparison of control (AG treatment group) with treatment (PAG treatment group) will be based on a stratified log-rank test at 2-sided $\alpha = 0.10$, where the stratum is the performance status. PFS will be summarized with Kaplan-Meier curves. The estimated hazard ratio (and 95% confidence interval) for the overall treatment effect will be prepared using a stratified Cox regression model with the same stratification.

The PFS between the two groups based on HA levels on tumor biopsy will be evaluated using a Cox regression model with HA level as a covariate.

11.1.5. Analysis of Other Efficacy Endpoints

ORR is defined as the proportion of responders, defined as subjects who achieve either a CR or PR response without confirmation. Subjects without an evaluable response are grouped as non-responders. A generalized Cochran-Mantel-Haenszel statistic with Karnofsky Performance Status as stratum (70% to 80% and 90% to 100%) will be used to test for difference between the two treatment groups. DCR will be analyzed using the same method as ORR.

OS is defined as the time from randomization until death from any cause. OS data from surviving subjects will be censored at time of the last contact. The OS data will be analyzed using the same methods as in the PFS analysis. DR will be estimated using the Kaplan-Meier method.

11.1.6. Analysis of Primary Safety Endpoint

The analysis of the primary safety endpoint will be conducted using the Safety Population of Stage 2.

The primary safety endpoint is the proportion of subjects in the PAG arm who experience any thromboembolic event in Stage 2 of the study (P). Subjects with multiple events will be counted only once for the primary safety analysis. The statistical test for the primary safety endpoint is as follows:

Null hypothesis: $P \leq 12\%$

Alternative hypothesis: $P > 12\%$

The hypothesis test will be conducted using the one-sided exact binomial test.

For 76 newly enrolled subjects in the PAG arm in Stage 2, four safety analyses, three interim and one final analyses, will be conducted when the last subject in each analysis has been treated for one PAG treatment cycle or has discontinued from PAG treatment during the first treatment cycle as follows:

- Interim #1: enoxaparin dose: 40 mg/day (12 PAG patients).
- Interim #2: enoxaparin dose: 1 mg/kg/day (12 PAG patients).
- Interim #3: enoxaparin dose: 1 mg/kg/day (29 PAG patients).
- Final analysis: enoxaparin dose: 1 mg/kg/day (58 PAG patients).

The DMC may recommend terminating the study when any of the four safety analyses cross the stopping boundaries as described in Table 19.

Table 19: Stopping Boundaries for Subjects in the PAG Arm of Study 202, Stage 2

Safety Analyses	1st Interim (IA#1)	Cumulative IA#1 Follow-up	2nd Interim (IA#2)	3rd Interim (IA#3)	Final
Prophylactic enoxaparin dose level	40 mg/day	40 mg/day OR 40 mg/day and 1 mg/kg/day	1 mg/kg/day	1 mg/kg/day	1 mg/kg/day
No. of Subjects in PAG Arm	12	18	12	29	58 (last subject)
Stopping boundary: TE** Rate	>25%	n/a	>25%	>24%	>22%
Stopping boundary: Subjects with TE**	>3	n/a	>3	>7	>12
Stopping boundary: p-value	<0.05*	n/a	<0.05*	<0.035	<0.035

The shaded columns indicate PAG patients who have received the 40 mg/day enoxaparin dose only (IA#1) or have received the 40 mg/day OR the 40 mg/day and the 1 mg/kg/day enoxaparin doses after IA#1.
* The p-value boundary for the 1st and 2nd safety analyses was increased to 0.05 from the Pocock boundary of 0.035 to increase the chance of early stop.
** Thromboembolic event

The same p-value boundaries will be used if timing of safety analyses is changed per DMC request.

For subjects in Stage 1 who are eligible to re-initiate PEGPH20 treatment, an interim analysis will be conducted after the last re-entry subject has had one cycle of PAG treatment or has discontinued from treatment during the first treatment cycle after re-entry. If the TE rate exceeds 25%, all re-entry subjects will be discontinued from PEGPH20 treatment.

11.1.7. Safety Analyses

Safety summaries will be analyzed using the overall safety population and the safety population of Stage 2. For the overall safety population analysis, sensitivity analyses will be conducted to assess the impact of potential bias of PEGPH20 treatment interruption and protocol amendment

limited to the PAG arm, such as PEGPH20 treatment re-initiation. For example, the following sensitivity analysis will be conducted to assess the impact of the criteria for re-initiating therapy applied to the PAG arm only. The four TE risk factors (Section 6.1.2.2) will be assessed for all subjects randomized to PAG or AG treatment. Subjects in the PAG arm who do not have any of the risk factors will be re-started with PEGPH20 treatment, other subjects will continue to receive AG treatment. Safety analysis will be conducted by excluding subjects in AG arm who have any of the risk factors in order to balance the Baseline risk level of subjects in PAG and AG arms.

All AEs will be presented in incidence tables coded by MedDRA preferred term and system organ class. Additionally, separate AE incidence tables, coded by MedDRA type, will be presented for each treatment group and overall by: 1) toxicity grade (severity) graded by CTCAE v4.03 or the current version; and 2) relationship to PEGPH20, NAB, and/or GEM as determined by the Investigator.

All AEs, SAEs, treatment discontinuations due to AEs, or deaths occurring during the course of the study will be summarized.

Laboratory toxicity will be summarized for all post-baseline data. Shift tables will be presented for selected laboratory parameters: liver function tests (ALT, AST, alkaline phosphatase, total bilirubin), WBC, ANC, hemoglobin, platelet count, PT, PTT, INR, and creatinine. Shift tables will use CTCAE grades, v4.03 or the current version. Selected laboratory parameters and vital signs (blood pressure, pulse, respiratory rate temperature) and the corresponding change from baseline over time will be summarized using descriptive statistics and data listings.

11.1.8. Pharmacokinetic Analysis

For PEGPH20, noncompartmental and population PK modeling will be performed. The AUC, C_{max}, and t_{max} will be summarized with descriptive statistics. Other PK/PD analyses will be performed, and estimation of PK parameters including half-life ($t_{1/2}$), volume of distribution, and clearance will be evaluated and reported if the data are sufficient.

11.1.9. Analysis of the Conduct of the Study

An accounting of all randomized subjects over the course of the study will be reported by treatment group. Analysis population, study treatment administration, reasons for premature discontinuation and time on study will be summarized.

11.1.10. Analysis of Treatment Group Comparability

The following demographic and baseline characteristics will be summarized by treatment group: age, race, ethnicity, country of residence, height, weight, BSA, Karnofsky Performance Status, site of primary tumor and other factors to be determined. Additional details for the analysis of the primary, secondary, and exploratory, and safety outcomes will be provided in the Statistical Analysis Plan.

11.1.11. Interim Analysis

No formal interim analyses of efficacy were initially planned for this study. However, 2 interim analyses of efficacy data from Stage 1 were performed to develop the tumor HA algorithm and

determine the cut-point to define HA-high subjects using a prototype HA assay and the investigational VENTANA HA RxDx assay, respectively. The 50% HA cut-point identified based on the Stage 1 data was defined based on the VENTANA HA RxDx assay prior to the analysis of Stage 2 data. Stage 2 data wer used to validate the tumor HA algorithm and 50% cut-point (additional details on the prototype HA assay and investigational VENTANA HA RxDx assay are given in the PEGPH20 Investigator's Brochure). A third, comprehensive interim analysis of efficacy and safety data was performed to validate the VENTANA HA RxDx assay algorithm and cut-point of 50% and to enable a thorough benefit/risk assessment based on HA status.

The participating Investigators, the Sponsor, and the independent safety physician will review the safety profile of all subjects in the first run-in phase and determine that the defined dose and regimen are acceptable for Phase 2. In addition, after the initiation of the Phase 2 portion, the DMC will review aggregated safety data collected to-date on a periodic basis. Safety data include AEs, laboratory data, and other safety clinical observations. Efficacy data will not be reviewed by the DMC unless there are safety concerns to warrant a risk versus benefit assessment. Details of the DMC (analysis, frequency, etc.) will be captured in a separate charter.

In addition, the PK and safety profiles of the new formulation of PEGPH20 will be assessed based on data from the second run-in phase. The Sponsor, the participating Investigators, and the independent safety physician will review available safety data from Cycle 1 from all subjects in the new formulation run-in phase. The PK profile will reviewed by the Sponsor. If the new formulation is deemed acceptable, it will be available to all subjects on the study. Subjects already on treatment will be switched to the new formulation.

In Stage 2 of this study, three interim safety analyses are planned to monitor thromboembolic risk. If any of the interim safety analyses crosses the stopping boundary, DMC may recommend terminating the study. The interim safety analyses are detailed in Section 11.1.6.

12. SPONSOR AND INVESTIGATOR RESPONSIBILITIES

12.1. Protocol Compliance

Except for a change intended to eliminate an apparent immediate hazard to a study subject, the study must be conducted as specified. Any such change must be reported immediately to Halozyme and to the IRB/EC according to the applicable IRB/EC policy.

12.1.1. Protocol Waivers

Halozyme, or its designee, will not prospectively authorize any protocol waivers to study inclusion/exclusion criteria.

12.1.2. Protocol Deviations

Written documentation of all major protocol deviations must be kept in the study site file and provided to Halozyme. Examples of possible major protocol deviations include, but are not limited to:

- Failure to obtain/maintain IRB/EC approval for the study.
- Failure to obtain subject's informed consent.
- Failure to collect, submit or file AE reports.
- Performance of an unapproved study procedure.
- Performance of the study at an unapproved location.
- Failure to adhere to the approved protocol.

The Investigator must notify the IRB/EC of all protocol deviations according to applicable IRB/EC policy. Halozyme will not authorize any protocol deviations.

12.2. Study Monitoring

Site visits will be conducted by an authorized Halozyme representative, who will inspect study data, subject's medical records, and eCRFs according to Good Clinical Practice (GCP) and FDA and ICH guidelines.

In addition to monitoring by Halozyme or its designees, the study may be audited by representatives of the FDA, who will also be allowed access to study documents. The Investigator should immediately notify Halozyme's Department of Clinical Development and Medical Affairs of any proposed or scheduled audits by regulatory authorities.

The Investigator will permit authorized representatives of Halozyme and national or local health authorities to inspect facilities and records relevant to this study.

12.3. Data Collection and Case Report Forms

CRFs must be completed for each subject enrolled in the study according to GCP and FDA guidelines. Data collected for each study subject will be recorded on eCRFs provided or approved by Halozyme.

CRF completion is the Investigator's responsibility. CRF completion may be delegated to other study personnel and documented on the log for delegation of authority. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of all data reported on CRFs and all required reports for each study subject. The Investigator is also responsible for maintaining any source documentation related to the study (e.g., operative reports, laboratory results, radiographic films, tracings, and computer discs or files).

12.4. Financial Disclosure

The Investigator is required to provide a financial disclosure statement or certification to Halozyme before study initiation. In accordance with 21 Code of Federal Regulations (CFR) 54, Investigators and all sub-Investigators are required to disclose all financial interests to the study Sponsor (Halozyme), to permit complete and accurate certification statements in an application for marketing authorization. This disclosure includes compensation affected by the outcome of a clinical study, significant equity interest in Halozyme's parent entity, Halozyme Therapeutics, Inc., and proprietary interest in the tested product. Investigators must promptly update this information if any relevant changes occur during the study and for one year following/ study completion (21 CFR 312.64(d)).

12.5. Investigator's Final Report

After completion of the Investigator's participation in the study, the Investigator will submit a written report to Halozyme. This report may be a copy of the Investigator's end-of-study report to the IRB/EC. The report to the IRB/EC will be consistent with applicable IRB/EC regulations and time frames.

12.6. Data Disclosure and Publication

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of Halozyme; it shall not be disclosed to others without written consent of Halozyme; and shall not be used except in the performance of this study.

The information compiled during the conduct of this study is also considered confidential and may be disclosed and/or used only by Halozyme as it deems necessary. To allow the use of the information derived from this study and to ensure compliance to current federal regulations, the Investigator is obliged to furnish Halozyme with the complete test results and all data compiled in this study.

This section of the protocol is intended to be a brief, high-level summary of the requirements for data disclosure and publication. The Clinical Study Agreement between Halozyme and the Investigator/Institution details the specific disclosure and publication requirements.

13. QUALITY CONTROL AND QUALITY ASSURANCE

In addition to routine monitoring procedures, audits of clinical research activities may be performed to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection during the study or after its completion. If an audit of this or any other study is requested by any regulatory authority, the Investigator must inform Halozyme immediately of the request (Section 12.2). The study site will permit access to all necessary records.

The study protocol, each step of the data recording process, and data handling, as well as any study report or publication, will be subject to independent review by Halozyme or its representatives.

14. ETHICS

This study will be conducted under a U.S. Investigational New Drug (IND) Application according to the provisions of the US CFR, the FDA regulations and guidelines, the Guidelines for GCP, and the Declaration of Helsinki, revised version of Seoul, October, 2008. All applicable U.S. regulations governing human subject protection must be followed. All ethical and regulatory requirements are necessary to comply with the principles of GCP. This includes inspection by the Sponsor, its representatives, health authority, or IRB/EC representatives at any time. The Investigator must agree to the inspection of study-related records by the health authority, the Sponsor, and/or the Sponsor's representatives.

To ensure ethical conduct of this study, the Investigator will be expected to adhere to basic principles provided by generally recognized guidelines such as the Belmont Report and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

14.1. Institutional Review Board and Approval

In accordance with 21 CFR Parts 50 and 56, the Investigator agrees to obtain IRB/EC approval of all appropriate material, including a copy of the protocol, ICF, Investigator's Brochure, and any proposed advertisement/study material prior to the start of the study and/or prior to its use on the study.

Halozyme must also agree to the proposed ICF and any proposed study advertisements. A copy of the IRB/EC approval letter(s) for the protocol and ICF must be supplied to Halozyme before subjects are screened.

The Investigator will supply Halozyme with the names, professions, and affiliations of IRB/EC member, to demonstrate compliance with membership requirements. If the Investigator or a sub-Investigator is a routine voting member of the IRB/EC, Halozyme will be provided with a statement from the IRB/EC that the Investigator/sub-Investigator did not vote on this study.

During the study, the Investigator is responsible for satisfying all IRB/EC regulations for reporting study progress. Copies of all reports to and correspondence with the IRB/EC must be provided to Halozyme. Furthermore, at the completion or early termination of the study, the Investigator should make a final report to the IRB/EC. A copy of this report should be provided to Halozyme (Section 12.5).

The Investigator must maintain an IRB/EC correspondence file and make this file available for review by Halozyme or its designated representatives as part of the study monitoring process.

14.2. Written Informed Consent

A copy of the proposed ICF must be submitted to Halozyme for review and comment before submission to the IRB/EC. The ICF must be approved by the IRB/EC and contain all elements required by all applicable federal, state, local, and institutional regulations or policies including subject compensation information (if applicable), before it is used to obtain a subject's informed consent. Authorization to use or disclose personal health information in accordance with requirements of the Health Insurance Portability and Accountability Act of 1996 should be provided in the ICF, or in a separate document to be signed by the subject.

Each subject (and/or legally authorized representative if the subject is a minor, mentally incompetent, or physically incapacitated, if applicable) found eligible for the study must have voluntarily provided written informed consent, using the IRB/EC-approved ICF, before study Screening (i.e., before any protocol-specified procedures that are not part of normal subject care).

15. DATA HANDLING AND RECORD KEEPING

15.1. Record Inspection

An audit may be performed at any time after completion of the study by Halozyme personnel or their designees, FDA, or other regulatory agencies. All study-related documentation must be made available to the designated auditors.

15.2. Study Documentation and Record Retention

The Investigator must retain all records of this study, including but not limited to, the following.

- Protocol and all protocol amendments.
- All signed versions of the Statement of Investigator, Form FDA 1572.
- All drug accountability records.
- All IRB/EC approvals, correspondence and reports.
- Signed and dated ICFs for each subject.
- Completed eCRFs for each subject.
- Copies of any other material distributed to subjects.
- Any advertisements for this study.
- The Investigator's final report to the IRB/EC.
- Source documents pertaining to the study, including but not limited to, any operative reports, laboratory results, radiographic films, tracings, and computer discs or files.

The period for which these documents must be retained is governed by U.S. law and, when applicable, non-U.S. regulations. The Investigator must retain all records for at least two years after the FDA has approved the new drug application, or until two years after all studies of the drug and indication have been discontinued. However, because of international regulatory requirements, Halozyme may request retention for a longer period. Halozyme or its designee will inform the Investigator when these documents may be destroyed. Halozyme or its designee must be notified in writing at least 30 days before the intended date of disposal of study records. The Investigator must obtain written approval from Halozyme before destruction of records.

The Investigator must advise Halozyme in writing if records are to be moved to a location other than the study site's archives. If the Investigator leaves the study site, the records will be transferred to an appropriate designee at the site, who will assume responsibility for record retention. Notice of this transfer will be documented in writing and provided to Halozyme.

If any study records are accidentally lost or destroyed, the Investigator will immediately notify Halozyme in writing.

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17. APPENDICES

APPENDIX A. ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation	Term
AE	Adverse event
AG	Nab-paclitaxel plus gemcitabine
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area-under-the-concentration time curve
AUC_{0-72}	Area-under-the-concentration time curve estimates for 0 to 72 hours
bid	Twice a day
BSA	Body surface area
BUN	Blood urea nitrogen
C	Celsius
CFR	Code of Federal Regulations
CIR	Central Imaging Reader
Cl	Clearance
C_{max}	Maximum-observed concentration
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident or
DCR	Disease control rate
dL	Deciliter
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DR	Duration of response
DVT	Deep vein thrombosis

Abbreviation	Term
EC	Ethics Committee
ECG	Electrocardiogram
ECM	Extracellular matrix
eCRF	Electronic case report form
5-FU	Fluorouracil
F	Fahrenheit
FDA	Food and Drug Administration
FNA	Fine needle aspirates
g	Gram
GCP	Good Clinical Practice
GEM	Gemcitabine
hr	Hour
HA	Hyaluronan
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
kg	Kilogram
LMWH	Low-molecular-weight heparin
m^2	Square meter
µg	Microgram
MedDRA	Medical Dictionary of Regulatory Activities
mg	Milligram
min	Minutes
mL	Milliliter
mm	Millimeter
MRI	Magnetic resonance imaging

Abbreviation	Term
MSE	Musculoskeletal event
MTD	Maximum-tolerated dose
NAB	Nab-paclitaxel
NaCl	Sodium chloride
NCI	National Cancer Institute
ng	Nanogram
ORR	Objective response rate
OS	Overall survival
PAG	PEGPH20 in combination with nab-paclitaxel plus gemcitabine
PD	Pharmacodynamics
PDA	Pancreatic ductal adenocarcinoma
PE	Pulmonary embolism
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PSA	Prostate specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	Recombinant human hyaluronidase PH20
SAE	Serious adverse event
SC	Subcutaneously
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvate transaminase
SUV	Standardized uptake volume
$t_{1/2}$	Terminal half-life
TGI	Tumor growth inhibition
TE	Thromboembolic event
TIA	Transient ischemic attack

Abbreviation	Term
t_{max}	Time-to-maximum concentration
U	Unit
ULN	Upper limit of normal
US	United States
VMSI	Ventana Medical Systems, Inc.
VTE	Venous thromboembolic event

APPENDIX B. KARNOFSKY/ECOG PERFORMANCE STATUS

ECOG[a]	Karnofsky	Definitions
0	100%[b]	Normal; no complaints; no signs or symptoms of disease.
1	90%[b]	Able to carry on normal activity; minor signs or symptoms of disease.
	80%[b]	Normal activity with effort; some signs or symptoms of disease.
2	70%[b]	Cares for self; unable to carry on normal activity or to do active work.
	60%	Requires occasional assistance, but is able to care for most of his or her needs.
3	50%	Requires considerable assistance and frequent medical care.
	40%	Disabled; requires special care and assistance.
4	30%	Severely disabled; hospitalization is indicated although death is not imminent.
	20%	Very sick; hospitalization necessary; active supportive treatment necessary.
	10%	Moribund; fatal processes progressing rapidly.
	0%	Dead.

[a] Eastern Cooperative Oncology Group.

[b] Acceptable status for enrollment in this study.

APPENDIX C. NEW YORK HEART ASSOCIATION CLASSIFICATIONS

1994 Revisions to Classification of Functional Capacity and Objective Assessment of Patients with Diseases of the Heart

Functional Capacity	**Objective Assessment**
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease.