CLINICAL STUDY PROTOCOL HALO-109-301

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination with nab-Paclitaxel Plus Gemcitabine Compared with Placebo Plus nab-Paclitaxel and Gemcitabine in Subjects with Hyaluronan-High Stage IV Previously Untreated Pancreatic Ductal Adenocarcinoma

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Sponsor: **Halozyme, Inc.**
11388 Sorrento Valley Road
San Diego, CA 92121, USA
Telephone: [redacted]

[Approval Signature Page to be Inserted here]

1. SYNOPSIS

Sponsor/Company
Halozyme, Inc.

Protocol Number
HALO-109-301

Study Title
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination With nab-Paclitaxel Plus Gemcitabine Compared With Placebo Plus nab-Paclitaxel and Gemcitabine in Subjects With Hyaluronan-High Stage IV Previously Untreated Pancreatic Ductal Adenocarcinoma

Study Objectives

Primary:

- To determine the overall survival (OS) benefit of PEGPH20 combined with nab-paclitaxel (NAB) plus gemcitabine (GEM) (PAG treatment), compared with placebo plus NAB/GEM (AG treatment), in subjects with hyaluronan (HA)-high Stage IV previously untreated pancreatic ductal adenocarcinoma (PDA)

Secondary:

- To determine the progression-free survival (PFS) benefit of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA
- To determine the objective response rate (ORR) and duration of response (DOR) of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA
- To assess the safety and tolerability of PAG treatment in subjects with HA-high Stage IV previously untreated PDA

Exploratory:

- To assess the treatment effect of PAG on serum levels of cancer antigen 19-9 (CA19-9)
- To assess the treatment effect of PAG on HA levels and other potential biomarkers in plasma and tumor biopsies (when available)
- To assess the pharmacokinetics (PK) of PEGPH20 in combination with NAB plus GEM
- To assess the potential effect of PEGPH20 on the PK of NAB and GEM
- To assess the impact of PAG treatment on patient-reported outcomes (PROs) including health-related quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30); other health outcomes using the European Quality of Life-5 Dimensions Scale (EQ-5D); and symptoms related to pancreatic cancer and to treatment-associated toxicities using a Numerical Rating Scale (NRS)

Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to compare the efficacy and safety of PAG versus AG treatment in subjects with Stage IV previously untreated PDA whose tumors are HA-high. For the purposes of this study, randomized study medication is defined as PEGPH20 or placebo and study medication is defined as PEGPH20, placebo, NAB, and GEM.

The study will involve a Screening Period. Eligible subjects will be randomized in a double-blind fashion to 1 of 2 treatment groups in a 2:1 ratio as follows:

1. PAG group: PEGPH20 (3.0 µg/kg) + NAB (125 mg/m^2) + GEM (1000 mg/m^2)
2. AG group: Placebo + NAB (125 mg/m^2) + GEM (1000 mg/m^2)

Randomization will be stratified by geographic region (North America, Europe, and Others).

The Treatment Period will consist of 4-week treatment cycles (28 days); Week 4 of every cycle will be a rest week (i.e., no treatment will be given). Randomized study medication will be administered as an intravenous (IV) infusion twice weekly for Weeks 1 to 3 of Cycle 1, then once weekly for Weeks 1 to 3 of Cycle 2 and beyond; NAB and GEM will be administered as IV infusions once weekly for Weeks 1 to 3 of all treatment cycles. (Table S-1). Treatment will continue until disease progression, unacceptable toxicity, death, or withdrawal of consent.

Table S-1: Study Medication Dosing and Treatment Schedule - PAG and AG Groups (HALO-109-301)

Time Point	Treatment
Cycle 1	
Week 1	
Day 1	Randomized study medication (PEGPH20 or placebo)
Day 2	NAB and GEM (24 ± 4 hours after Day 1 dose of randomized study medication)
Day 4	Randomized study medication
Week 2	
Day 8	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Day 11	Randomized study medication
Week 3	
Day 15	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Day 18	Randomized study medication
Week 4	
Day 22 -28	No treatment (rest week)

Table S-1: Study Medication Dosing and Treatment Schedule - PAG and AG Groups (HALO-109-301) (Continued)

Cycle 2 and Beyond	
Weeks 1 - 3	
Day 1	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Day 8	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Day 15	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Week 4	
Day 22 -28	No treatment (rest week)

Abbreviations: AG = placebo for PEGPH20 plus NAB and GEM; GEM = gemcitabine; NAB = nab-paclitaxel; PAG = PEGPH20 plus NAB and GEM.
Notes: Randomized study medication is defined as PEGPH20 or placebo. Subjects randomized to the PAG treatment group will receive PEGPH20, and subjects randomized to the AG treatment group will receive placebo.
Each treatment cycle is 28 days. Dose interruption and modifications are permitted; refer to Section 8.3 for further guidance.
The dose and schedule for NAB and GEM are per respective Prescribing Information with the exception that first doses of NAB and GEM will be given on Day 2 vs. Day 1, based on preclinical data indicating that maximum depletion of tumor levels of HA occurs by 24 hours after the first dose of PEGPH20, potentially making tumors more responsive to the cytotoxic effects of chemotherapy. Starting from Week 2, NAB and GEM will be given 2-4 hours after completion of the randomized study medication infusion to allow time for PEGPH20 to act on HA in the tumor microenvironment.
Dosing window is ± 2 days of the specified dates, relative to Day 1 of Cycle 1, as long as doses are separated by the appropriate amount of time (e.g., a minimum of 2 days when visits are twice a week).

In addition to study medication, all subjects will be administered dexamethasone to reduce potential musculoskeletal symptoms, which have been reported to be associated with PEGPH20. Dexamethasone 8 mg will be administered, preferably orally (PO), within 2 hours prior to the beginning of each PEGPH20/placebo infusion and 8 to 12 hours after completion of the randomized study medication infusion (total dose 16 mg on dosing days). Parenteral administration is allowed if the subject cannot tolerate oral dexamethasone. Additional doses of dexamethasone may be given 24 hours prior to infusions of randomized study medication or at any other time at the discretion of the Investigator based on tolerability. The Investigator may adjust (increase or decrease) the dose and/or frequency of dexamethasone based on the clinical need (e.g., tapering off if subject is tolerating study medication).

Enoxaparin will be administered to all subjects to minimize the risk of thromboembolic (TE) events, which is a common complication of pancreatic cancer and is reported to occur with PEGPH20 administration. Enoxaparin will be administered subcutaneously (SC) at a dose of 1 mg/kg/day. Rounding of the dose may be done per Institution policy and when using prefilled syringes. All efforts should be made to administer the calculated 1 mg/kg dose (± 10%); however, if prefilled syringes are used, the treating physician may use medical judgment regarding the

appropriate pre-filled syringe. If the rounded dose is less or greater than 20% of the expected dose based on weight, the Sponsor should be consulted. Refer to Table S-2 for examples of rounding based on the expected enoxaparin dose.

Table S-2 Enoxaparin Dosing (HALO-109-301)

Expected Enoxaparin Dose (mg)	Rounded Enoxaparin Dose (mg)	Syringes Dispensed
35-49	40	40 mg ×1
50-69	60	60 mg ×1
70-89	80	80 mg ×1
90-109	100	100 mg ×1
110-134	120	120 mg ×1
135-164	150	150 mg ×1

Provisions and Procedures Post-final Analysis:

If the final analysis supports a positive benefit-risk assessment for PEGPH20, the provisions and procedures described in this section will be implemented upon communication by the Sponsor. Until then, all procedures documented in this protocol, which reflect Protocol Amendment 5, will remain in effect.

- Subjects in the PAG arm post-final analysis will be offered the option to continue PAG treatment if the Investigator deems it in their best interest.
- Subjects in the AG arm post-final analysis will be offered the option to switch to and continue on PAG treatment.
- Subjects in the AG arm post-final analysis who choose not to switch to PAG treatment will be discontinued from the study. These subjects will be treated according to the Investigator's discretion and local standard-of-care.

All subjects continuing study treatment under Protocol Amendment 6 will receive PAG treatment (including PAG subjects continuing on PAG treatment and AG subjects switched to PAG treatment). Post-final analysis procedures for these subjects will be reduced in scope (vs. study procedures per Protocol Amendment 5) and will include the following (details in Table 5):

- Signing of revised Informed Consent Form (ICF) for all subjects receiving study treatment post-final analysis
- Administration of study medications (PEGPH20, NAB, and GEM) as detailed in Section 8.1.2 and Section 8.3 except that study medication will be administered in an open-label fashion (PEGPH20 vs. randomized study medication [Table 4]).
    - The dosing schedule for the Initial Cycle Post-final Analysis is only applicable to subjects who have chosen to switch from AG treatment to PAG treatment. Subjects continuing on PAG treatment post-final analysis will follow the dosing schedule for Subsequent Cycles Post-final Analysis.

- Subjects will continue to receive study medication until disease progression or other protocol-specified reasons for treatment discontinuation (see Section 7.3.1) or study discontinuation (see Section 7.3.2).
- Subjects who discontinue treatment will undergo an End of Treatment Visit as detailed in Section 8.1.2.3.

- Administration of enoxaparin and dexamethasone as detailed in Section 8.1.2 and Section 10.1.1, respectively
- Disease assessment performed locally (vs. by the Central Imaging Vendor (CIV) in Protocol Amendment 5) via computed tomography (CT)/magnetic resonance imaging (MRI) scan per standard-of-care and at the discretion of the Investigator
- Standard-of-care blood samples may be drawn at the Investigator's discretion and assessed by the local laboratory before NAB and GEM dosing
- Collection and recording of SAEs, TE events, and AEs leading to discontinuation of study treatment as follows:
  - Serious adverse events will be reported as described in Section 10.3 and Section 10.5.
  - TE events will be reported as described in Section 10.4.
  - Adverse events leading to discontinuation of any study medication (PEGPH20, NAB, or GEM) will be collected for 30 days after the last dose of study treatment as described for AEs in Section 10.5.

Post-final analysis long-term follow-up:

- Subjects continuing PAG treatment and subjects switched from AG to PAG treatment post-final analysis will enter long-term follow-up after treatment discontinuation as mandated in Protocol Amendment 5 (details in Section 8.1.3).
- All subjects who have discontinued either PAG or AG treatment and are in long-term follow-up will continue to be followed up per Protocol Amendment 5 (details in Section 8.1.3).

Study Population

All subjects with newly diagnosed, previously untreated Stage IV pancreatic cancer who meet the inclusion/exclusion criteria and whose tumors are determined to be HA-high will be enrolled in the study. See below for a list of all inclusion and exclusion criteria.

Inclusion Criteria

Subjects must satisfy all the following inclusion criteria to be enrolled in the study:

1. Signed, written Institutional Review Board/Ethics Committee-approved Informed Consent Form(s).
2. Stage IV pancreatic ductal adenocarcinoma (PDA) with histological or cytological confirmation of PDA.

3. Subjects must be determined to be HA-high based on archived or fresh tumor core biopsy or sample obtained after the subject has documented metastatic disease. Biopsies/samples must meet the following requirements:
   a. Pancreas tumor biopsies/samples obtained on or after the date that metastatic disease is documented or tumor biopsies/samples from a metastatic lesion are acceptable.
   b. Tumor biopsies or samples must meet the requirements provided in the Study Laboratory Manual with regard to tumor tissue architecture. Note: cytology samples from fine needle aspirates without maintained tissue architecture or brushing biopsies are not acceptable.
   c. Tumor tissue (formalin-fixed paraffin-embedded [FFPE] block preferred) must include enough tumor to make a minimum of 5-10 unstained, consecutive FFPE slides (10 slides are preferred) of 1 archival block that meet specific tissue sample requirements (see Study Laboratory Manual).
4. Radiographic confirmation of Stage IV PDA with at least 1 tumor metastasis measurable on CT scan or MRI per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, excluding the primary pancreatic lesion.
5. If a subject has had adjuvant/neoadjuvant therapy and/or therapy for locally advanced disease (chemotherapy for non-metastatic pancreatic cancer in combination with or without radiation therapy), tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of the aforementioned therapies, provided all toxicities have returned to baseline or ≤ Grade 1.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
7. Life expectancy ≥3 months.
8. Age ≥18 years.
9. A negative urine or serum pregnancy test within 7 days before Cycle 1, Day 1 (C1D1; first dose of study medication) if female subject is of childbearing potential.
10. Screening clinical laboratory values as follows (Section 8.2.7)
    a. Total bilirubin ≤1.5 times upper limit of normal (ULN) (subjects with Gilbert syndrome are eligible independent of bilirubin levels).
    b. 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).
    c. Serum creatinine ≤2.0 mg/dL or calculated creatinine clearance ≥40 mL/min.
    d. Serum albumin ≥2.5 g/dL.
    e. Prothrombin time or international normalized ratio (INR) within normal limits (±15%), unless subject takes warfarin, in which case prothrombin time or INR result must be within therapeutic range.
    f. Partial thromboplastin time (PTT) within normal limits (±15%).
    g. Hemoglobin ≥9 g/dL (transfusion and erythropoietic agents allowed).
    h. Absolute neutrophil count ≥1,500 cells/mm^3.
    i. Platelet count ≥100,000/mm^3.

11. For women of childbearing potential (WOCBP) and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 1 month (WOCBP) or 6 months (men) after administration of the last dose of any study medication. Highly effective contraceptive methods consist of prior sterilization, intra-uterine device (IUD), intrauterine hormone-releasing system (IUS), oral or injectable contraceptives, barrier methods, and/or true sexual abstinence (Section 8.2.9).

Exclusion Criteria

Subjects are ineligible for enrollment if they meet any of the following exclusion criteria:

1. Clinical evidence of deep vein thrombosis (DVT), pulmonary embolism (PE) or other known TE event present during the screening period (see Section 8.2.11.1 and Section 8.2.12).
    a. Subjects with superficial vein thrombosis are eligible.
    b. Subjects with visceral/splanchnic vein thrombosis are still eligible if, in the opinion of the Investigator, the visceral/splanchnic vein thrombosis is primarily associated with the anatomic location of the underlying disease of metastatic pancreatic cancer (i.e., there must be primary or metastatic disease in reasonable proximity to the thrombosis, and the Investigator determines that the thrombosis is due to a local tumor event and not a coagulation issue).
2. Previous radiotherapy, surgery, chemotherapy, or investigational therapy for the treatment of metastatic disease.
    a. Palliative radiotherapy for pain control of metastatic bone lesions is allowed.
3. Known central nervous system involvement or brain metastases.
4. New York Heart Association Class III or IV cardiac disease (Appendix C) or myocardial infarction within the past 12 months.
5. History of cerebrovascular accident or transient ischemic attack.
6. Clinically significant pre-existing carotid artery disease.
7. Known infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C within the past 12 months.
8. Known allergy to hyaluronidase.
9. Current use of megestrol acetate or megestrol acetate-containing drugs (use within 10 days of Day 1).
10. Contraindication to heparin as per institutional guidelines.
11. Women currently pregnant or breastfeeding.
12. Intolerance to dexamethasone.
13. 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.
14. Any other disease, active, uncontrolled bacterial, viral or fungal infection requiring systemic therapy, 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, or that may affect the interpretation of the results, or that may render the subject at high risk for treatment complications.
15. Immunization with a live vaccine up to 2 weeks prior to Day 1.

16. Hypersensitivity to the active substance or ingredients of PEGPH20, gemcitabine, and nab-paclitaxel.
17. Inability to comply with study and follow-up procedures as judged by the Investigator.

Planned Total Sample Size

This study will enroll approximately 500 HA-high subjects to be randomized in a 2:1 ratio to 1 of 2 treatment groups (PAG group [PEGPH20 + NAB + GEM] and AG group [placebo + NAB + GEM]).

Study Medications

All protocol-specified investigational (PEGPH20 and placebo) and non-investigational (NAB and GEM) products are considered study medications.

PEGPH20: PEGPH20 is a PEGylated, neutral-pH-active human hyaluronidase PH20 produced by recombinant DNA technology. PEGPH20 drug product 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 mL (0.3 mg, commercial-scale material) of PEGPH20 drug product.

PEGPH20 investigational drug product will be administered at a dose of 3.0 µg/kg as an IV infusion over 10 minutes (+ 2-minute window), approximately 1 mL/minute.

The current investigational PEGPH20 material will be administered initially in this study. When the commercial-scale material becomes available and after it has been deemed to have met all comparability criteria, it will be used in this study.

Placebo: Matching placebo for PEGPH20 is a normal saline solution and will be used to maintain the double blind. Placebo will be administered as an IV infusion over 10 minutes (+ 2-minute window), approximately 1 mL/minute.

Nab-paclitaxel: NAB, an albumin-bound form of paclitaxel, is an approved anticancer therapy. It will be given as an IV infusion at 125 mg/m^2 over 30 to 40 minutes.

Gemcitabine: GEM is an approved chemotherapy. It will be given as an IV infusion at 1000 mg/m^2 over 30 minutes immediately after completion of the NAB infusion.

Refer to the NAB and GEM current Prescribing Information for drug description and dosing administration directions.

Dose interruption/modifications of study medications are permitted (see Section 8.3.1.2 and Section 8.3.2.3 for additional details).

Study Duration

Subject may continue treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, or per Investigator discretion if determined to be in the best interest of the subject.

Subjects who discontinue treatment should remain in the study for long-term follow-up on survival and subsequent anticancer therapy until they withdraw consent, die, or become lost to follow up.

The end of the study is defined by the time of the last subject last visit (final data point collection).

Criteria for Evaluation

Primary Endpoints

- Overall survival

Secondary Endpoints

- Progression-free survival
- Objective response rate
- Duration of response
- Incidence of adverse events (AEs), changes in clinical safety laboratory values, and changes in cardiovascular parameters (ECG and vital signs)

Exploratory Endpoints

- Change in serum CA19-9 levels
- Change in plasma and tumor biopsy (when available) HA levels and other potential biomarkers
- Pharmacokinetics of PEGPH20 in combination with NAB plus GEM
- Pharmacokinetics of NAB and GEM in the PAG group versus the AG group
- Patient-reported outcome measures including the EORTC QLQ-C30, EQ-5D, and NRS

Efficacy Assessments (See STUDY SCHEDULES OF EVENTS for details)

Tumor response and progression will be assessed using RECIST version 1.1 criteria. Imaging protocols, including CT scans with contrast evaluations or MRI (must include venous phase chest, abdomen and pelvis contrast enhanced CT), will be provided by an independent CIV. In the event a subject is intolerant to the CT contrast agent, either a non-contrast chest CT or an iodinated contrast enhanced MRI of the abdomen and pelvis is acceptable.

The CT scans will be performed on a strict schedule regardless of treatment group to avoid ascertainment bias. All scans will be sent to a CIV for disease assessment. Submission of CT/MRI to the CIV is mandatory; however, local imaging results may be used to determine subject eligibility prior to randomization. During the study, CT scans will be performed at the end of Cycle 2 and at the end of every subsequent second treatment cycle after the last dose or the following week (i.e., Days 15 to 28 of Cycles 2, 4, 6, 8, and beyond), to allow time for reading of the scans by the CIV prior to the start of subsequent cycles. The results of the scans should be interpreted by the blinded CIV and sent to the site before dosing in the next cycle begins. If the results are not received by the site before the next cycle begins, dosing should proceed; however, if the results (when received) indicate radiologic disease progression, study medication treatment will be discontinued. At the End of Treatment visit, a CT scan must be obtained if radiologic disease progression was not documented in the previous CT scan, unless the latter was performed within the last 14 days.

After the End of Treatment visit, subjects will enter long-term follow-up during which information on the subject's survival and subsequent anticancer therapy will be obtained by the site monthly until the subject dies, is lost to follow-up, or withdraws consent.

Safety Assessments (see STUDY SCHEDULES OF EVENTS for details)

Safety will be assessed during the study by evaluation of AEs, clinical safety laboratory tests (hematology, blood chemistry (including C-reactive protein [CRP]), coagulation, urinalysis, and PEGPH20 immunogenicity), vital signs, 12-lead ECGs, and physical examinations.

The severity of AEs will be graded by Investigators using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (at time of study initiation).

Safety data will be periodically reviewed by an independent Data Monitoring Committee (DMC) to protect subject welfare and identify potential safety signals.

Exploratory Pharmacokinetic Assessments (see STUDY SCHEDULES OF EVENTS for details)

PEGPH20 PK: Plasma samples will be collected during the study to monitor the exposure-response relationship.

NAB and GEM PK: Plasma samples will be collected during the study to evaluate the potential effect of PEGPH20 on the PK of NAB and GEM.

Postdose PK time points should be relative to the stop time of the study medication infusion.

Other Exploratory Assessments (see STUDY SCHEDULES OF EVENTS for details)

CA19-9. Serum samples will be collected from all subjects to assess the effect of treatment on CA19-9 levels.

Hyaluronan. Plasma samples will be collected from all subjects to assess changes in plasma HA levels.

Biomarkers. Tumor, whole blood, and plasma samples will be collected for biomarker assessments including pharmacogenetic analysis. An optional tumor biopsy may be obtained upon determination of disease progression in subjects who consent to it. Samples may be analyzed for biomarkers relevant to PEGPH20 mechanism of action and/or dysregulation in tumor-relevant pathways as well as for exploratory studies to determine clinical response biomarkers.

All biomarker samples may be stored for up to 15 years after study completion to assist in any research related to PEGPH20 or cancer and for potential diagnostic development.

Patient-reported Outcome Measures. The EORTC QLQ-C30, EQ-5D, and NRS will be administered to assess the impact of treatment on quality of life; other health outcomes; and symptoms related to pancreatic cancer and to treatment-associated toxicities, respectively.

Statistical Methods:

Analysis Populations

Intent-to-Treat (ITT) Population: All randomized subjects will be included in the ITT Population. The ITT population will be analyzed by treatment randomized. This population will be used for all efficacy analyses as well as for analyses of subject disposition, protocol deviations, and demographic and baseline characteristics.

Safety Population: All subjects who receive any study medication will be included in the Safety Population. The Safety population will be analyzed by treatment received. This population will be used for all safety analyses as well as for demographic and baseline characteristics.

PK Analysis Population:

PEGPH20 PK: All subjects who receive any part of a dose of PEGPH20 and have at least 1 measurable PEGPH20 concentration will be included in the PK Analysis Population.

NAB and GEM PK: All subjects who receive any part of a dose of NAB and GEM in both treatment groups (PAG and AG) and have at least 1 measurable NAB and GEM concentration will be included in the PK Analysis Population for the PK analysis of NAB and GEM.

Samples for the above analyses deemed to be below the limit of quantitation (BLQ) will be included in the PK analysis and the BLQ value will be handled accordingly by the modeling software.

Statistical Analysis

Efficacy Analyses

The primary efficacy endpoint is OS, and the secondary efficacy endpoints are PFS, ORR, and DOR.

Type I Error Control:

The overall family-wise type I error for the superiority tests of OS, PFS, and ORR will be controlled at the 2-sided 0.05 alpha level using the following fixed-sequence method:

- The 2-sided alpha of 0.05 is assigned to OS.
- PFS will be tested at the 2-sided significance level of 0.05 only if OS is statistically significant.
- ORR will be tested at the 2-sided significance level of 0.05 only if both OS and PFS are statistically significant.

Analysis of the Primary and Secondary Efficacy Endpoints:

Overall survival is defined as the time from randomization until death at any time from any cause. Subjects will be censored for OS at the time of the last "known alive" contact.

Progression-free survival is defined as the time from randomization until the first occurrence of radiological disease progression, as determined by the blinded CIV based on RECIST version 1.1 criteria, or death from any cause during the treatment period. Because the dosing interval between treatment cycles is 14 days, the treatment period will include 14 days post-last dose of study treatment. Thus, subjects without radiological disease progression who die within 14 days of last dose of study treatment or randomization will be considered as having PFS events. Subjects with no PFS event will be censored for PFS on the date of the last post-baseline tumor assessment or on Day 1 if they have no post-baseline tumor assessments.

Median OS and PFS will be estimated using the Kaplan-Meier (KM) method. The median and its 95% confidence intervals (CIs), quartiles, and KM rates at Months 6, 9, 12, 18, and 24 will be presented by treatment group. The PFS and OS comparisons of the 2 treatment groups will be based on the stratified log-rank test stratified by the randomization stratification factor. The hazard ratio (HR) and its 95% CI for the treatment effect will be estimated using the stratified Cox proportional hazards regression model with Efron's method of handling ties, stratified by the randomization stratification factor.

Objective response rate is defined as the percentage of subjects with a complete response [CR] or partial response [PR] as determined by the blinded CIV based on RECIST version 1.1 criteria. Treatment group differences in ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization stratification factor.

Duration of response is defined as the time from the first objective response of CR/PR until disease progression or death within 14 days of last dose of study treatment or randomization. The DOR will be estimated using the KM method.

Safety Analyses

Safety data will be summarized by treatment group using descriptive statistics. Treatment-emergent AEs will be coded and tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Adverse events will also be analyzed by severity and relationship to study medication.

All AEs, serious adverse events (SAEs), treatment discontinuations due to AEs, and deaths occurring during the study will be summarized.

Clinical laboratory data will be summarized using descriptive statistics. Shift tables will be presented for selected laboratory parameters. All AEs and laboratory parameters that can be graded will be graded using the CTCAE Version 4.03 (at time of study initiation).

Selected laboratory parameters, vital signs, and ECG results and the corresponding change from baseline over time will be summarized using descriptive statistics.

Interim Analysis

No interim efficacy analysis will be conducted. Interim safety data will be analyzed and evaluated periodically by an independent DMC, as described in a separate DMC charter.

Sample Size Determination

This study is event driven. Approximately 500 eligible subjects will be randomized to receive PAG or AG in a 2:1 ratio. No interim efficacy analysis will be conducted. The study is powered for the final OS with 330 deaths. The statistical power and sample size calculation below are based on the comparison of treatment difference in OS between PAG and AG groups and obtained from East 6.3.1, Cytel Inc.

The median OS in the AG group is expected to be approximately 8.5 months. If PAG therapy improves median OS by 50% to 12.7 months with an HR of 0.67, the study will have 93% statistical power to show statistically significant improvement in OS at the significance level of 0.05 at the final OS analysis based on a 2-sided log-rank test after 330 deaths have been observed.

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3. STUDY SCHEDULES OF EVENTS

Table 1: Study Schedule of Events: Screening (HALO 109-301)

Tests and Assessments (All Within 28 Days Prior to Study Day 1 Unless Otherwise Indicated)	**Screening Visit**
Sign and Date Informed Consent Form(s):	
Main Study ICF — mandatory for all subjects prior to Screening procedures; Main Study ICF signature initiates 28-day Screening window	X
Prescreening ICF — if applicable; limited to tumor tissue HA testing only; may be signed in advance of Main Study ICF	X
HA Testing of Tumor Tissue [a]	X
Subject Registration into IWRS for Screening	X
Inclusion/Exclusion Criteria	X
Medical History	X
Prior Medication History	X
Physical Examination [b]	X
Vital Signs [b]	X
ECOG Performance Status	X
Height [b]	X
Weight/BSA [b]	X
Disease Assessment (CT Scans or MRI) [b, c, d]	X
Doppler Ultrasound of Lower Extremities	X
Local Laboratory Tests	
Urine/Serum Pregnancy Test [e] (WOCBP)	X
Central Laboratory Tests [f]	
Hematology [f]	X
Blood Chemistry (including CRP) [f]	X
Urinalysis [f]	X
Coagulation (PT, PTT, INR) [f, g]	X
Serum CA19-9	X
Plasma HA	X
Biomarker Plasma Sample	X
Subject Enrollment and Randomization [h]	X

(Table abbreviations and notes on next page)

Abbreviations: BSA = body surface area; CIV = Central Imaging Vendor; CRP = C-reactive protein; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin-embedded; HA = hyaluronan; ICF = Informed Consent Form; IWRS = Interactive Web Response System; INR = International normalized ratio; MRI = magnetic resonance imaging; PT = prothrombin time; PTT = partial thromboplastin time; WOCBP = women of childbearing potential.

Table 1 Notes:

- See Section 8.1 for procedures by visit and Section 8.2 for details on individual assessments.
- The screening window starts from the time of Main Study ICF signature (i.e., signature on the Prescreening ICF does not initiate the 28-day screening window [details in Section 8.2.1.1]).
- Starting from time of ICF signature (Main Study or Prescreening ICF, whichever is first), study procedure-associated AEs that meet the definition of serious will be reported as SAEs (details in Section 10.2).
- Screening procedures should be performed as rapidly as possible to facilitate subject entry requirements.
- If medically indicated, Screening tests and assessments may be retaken within 28 days prior to Cycle 1, Day 1 (C1D1) unless otherwise specified.
- If medically indicated, subjects are allowed to be re-screened for the study provided they were never randomized into the study. In such cases, the only tests and assessments that must be repeated are those which fall outside of the 28-day Screening window (i.e., more than 28 days prior to C1D1) unless otherwise specified. See Section 8.1.1.1 for instructions regarding tumor HA testing and other details for Re-screening.

[a] Archived or fresh tissue from the primary lesion or a metastatic lesion is required. Tumor tissue (FFPE block preferred) with enough tumor to make a minimum of 5-10 unstained, consecutive FFPE slides (10 slides are preferred) of 1 archival block are required to send to the central laboratory to assess HA status for subject eligibility into the study. With the subject's consent, 1 tumor tissue sample may be optionally obtained upon determination of disease progression.

[b] If these procedures were performed as part of standard-of-care prior to the subject signing the ICF, the results may be used for screening purposes providing they were performed within 28 days prior to C1D1, unless otherwise specified.

[c] If a subject is intolerant to the CT contrast agent, either a non-contrast chest CT or an iodinated contrast-enhanced MRI of the abdomen and pelvis is acceptable.

[d] In addition to being assessed by a blinded CIV, chest CT scans should be read locally to screen for the presence of pulmonary embolism (PE). These can be the same scans that are sent to the CIV. If a subject shows signs or symptoms of PE after the initial scan was completed, the chest scan should be repeated prior to randomization to assess for the presence of PE. If a PE is present, the subject will be considered a screening failure and will not be randomized.

[e] Pregnancy test to be performed for WOCBP within 7 days prior to C1D1.

[f] Central laboratory testing is mandatory and must be performed; however, if central laboratory results cannot be obtained prior to randomization, then local laboratory results may be used for eligibility purposes. In such cases, results and reference ranges of the local laboratory will take precedence over those of the central laboratory (Section 8.2.7).

[g] After the screening (baseline) assessment, coagulation tests (PT, PTT, INR) will be performed upon determination of disease progression.

[h] Within 4 days prior to C1D1.

Table 2: Study Schedule of Events: Treatment Period (HALO-109-301)

	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2 and Beyond (Repeats Every 4 Wks)				End of Treat. [a]	Long-Term Follow-up
	Wk 1			Wk 2		Wk 3		Wk 4	Wk 1, Wk 2, Wk 3			Wk 4		
Tests and Assessments	**D 1**	**D 2**	**D 4**	**D 8**	**D 11**	**D 15**	**D 18**	**D 22**	**D 1**	**D 8**	**D 15**	**D 22**		
Physical Examination [b]	X							NO VISIT / ASSESSMENTS	X				X	
Vital Signs [b]	X	X	X	X	X	X	X		X	X	X		X	
ECOG Performance Status [b]	X								X				X	
Weight/BSA [b]	X								X				X	
12-lead ECG [c]	X					X			X					
Disease Assessment (CT Scan)												X [d]	X [e]	
Pregnancy Test (local laboratory), before Dosing (WOCBP)									X					
Central Laboratory Tests														
Hematology [b]	X			X		X			X	X	X		X	
Blood Chemistry (including CRP) [b]	X			X		X			X	X	X		X	
Immunogenicity (PEGPH20 ADA, NAb) [b]	X								X				X	
CA19-9 Serum Samples									X				X	
PEGPH20 PK Plasma Samples	X [f]	X [g]	X [h]											
NAB & GEM PK Plasma Samples [i]		X							X					
HA Plasma Samples	X [j]	X [g]							X [k]					

(Table continued on next page)

Table 2: Study Schedule of Events: Treatment Period (HALO-109-301) (Continued)

Tests and Assessments	Treatment Cycle 1 (4 Weeks)								Treatment Cycles 2 and Beyond (Repeats every 4 wks)				End of Treat. [a]	Long-term Follow-up
	Wk 1			Wk 2		Wk 3		Wk 4	Wk 1, Wk 2, Wk 3			Wk 4		
	D 1	D 2	D 4	D 8	D 11	D 15	D 18	D 22	D 1	D 8	D 15	D 22		
Biomarker Plasma Samples [l]	X	X	X	X	X			NO VISIT / ASSESSMENTS	X	X			X	
Pharmacogenetic Whole Blood Sample	X													
Dexamethasone Admin. [m]	X		X	X	X	X	X		X	X	X			
Enoxaparin Admin. [n]	X													
Randomized Study Medication Admin. (PEGPH20/Placebo)	X		X	X	X	X	X	NO VISIT / ASSESSMENTS	X	X	X			
NAB Admin.		X [o]		X [p]		X [p]			X [p]	X [p]	X [p]			
GEM Admin.		X [o]		X [p]		X [p]			X [p]	X [p]	X [p]			
EORTC QLQ-C30, EQ-5D, and NRS [q]	X					X			X					
Concomitant Medication and Procedure Recording	X								X				X	
Adverse Event Recording [r]	X								X				X	
Long-term Follow-up [s]														X
SAE Recording [r]	X												X	X

Abbreviations: ADA = anti-drug antibody(ies); admin. = administration; BSA, body surface area; CIV = Central Imaging Vendor; CRP = C-reactive protein; CT, computed tomography; D = study day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D = European Quality of Life-5 Dimensions Scale; GEM = Gemcitabine; HA, hyaluronan; IM = intramuscular; IV = intravenous(ly); NAB = nab-Paclitaxel; NAb = neutralizing antibodies; NRS = Numerical Rating Scale; PD = progressive disease; PEGPH20 = pegylated recombinant human hyaluronidase; PK = pharmacokinetic(s); PRO = patient reported outcomes; SAE = serious adverse event; SC = subcutaneous(ly); treat = treatment; Wk = study week; WOCBP = women of childbearing potential.

(Table notes on next page)

Note: see Section 8.1 for procedures by visit and Section 8.2 for details on individual assessments.

[a] Subjects should return to the study site for an End of Treatment visit within approximately 7 days after treatment discontinuation of all study medications (PEGPH20/placebo, GEM, and NAB) and prior to initiation of subsequent anticancer therapy.

[b] On dosing days, assessments will be performed before the first dose of study medication. For Treatment Cycles 2 and Beyond, physical examination, vital signs, ECOG Performance Status, weight/BSA, and clinical laboratory tests (hematology, blood chemistry, and immunogenicity) may be performed up to 2 days before Days 1, 8, and/or 15.

[c] Twelve-lead ECGs will be obtained as follows: Cycle 1 Day 1 and Day 15, each done in triplicate within a 5-min period, before the start and between 1 and 4 h after completion of the infusion of randomized study medication but before the start of the NAB infusion; Cycles 2-6 Day 1, a single ECG prior to administration of randomized study medication.

[d] CT scans will be performed and sent to the blinded CIV at the end of Cycle 2 and at the end of every subsequent second treatment cycle after the last dose or the following week (i.e., Days 15 to 28 of Cycles 2, 4, 6, 8, and beyond), to allow time for reading of the scans by the CIV prior to the start of subsequent cycles. The results should be interpreted and sent to the site before dosing in the next cycle begins (additional details in Section 8.2.11).

[e] CT scans must be obtained if radiologic disease progression was not documented in the previous CT scan, unless the latter was performed within 14 days.

[f] Samples for PEGPH20 PK analysis on Day 1 will be collected any time before the start of randomized study medication infusion within 5 min after completion of randomized study medication infusion.

[g] Samples for PEGPH20 PK and HA analyses on Day 2 will be collected immediately prior to the start of NAB infusion.

[h] Samples for PEGPH20 PK analysis on Day 4 will be collected immediately prior to the start of randomized study medication infusion and will also be analyzed for plasma HA.

[i] Samples for PK analysis of NAB and GEM will be collected immediately after the end of the NAB and GEM infusions, respectively, in Cycle 1 through Cycle 3.

[j] Samples for HA analysis on Day 1 will be collected any time before the start of randomized study medication infusion.

[k] A sample for HA analysis will be collected either before the start of randomized study medication infusion or after completion of the GEM infusion.

[l] Plasma samples will be collected predose in Cycle 1 on Days 1, 2, 4, 8, and 11; and predose in Cycle 2 and every other cycle thereafter on Days 1 and 8; and at the End of Treatment visit.

[m] Dexamethasone 8 mg will be given preferably PO within 2 h prior to the start of and 8-12 h after completion of each infusion of randomized study medication (total dose of 16 mg on dosing days). Subjects will self-administer dexamethasone PO unless given by study site personnel. Parenteral administration is allowed if the subject cannot tolerate oral dexamethasone. Additional doses of dexamethasone (PO, IM, or IV) may be given 24 hours prior to infusions of randomized study medication or at any other time at the discretion of the Investigator based on tolerability.

[n] All subjects will self-administer enoxaparin 1 mg/kg SC once a day during the Treatment Period. On dosing days, enoxaparin will either be self-administered by subjects or administered by study site personnel prior to the infusion of randomized study medication (additional details in Section 10.1.1).

[o] NAB and GEM will be administered on Day 2, 24 h (± 4 h) after completion of the Day 1 randomized study medication infusion. NAB will be given first. Standard-of-care blood samples should be drawn and assessed at the central laboratory before NAB and GEM dosing to confirm the subject meets the required criteria for dosing (additional details in Section 8.2.7).

[p] NAB and GEM will be given 2 to 4 h after completion of the randomized study medication infusion. NAB will be given first. Standard-of-care blood samples should be drawn and assessed at the central laboratory before NAB and GEM dosing to confirm the subject meets the required criteria for dosing (additional details in Section 8.2.7).

[q] Subjects will complete PRO measures prior to the randomized study medication infusion.

[r] Details on AE/SAE recording are provided in Section 10.5.

[s] After the End of Treatment visit, subjects will enter long-term follow-up during which information on survival and subsequent anticancer therapy will be obtained by the site monthly until the subject dies, is lost to follow-up, or withdraws consent.

4. BACKGROUND AND RATIONALE

4.1. Background on Pancreatic Ductal Adenocarcinoma

Pancreatic cancer is a heterogeneous disease with malignancies developing from pancreatic ductal, acinar, and islet cells. The incidence of pancreatic cancer has continued to increase during the past several decades. Pancreatic cancer currently ranks as the seventh leading cause of cancer death globally (Cancer Worldwide 2014) and the fourth in the United States (US; American Cancer Society 2014). In Europe, pancreatic cancer is the seventh most frequent cancer and the fifth leading cause of cancer-related death and is predicted to take fourth place within the decade (Seufferlein 2012; Malvezzi 2013). Adenocarcinoma of pancreatic ductal (PDA) origin accounts for approximately 90% of all pancreatic cancers (Seufferlein 2012). Pancreatic cancer may be associated with certain environmental factors, genetic alterations, and hereditary disorders that increase the chance of developing the disease. Due to a lack of specific symptoms and limitations in diagnostic methods, more than 50% of patients with PDA are diagnosed at Stage IV, resulting in poor prognosis with limited options for surgical resection. For most PDA patients, a late stage diagnosis results in a median survival time of less than 1 year following diagnosis. Pancreatic cancer is most frequently diagnosed in adults 65-84 years of age, with approximately 46,400 new cases diagnosed in the US in 2014 and approximately 39,600 deaths (American Cancer Society 2014).

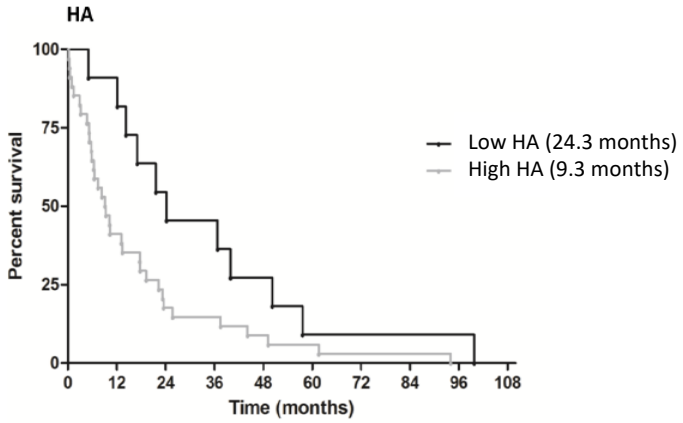
The past few decades have brought few treatment advances for patients with Stage IV PDA, and the number of treatment options approved by the Food and Drug Administration (FDA) or authorized/commonly used in the European Community (EU) remains limited, including gemcitabine (GEM) monotherapy, erlotinib (in combination with GEM), nab-paclitaxel (NAB) (in combination with GEM), and less effective mono- or combination therapies with other chemotherapeutics or palliatives such as fluorouracil (5-FU) or capecitabine.

4.2. Background on PEGPH20

Halozyme, Inc. (Halozyme) has developed an investigational new molecular entity, PEGylated recombinant human hyaluronidase (PEGPH20), which uses a novel mechanism of action to target tumors that accumulate the substrate for this enzyme, hyaluronan (HA). PEGPH20, a PEGylated version of the human recombinant PH20 hyaluronidase (rHuPH20), remodels the tumor microenvironment (TME) by degrading HA and decompressing the tumor vasculature. Administration of PEGPH20 results in increased delivery of anticancer agents to tumors in nonclinical models, which is thought to be mediated by this remodeling of the TME. In nonclinical 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). Enzymatic HA depletion from the TME by PEGPH20, either alone or in combination with chemotherapy, represents an innovative potential treatment that may provide improved therapeutic outcomes for a broad range of cancer patients (Sironen 2011, Jacobetz 2013). High levels of HA accumulation have been reported in a variety of solid malignancies, including PDA, breast cancer, and prostate cancer (Jacobetz 2013). Hyaluronan accumulation, and the subsequent increase in water molecules within a tumor, contributes to an elevated tumor interstitial pressure, resulting in tumor vascular collapse, hypoxia, and impedance

to chemotherapeutic agent perfusion (Thompson 2010). Elevated levels of HA frequently correlate with poor prognosis in tumors, such as pancreatic, breast, gastric, colorectal, ovarian, prostate, and lung carcinoma. Notably, a log-rank retrospective analysis of HA levels in baseline tumor tissue biopsies from surgically resected PDA patients revealed that the median survival rate was significantly lower among patients with high HA accumulation compared with subjects with low HA accumulation (9.3 vs. 24.3 months, respectively; $p<0.05$) These data suggest that HA levels in tumors of patients with PDA may be predictive of survival (Whatcott 2015; Figure 1).

Figure 1: Correlation of High Hyaluronan Levels in Pancreatic Ductal Adenocarcinoma Tumors and Survival



Note: Retrospective study utilizing a biotinylated HA-binding protein-based staining method in a tissue microarray constructed from 43 resected pancreatic ductal adenocarcinoma (PDA) samples from patients whose survival had been followed for >8 years. Staining was scored according to the percentage area of HA-positivity relative to the total tissue area (Whatcott 2015).

Nonclinical studies have attributed chemopotentiation by hyaluronidase to a reduction in tumor interstitial fluid pressure and an expansion of tumor vasculature, which is thought to induce a transcapillary pressure gradient that facilitates increased delivery of therapeutic anticancer agents to HA-accumulating tumors (Eikenes 2005, Thompson 2010, Provenzano 2012). Substantial human data exist for non-PEGylated, animal-derived hyaluronidase products for multiple therapeutic applications (Dunn 2010, Frost 2007). Intravenously (IV) 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).

Halozyme has developed PEGylated recombinant human hyaluronidase (PEGPH20), a multi-site PEGylated enzyme generated by conjugating N-hydroxysuccinimidyl ester of methoxypoly(ethylene glycol)-butanoic acid (MSBA30K/B or PEG) and recombinant human hyaluronidase (rHuPH20). PEGPH20 has a half-life of approximately 2 days, thereby enabling systemic activity and sustained duration of action to degrade HA. 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).

For additional details of HA in tumors and PEGPH20, refer to the PEGPH20 Investigator's Brochure.

4.3. Thromboembolic Events in Cancer

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 (TE) disease, including deep vein thrombosis (DVT), pulmonary embolism (PE), disseminated intravascular coagulation, portal vein thrombosis, and arterial thromboembolism, in pancreatic cancer is well documented (Heit 2000, Epstein 2012a, Timp 2013). Patients with cancer are at a higher risk for TE events, specifically of venous origin (venous thromboembolic events [VTE]), than the general population. The risk of VTE is increased by 4-fold (Odds Ratio [OR] of 4.05; 95% confidence interval [CI]: 1.93-8.52) to 7-fold (OR of 6.7; 95% CI: 5.2-8.6) in patients with malignancies versus individuals without malignancies (Heit 2000, Blom 2005). Chemotherapy increases the malignant neoplasm-associated risk of VTE in patients receiving concurrent chemotherapy (OR of 6.5; 95% CI: 2.1-20.2) versus those without concurrent chemotherapy (OR of 4.1; 95% CI: 1.9-8.5; Heit 2000). 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).

Pancreatic cancer is associated with a high risk of VTE among various cancer types (National Comprehensive Cancer Network [NCCN] Guidelines; NCCN Guidelines 2013). Incidence rates have been reported of 5% to 36% in retrospective studies and 19% to 67% in autopsy case series (Epstein 2012a). In a meta-analysis of data on cancer patients from 38 papers, pancreatic cancer was associated with a VTE incidence rate of 102 per 1000 person years (PY), as compared to 116/1000 PY for brain, 52/1000 PY for lung, and 35/1000 PY for hematologic cancer (Horsted 2012). Clinical and treatment variables relevant to pancreatic cancer and thrombosis include 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 2012a).

A comprehensive analysis of the incidence and clinical outcomes in patients with TE and pancreatic cancer conducted at Memorial Sloan Kettering Cancer Center identified 1,915 patients who had a diagnosis of pancreatic cancer between Jan 2000 and Dec 2009, of which 36% (N = 690) had at least 1 documented TE event. Of the 690 subjects, venous events predominated in 614 of patients presenting with a noncatheter-related deep vein TE event and/or a PE (89%, 614/690) (Epstein 2012b). 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 (4.4%) patients. The majority of patients (n = 638, 92.5%) had locally advanced or metastatic disease at the time of first TE event, of whom 78% had Stage IV.

Two randomized clinical studies conducted specifically to assess the rate of TE events with or without the use of prophylactic anticoagulation in patients with locally advanced or metastasized pancreatic adenocarcinoma receiving standard chemotherapy agents indicate reductions in the incidence of TE events in patients who received prophylaxis (TE events [venous and arterial combined] 1.3% and 5% in patients receiving low molecular weight heparin [LMWH] vs. 10% and 15% at 3 and 12 months, respectively, in patients who did not [Riess 2010]; VTE 12% in patients receiving dalteparin vs. 28% in patients who did not [Maraveyas 2012]).

4.4. Clinical Experience with PEGPH20

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.

In the PEGPH20 PDA clinical development program to date, 4 Sponsor clinical studies (plus 2 investigator-initiated studies and a Sponsor single-patient compassionate use Investigational New Drug [IND]) have been conducted or are ongoing. The Sponsor's 2 single agent Phase 1 studies (109-101 and 109-102) were conducted in subjects with advanced solid tumors. A Phase 1b (109-201) and an ongoing Phase 2 Study (109-202), in combination with chemotherapy, enrolled subjects with previously untreated Stage IV PDA. As of 31 March 2015, approximately 180 subjects participating in the 4 Sponsor clinical studies have been exposed to PEGPH20 either as a single agent, in combination with GEM, or in combination with NAB + GEM. These studies are summarized in Section 4.4.1 through Section 4.4.4.

4.4.1. Phase 1 Study HALO-109-101

The first-in-human Phase 1 study (109-101) was initiated in 2009 to evaluate PEGPH20 in subjects with advanced solid tumors who had experienced disease progression after previous therapy. Dosing began at 50 µg/kg PEGPH20 twice weekly for 3 weeks of each 4-week cycle and was then decreased to 0.5 µg/kg twice weekly due to musculoskeletal events (MSEs), including Grade 4 serious adverse events (SAEs) of arthralgia, myalgia, and muscular weakness, Grade 3 SAEs of musculoskeletal pain, and myalgia, and Grade 1-2 non-serious adverse events (AEs) of muscle spasms (reported in 3 subjects). Due to the severe MSEs observed in the first 3 subjects, the PEGPH20 dosing was reduced to 1 dose every 21 days, and the next 11 subjects received doses ranging from 0.5 µg/kg to 1.5 µg/kg prior to disease progression. No dose-limiting toxicities (DLTs) occurred at these dose ranges. The majority of MSEs reported were Grade 1 or 2 and were variable in duration. A total of 14 subjects received PEGPH20. This study was closed due to musculoskeletal toxicities and suboptimal dosing frequency.

4.4.2. Phase 1 Study HALO-109-102

Study 109-102 was initiated in 2010 to evaluate the safety profile and define the maximum-tolerated dose (MTD) of PEGPH20 given once or twice weekly with dexamethasone treatment to alleviate potential MSEs in subjects with advanced solid malignancies who either did not respond to standard therapy or for whom no standard therapy existed. PEGPH20 was administered at doses from 0.5 to 5.0 µg/kg once or twice weekly in the first cycle (4 weeks) and once per week in subsequent 4-week cycles. Subjects received 4 or 8 mg dexamethasone 1 hour prior to and 8 to 12 hours after PEGPH20 administration.

A total of 6 DLTs were experienced by 3 (17%) subjects dosed at 3.0 µg/kg and 5.0 µg/kg of PEGPH20. All 3 subjects experienced muscle spasms of Grade 2/3 severity. In addition, 1 subject dosed at 5.0 µg/kg experienced an event of Grade 3 myalgia. The MTD was determined to be 3.0 µg/kg once or twice weekly.

In this study, PEGPH20 doses up to 3.0 µg/kg once or twice weekly with 8 mg dexamethasone were well tolerated, with mostly Grade 1 or 2 MSEs, including 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 muscle relaxants and pain medications. Of the 26 subjects who received PEGPH20, 4 had advanced pancreatic cancer; 1of these subjects experienced a Grade 2, non-serious TE event (embolism), which was treated with warfarin and resolved without sequelae. Based on these results, the recommended Phase 2 dose was 3.0 µg/kg PEGPH20.

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

Study 109-201 was initiated in 2011 as a Phase 1b/2 multicenter, randomized, double-blind, placebo-controlled study to evaluate PEGPH20 in combination with GEM in previously untreated subjects with Stage IV PDA. Primary objectives of the Phase 1b portion of the study were to assess the safety and tolerability of the combination treatment and to identify the recommended Phase 2 dose of PEGPH20 in combination with GEM for the Phase 2 portion of the study. The study also investigated the efficacy of the PEGPH20 plus GEM combination. Due to the anticipated change in standard-of-care from GEM alone to NAB + GEM, this study was closed prior to the initiation of the randomized Phase 2 portion.

In the Phase 1b, single-arm portion, the safety profile of PEGPH20 in combination with GEM was similar to that observed in the first 2 Phase 1 studies, with MSEs being the most common toxicities. Most of the AEs related to GEM were similar in frequency and severity regardless of the PEGPH20 dose levels. In general, the most commonly reported toxicities associated with PEGPH20 were MSEs (e.g., muscle, joint, and bone pain; muscle cramping; and other involuntary contractions). Treatment-emergent TE events were reported in 8 of 28 subjects, the most frequent being PE (5 of 28 subjects, 18%).

Tumor responses were assessed by an independent central imaging vendor (CIV) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria (Eisenhauer 2009). Partial responses (PRs) were reported in 7 of 24 (29.2%) patients who received PEGPH20 at either 1.6 or 3.0 µg/kg. Subjects who had high HA in tissue biopsies experienced better responses (5/6 subjects with either PR or stable disease), which correlated with prolonged progression-free survival (PFS; 219 days) and overall survival (OS; approximately 395 days) vs. the low-HA group (PFS 108 days and OS 174 days) (Hingorani 2015).

Based on the results, the recommended Phase 2 dose of PEGPH20 in combination with GEM was 3.0 µg/kg twice weekly for the first 4 weeks and once weekly thereafter.

4.4.4. Phase 2 Study HALO-109-202

Study HALO-109-202 was initiated in 2013 as a Phase 2, randomized, multicenter study to investigate the efficacy and safety of PEGPH20 combined with NAB plus GEM (PAG treatment), compared with NAB plus GEM (AG treatment) alone, in subjects with Stage IV previously untreated PDA. Based on Data Monitoring Committee (DMC) findings of a potential imbalance in TE events between treatment groups, the study was placed on a temporary clinical hold in April 2014. All 29 ongoing subjects in the PAG group stopped PEGPH20 therapy and remained on AG therapy alone until the partial hold was lifted. In June 2014, the temporary clinical hold was lifted and the study protocol was amended to exclude subjects with current

evidence of a DVT or PE and subjects determined to be at high risk for TE events; and to add LMWH (enoxaparin) prophylaxis (initially, 40 mg/day and subsequently increased to 1 mg/kg/day subcutaneously [SC]) to both treatment groups. Stage 1 of this study includes subjects who were enrolled prior to the clinical hold (N = 146 randomized). Stage 2, which is ongoing, includes subjects who were enrolled after the clinical hold and subsequent protocol amendment (N = 133 randomized).

Number of subjects who discontinued treatment and safety data presented below are as of a data cutoff of 12 February 2018. A total of 100% of subjects in Stage 1, 99.2% (132/133) of subjects in Stage 2, and 99.6% (278/279) of subjects in Stage 1 + Stage 2 combined were off treatment. Efficacy data are based on an analysis performed using a data cut of 16 December 2016. Tumor samples were collected and analyzed in a prospective-retrospective fashion using an affinity histochemistry diagnostic assay (VENTANA HA RxDx assay), the same assay being used in this study, HALO-109-301. Efficacy results for the HA-high subgroups of the prespecified analysis populations in this study - Safety (all treated subjects) for Stage 1 and Stage 2, and Intent-to-Treat (ITT; all randomized subjects) for Stage 1 + Stage 2 combined are summarized below (Halozyme internal data). The median follow-up duration for these subject populations was 8.8, 8.7, and 8.5 months, respectively.

- **In the Stage 1 Safety HA-high Population** (n = 45 [24 PAG, 21 AG]), there was a 53% improvement in median PFS with PAG (9.2 months vs. 6.0 months with AG; Hazard Ratio [HR]: 0.48). The median OS was similar for PAG (11.5 months) and AG (10.9 months) (HR: 1.37). The Stage 1 OS data may have been impacted by (1) the approximately 40% of HA-high subjects in the PAG group stopping PEGPH20 treatment, most of whom continuing on AG treatment alone, at the clinical hold; and (2) an imbalance in baseline history of indolent disease between the PAG and AG groups, potentially contributing to a worse prognosis for the PAG group.
- **In the Stage 2 Safety HA-high Population** (n = 35 [24 PAG, 11 AG]), which is the most similar to the subject population of this current HALO-109-301 study, there was a 91% improvement in median PFS with PAG (8.6 months vs. 4.5 months with AG; HR: 0.63); and a 50% improvement in median OS with PAG (11.7 months vs. 7.8 months with AG; HR: 0.52).

  In the Stage 2 Safety HA-low Population (n = 76 [53 PAG, 23 AG]), the median PFS was 6.0 months with PAG vs. 7.2 months with AG (HR: 1.21), and the median OS was 11.9 months with PAG vs.10.2 months with AG (HR: 0.69).
- **In the combined Stage 1 + Stage 2 ITT HA-high Population** (n = 84 [49 PAG, 35 AG]), the median PFS was 9.2 months with PAG vs. 5.2 months with AG (HR: 0.51; p-value: 0.048) representing a statistically significant, 77% improvement with PAG for the total HA-high study population. Despite the limitations of the Stage 1 data set due to the clinical hold, there was a 35% improvement in median OS with PAG: 11.5 months vs. 8.5 months with AG (HR: 0.96).

Based on the data from the Stage 2 population in HA-high subjects (median PFS and OS 4.5 months and 7.8 months, respectively) vs. HA-low subjects (7.2 months and 10.2 months, respectively) within the AG group, HA-high tumors may lead to a worse prognosis when treated with the standard of care AG therapy, suggesting that high levels of HA are a negative prognostic biomarker in PDA and supporting the rationale for the addition of PEGPH20 treatment to anti-cancer therapies in PDA. The substantial improvements seen with PAG, compared with AG, in both median PFS and median OS in the Stage 2 HA-high population confirm the hypothesis of HA being a potential predictive biomarker for subject selection for PEGPH20 treatment.

In the Stage 1 + Stage 2 combined Safety Population (all treated subjects, N = 260 [160 PAG, 100 AG]), the most common (occurring in ≥25% of subjects) treatment-related AEs in either treatment group were fatigue (73%), peripheral edema (63%), muscle spasms (56%), nausea (50%), and diarrhea (40%) in the PAG group; and fatigue (66%), and nausea (47%) in the AG group.

The following treatment-related AEs were observed at higher incidence in the PAG group than the AG group: peripheral edema (63.1% vs 27.0%), muscle spasms (55.6% vs 3.0%), neutropenia (33.8% vs. 19.0%), myalgia (25.6% vs 7.0%), and thrombocytopenia (25.6% vs. 17.0% AG). Musculoskeletal events have previously been identified as DLTs from earlier studies of PEGPH20 and in this study, infrequently led to treatment discontinuation.

For additional information on clinical studies of PEGPH20, refer to the PEGPH20 Investigator's Brochure.

4.4.4.1. Thromboembolic Events in Study HALO-109-202

In Stage 1 of study HALO-109-202, the DMC observed an imbalance in the rate of TE events between the PAG and AG treatment groups (28.4% vs. 14.8%), leading to the implementation of risk mitigation measures, including the exclusion of high-TE event risk subjects and the administration of enoxaparin prophylaxis to all subjects.

As of 12 February 2018, the rate of TE events in Stage 1 (no enoxaparin prophylaxis) was 43% (32/74 subjects) for PAG and 25% (15/61 subjects) for AG.

In Stage 2, since the implementation of these measures, the incidence of TE events has decreased, especially in subjects who initiated enoxaparin at 1 mg/kg/day. The TE event rate was 28% (5/18 subjects) for PAG and 29% (2/7 subjects) for AG in subjects who started enoxaparin at 40 mg/day, and was considerably reduced to 10% (7/68 subjects) for PAG and 6% (2/32 subjects) for AG in subjects who started enoxaparin at 1 mg/kg/day. In Stage 2, 2 subjects had arterial events of acute myocardial infarction and coronary artery occlusion in the AG group; and 1 subject had a cerebrovascular accident in the PAG group. The concomitant use of enoxaparin in Stage 2 was not associated with additional toxicities (i.e., bleeding) in the PAG arm compared with Stage 1.

4.5. Study Rationale

For the majority of patients diagnosed with Stage IV PDA, palliative care and GEM have been considered the standard-of-care. Single-agent GEM provided modest improvement in survival, with median OS of 5.7 months and a 1-year survival rate of 18% (Burris 1997).

More recently, 2 regimens have demonstrated improvements in OS outcomes compared to GEM alone: (1) GEM combined with NAB and (2) the non-approved FOLFIRINOX (oxaliplatin, leucovorin, irinotecan, and 5-FU). A Phase 3 study of 861 patients randomized to receive either the combination of NAB at 125 mg/m^2 followed by GEM at 1000 mg/m^2 or GEM alone achieved a median OS of 8.5 months for the combination compared with 6.7 months for GEM alone (HR = 0.72, p-value = <0.001). Moreover, the median PFS was prolonged to 5.5 months for the combination compared with 3.7 months for GEM alone (HR = 0.69, p-value <0.001) (Von Hoff 2013). In September 2013, the FDA approved the combination of NAB plus GEM as first-line treatment for patients with metastatic PDA (FDA Approval Letter 2013). A Phase 3, randomized study of the multi-drug regimen FOLFIRINOX resulted in a median OS of 11.1 months compared with 6.8 months for single agent GEM (HR = 0.57, p-value <0.001; Conroy 2011). FOLFIRINOX is administered to patients with a good performance status but is associated with tolerability concerns making it an unsuitable regimen for some patients.

Despite the modest improvements in clinical outcome with the GEM + NAB combination in patients with PDA, this patient population represents an area of high and urgent unmet medical need.

The combination of NAB and GEM is presently considered a standard-of-care for patients with Stage IV pancreatic cancer. PEGPH20 is an investigational anticancer product. The efficacy and safety data from nonclinical studies and randomized Phase 2 clinical studies of PEGPH20 provide the rationale for its further development in combination with NAB and GEM in Stage IV pancreatic cancer.

In clinical studies (109-201 and 109-202), PEGPH20 in combination with GEM or with NAB plus GEM led to statistically and clinically significant improvements in efficacy in terms of objective response rate (ORR), PFS, and prolonged duration of response (DOR), with the greatest improvements reported in subjects determined to be HA-high (see results summarized in Section 4.4.3 and Section 4.4.4).

Given the poor prognosis of patients with pancreatic cancer, especially those found to be HA-high, the clinical data described above indicate that the addition of PEGPH20 to AG therapy improves ORR, DOR, PFS, and OS. The addition of PEGPH20 to AG therapy in subjects with HA-high tumors will be evaluated in the proposed registrational Phase 3 study, with PFS and OS as primary endpoints.

4.5.1. Rationale for Dose and Schedule Selection

The dose and schedule for PEGPH20 for this study - 3.0 µg/kg twice a week for Cycle 1 and once a week for Cycle 2 and beyond - were selected based on pharmacokinetic (PK) modeling and prior clinical studies. In the Phase 1 study in advanced solid malignancies (109-102), PEGPH20 administered once weekly and twice weekly increased circulating concentrations of HA catabolites and reduced tumor-associated HA at a dose of 1.6 µg/kg, and the MTD was 3.0 µg/kg (Infante 2012). The Phase 1b/2 study in subjects with metastatic pancreatic cancer (109-201) identified 3.0 µg/kg as the recommended Phase 2 dose of PEGPH20 when given in combination with GEM. Antitumor activity was also observed in this study. Additionally, the ongoing Phase 2 study HALO-109-202 is treating subjects with 3.0 µg/kg of PEGPH20 plus AG, and this dose level has been shown to be tolerable. Results from this study continue to be followed by a DMC.

This Phase 3 study will evaluate PEGPH20 3.0 µg/kg in combination with NAB and GEM. The dose and schedule for NAB and GEM are per respective Prescribing Information (PI) with the exception that the first doses of NAB and GEM will be given on Day 2 instead of Day 1. This is based on preclinical data indicating that maximum depletion of tumor levels of HA occurs by 24 hours after the first dose of PEGPH20, potentially making tumors more responsive to the cytotoxic effects of chemotherapy. Starting from Week 2, NAB and GEM will be given 2 to 4 hours after completion of the randomized study medication infusion to allow time for PEGPH20 to act on HA in the tumor microenvironment.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objectives

- To determine the OS benefit of PEGPH20 combined with NAB plus GEM (PAG treatment), compared with placebo plus NAB/GEM (AG treatment), in subjects with HA-high Stage IV previously untreated PDA

5.1.2. Secondary Objectives

- To determine the PFS benefit of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA
- To determine the ORR and DOR of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA
- To assess the safety and tolerability of PAG treatment in subjects with HA-high Stage IV previously untreated PDA

5.1.3. Exploratory Objectives

- To assess the treatment effect of PAG on serum levels of cancer antigen 19-9 (CA19-9)
- To assess the treatment effect of PAG on HA levels and other potential biomarkers in plasma and tumor biopsies (when available)
- To assess the PK of PEGPH20 in combination with NAB plus GEM
- To assess the potential effect of PEGPH20 on the PK of NAB and GEM
- To assess the impact of PAG treatment on patient-reported outcomes (PROs) including health-related quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30); other health outcomes using the European Quality of Life-5 Dimensions Scale (EQ-5D); and symptoms related to pancreatic cancer and to treatment-associated toxicities using a Numerical Rating Scale (NRS).

5.2. Study Endpoints

5.2.1. Primary Endpoints

- Overall survival

5.2.2. Secondary Endpoints

- Progression-free survival
- Objective response rate
- Duration of response

- Incidence of AEs, changes in clinical safety laboratory values, and changes in cardiovascular parameters (electrocardiogram [ECG] and vital signs)

5.2.3. Exploratory Endpoints

- Change in serum CA19-9 levels
- Change in plasma and tumor biopsy (when available) HA levels and other potential biomarkers
- Pharmacokinetics of PEGPH20 in combination with NAB plus GEM
- Pharmacokinetics of NAB and GEM in the PAG group versus the AG group
- Patient-reported outcome measures including the EORTC QLQ-C30, EQ-5D, and NRS

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan: Description

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to compare the efficacy and safety of PAG versus AG treatment in subjects with Stage IV previously untreated PDA whose tumors are HA-high. For the purposes of this study, randomized study medication is defined as PEGPH20 or placebo; and study medication is defined as PEGPH20, placebo, NAB, and GEM.

The study will involve a Screening Period. Eligible subjects will be randomized in a double-blind fashion to 1 of 2 treatment groups in a 2:1 ratio as follows:

- PAG group: PEGPH20 (3.0 µg/kg) + NAB (125 mg/m^2) + GEM (1000 mg/m^2)
- AG group: Placebo + NAB (125 mg/m^2) + GEM (1000 mg/m^2)

Randomization will be stratified by geographic region (North America, Europe, and Others).

The Treatment Period will consist of 4-week treatment cycles (28 days); Week 4 of every cycle will be a rest week (i.e., no treatment will be given). Study medication will be administered as follows:

- Randomized study medication will be administered as an intravenous (IV) infusion twice weekly for Weeks 1 to 3 of Cycle 1, then once weekly for Weeks 1 to 3 of Cycle 2 and beyond.
- NAB and GEM will be administered as IV infusions once weekly for Weeks 1 to 3 of all treatment cycles.

Treatment will continue until disease progression, unacceptable toxicity, death, or withdrawal of consent.

The study design is shown in Figure 2. The Study Medication Dosing and Treatment Schedule are shown in Table 3.

In addition to study medications, all subjects will be administered dexamethasone 8 mg, preferably orally (PO), prior to and after completion of the randomized study medication infusion (total dose 16 mg on dosing days; refer to Section 10.12.1), to reduce potential musculoskeletal symptoms, which have been reported to be associated with PEGPH20.

To minimize the risk of TE events, which is a common complication of pancreatic cancer and is reported to occur with PEGPH20 administration, enoxaparin will be administered to all subjects SC at a dose of 1 mg/kg/day according to guidelines issued by the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis for all patients undergoing outpatient therapy for advanced pancreatic cancer (Khorana 2014) (refer to Section 10.1).

Tumor response and progression will be assessed using RECIST version 1.1 criteria (Appendix B). Imaging assessments (computed tomography [CT] scans or Magnetic Resonance Imaging [MRI]) will be conducted by an independent, blinded CIV. Tumor assessment will be performed at the end of Cycle 2 and at the end of every subsequent second treatment cycle after the last dose or the following week (i.e., Days 15 to 28 of Cycles 2, 4, 6, 8, and beyond), to allow

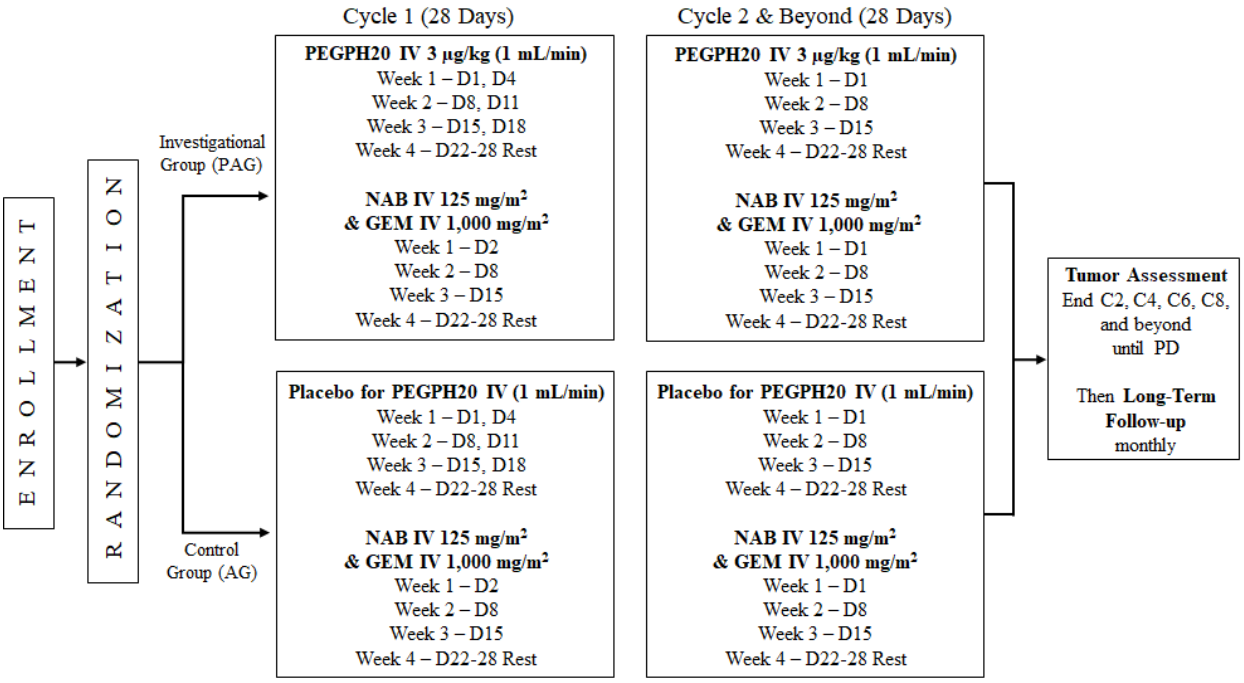
time for reading of the scans by the CIV prior to the start of subsequent cycles. At the End of Treatment Visit, a CT scan will be obtained if radiologic disease progression was not documented in the previous CT scan unless the latter was performed within the last 14 days.

Toxicities will be graded by the Investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (at time of study initiation). Safety data will be periodically reviewed by an independent DMC to protect subject welfare and identify potential safety signals.

After the End of Treatment Visit, subjects will enter long-term follow-up during which information on the subject's survival and subsequent anticancer therapy will be obtained by the site monthly until the subject dies, is lost to follow-up, or withdraws consent.

The end of the study is defined by the time of the last subject last visit (final data point collection).

Figure 2: Study Schema (HALO-109-301)



Abbreviations: AG = placebo for PEGPH20 plus NAB and GEM; C = Cycle; D = Study Day; GEM = gemcitabine; NAB = nab-paclitaxel; PAG = PEGPH20 plus NAB and GEM; PD = progressive disease; PO = per os (orally); SC = subcutaneous(ly).
Figure Notes: Dexamethasone 8 mg preferably PO will be administered to all subjects prior to and after completion of the randomized study medication (PEGPH20 or placebo) infusion (total dose 16 mg on dosing days). Enoxaparin 1 mg/kg/day SC will be administered to all subjects; on dosing days, it will be administered prior to the infusion of randomized study medication.

6.1.1. Overview of Treatment Schedule

All protocol-specified investigational (PEGPH20 and placebo) and non-investigational (NAB and GEM) products are considered study medications.

The treatment schedule for the PAG and AG treatment groups is described in Table 3. Dose interruption and modifications are permitted; refer to Section 8.3 for further guidance.

Table 3: Study Medication Dosing and Treatment Schedule - PAG and AG Groups (HALO-109-301)

Time Point	Treatment
Cycle 1	
Week 1	
Day 1	Randomized study medication (PEGPH20 or placebo)
Day 2	NAB and GEM (24 ± 4 hours after Day 1 dose of randomized study medication)
Day 4	Randomized study medication
Week 2	
Day 8	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Day 11	Randomized study medication
Week 3	
Day 15	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Day 18	Randomized study medication
Week 4	
Day 22 -28	No treatment (rest week)
Cycle 2 and Beyond	
Weeks 1 - 3	
Day 1	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Day 8	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Day 15	Randomized study medication NAB and GEM (2-4 hours after randomized study medication)
Week 4	
Day 22 -28	No treatment (rest week)

Abbreviations: AG = placebo for PEGPH20 plus NAB and GEM; GEM = gemcitabine; NAB = nab-paclitaxel; PAG = PEGPH20 plus NAB and GEM; PO = per os (orally); SC = subcutaneous(ly).

(Table notes on next page)

Table 3 Notes:

- Randomized study medication is defined as PEGPH20 or placebo. Subjects randomized to the PAG treatment group will receive PEGPH20 3.0 μg/kg + NAB 125 mg/m^2 + GEM 1000 mg/m^2, and subjects randomized to the AG treatment group will receive placebo + NAB 125 mg/m^2 + GEM 1000 mg/m^2.Each treatment cycle is 28 days. Dose interruption and modifications are permitted; refer to Section 8.3 for further guidance.
- Dosing window is ± 2 days of the specified dates, relative to Day 1 of Cycle 1, as long as doses are separated by the appropriate amount of time (e.g., a minimum of 2 days when visits are twice a week).
- In addition to study medications, all subjects will be administered dexamethasone 8 mg preferably PO within 2 h prior to the start of and 8-12 h after completion of each infusion of randomized study medication (total dose of 16 mg on dosing days). For additional details regarding dexamethasone administration, refer to Section 10.12.1.
- All subjects will be administered enoxaparin 1 mg/kg/day SC during the treatment period; on dosing days, enoxaparin will be administered prior to the infusion of randomized study medication. For additional details regarding enoxaparin administration, refer to Section 10.12.2.

6.2. Provisions and Procedures Post-final Analysis

If the final analysis supports a positive benefit-risk assessment for PEGPH20, the provisions and procedures described in this section will be implemented upon communication by the Sponsor. Until then, all procedures documented in this protocol, which reflect Protocol Amendment 5, will remain in effect.

- Subjects in the PAG arm post-final analysis will be offered the option to continue PAG treatment if the Investigator deems it in their best interest.
- Subjects in the AG arm post-final analysis will be offered the option to switch to and continue on PAG treatment.
- Subjects in the AG arm post-final analysis who choose not to switch to PAG treatment will be discontinued from the study. These subjects will be treated according to the Investigator's discretion and local standard-of-care.

All subjects continuing study treatment under Protocol Amendment 6 will receive PAG treatment (including PAG subjects continuing on PAG treatment and AG subjects switched to PAG treatment). Post-final analysis procedures for these subjects will be reduced in scope (vs. study procedures per Protocol Amendment 5) and will include the following (details in Table 5):

- Signing of revised Informed Consent Form (ICF) for all subjects receiving study treatment post-final analysis
- Administration of study medications (PEGPH20, NAB, and GEM) as detailed in Section 8.1.2 and Section 8.3 except that study medication will be administered in an open-label fashion (PEGPH20 vs. randomized study medication [Table 4]).
    - The dosing schedule for the Initial Cycle Post-final Analysis is only applicable to subjects who have chosen to switch from AG treatment to PAG treatment. Subjects continuing on PAG treatment post-final analysis will follow the dosing schedule for Subsequent Cycles Post-final Analysis.
    - Subjects will continue to receive study medication until disease progression or other protocol-specified reasons for treatment discontinuation (see Section 7.3.1) or study discontinuation (see Section 7.3.2).
    - Subjects who discontinue treatment will undergo an End of Treatment Visit as detailed in Section 8.1.2.3.
- Administration of enoxaparin and dexamethasone as detailed in Section 8.1.2 and Section 10.1.1, respectively
- Disease assessment performed locally (vs. by the CIV in Protocol Amendment 5) via CT/MRI scan per standard-of-care and at the discretion of the Investigator
- Standard-of-care blood samples may be drawn at the Investigator's discretion and assessed by the local laboratory before NAB and GEM dosing
- Collection and recording of SAEs, TE events, and AEs leading to discontinuation of study treatment as follows:

- Serious adverse events will be reported as described in Section 10.3 and Section 10.5.
- TE events will be reported as described in Section 10.4.
- Adverse events leading to discontinuation of any study medication (PEGPH20, NAB, or GEM) will be collected for 30 days after the last dose of study treatment as described for AEs in Section 10.5.

Post-final analysis long-term follow-up:

- Subjects continuing PAG treatment and subjects switched from AG to PAG treatment post-final analysis will enter long-term follow-up after treatment discontinuation as mandated in Protocol Amendment 5 (details in Section 8.1.3).
- All subjects who have discontinued either PAG or AG treatment and are in long-term follow-up will continue to be followed up per Protocol Amendment 5 (details in Section 8.1.3).

Table 4: Study Medication Dosing and Treatment Schedule Post-final Analysis – PAG Treatment (PAG Subjects and AG Subjects Switched to PAG) (HALO-109-301)

Time Point	Treatment
Initial Cycle Post-final Analysis	
Week 1	
Day 1	PEGPH20
Day 2	NAB and GEM (24 ± 4 hours after Day 1 dose of PEGPH20)
Day 4	PEGPH20
Week 2	
Day 8	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)
Day 11	PEGPH20
Week 3	
Day 15	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)
Day 18	PEGPH20
Week 4	
Days 22-28	No treatment (rest week)
Subsequent Cycles Post-final Analysis	
Weeks 1-3	
Day 1	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)
Day 8	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)
Day 15	PEGPH20 NAB and GEM (2-4 hours after PEGPH20)
Week 4	
Days 22-28	No treatment (rest week)

Abbreviations: AG = placebo for PEGPH20 plus NAB and GEM; PEGPH20 = pegylated recombinant human hyaluronidase; GEM = gemcitabine; NAB = nab-paclitaxel; PAG = PEGPH20 plus NAB and GEM; PO = per os (orally); SC = subcutaneous(ly).

(Table notes on next page)

Table 4 Notes:

- The dosing schedule for the Initial Cycle Post-final Analysis is only applicable to subjects who have chosen to switch from AG treatment to PAG treatment. Subjects continuing on PAG treatment post-final analysis will follow the dosing schedule for Subsequent Cycles Post-final Analysis.
- Study medication post-final analysis is defined as PEGPH20. Subjects will receive PEGPH20 3.0 µg/kg + NAB 125 mg/m^2 + GEM 1000 mg/m^2. Each treatment cycle is 28 days. Dose interruption and modifications are permitted; refer to Section 8.3 for further guidance.
- Dosing window is ± 2 days of the specified dates, relative to Day 1 of Cycle 1 (subjects continuing on PAG treatment) or Day 1 of the Initial Cycle Post-final Analysis (subjects switched from AG to PAG), as long as doses are separated by the appropriate amount of time (e.g., a minimum of 2 days when visits are twice a week).
- In addition to study medications, all subjects will be administered dexamethasone 8 mg preferably PO within 2 h prior to the start of and 8-12 h after completion of each infusion of PEGPH20 (total dose of 16 mg on dosing days) (additional details in Section 10.12.1).
- All subjects will be administered enoxaparin 1 mg/kg/day SC during the treatment period; on dosing days, enoxaparin will be administered prior to the infusion of PEGPH20 (additional details in Section 10.12.2).

Table 5: Study Schedule of Events: Post-final Analysis Procedures – PAG Treatment (PAG Subjects and AG Subjects Switched to PAG) (HALO-109-301)

	Initial Cycle Post-final Analysis (4 Weeks) [a]								Subsequent Cycles Post-final Analysis (Repeats Every 4 Wks)				End of Treat. [b]	Long-term Follow-up
	Wk 1			Wk 2		Wk 3		Wk 4	Wk 1, Wk 2, Wk 3			Wk 4		
Tests and Assessments	**D 1**	**D 2**	**D 4**	**D 8**	**D 11**	**D 15**	**D 18**	**D 22**	**D 1**	**D 8**	**D 15**	**D 22**		
Sign Revised ICF [c]								NO VISIT / ASSESSMENTS				NO VISIT / ASSESSMENTS		
Disease Assessment (CT/MRI Scan) [d]	X								X				X	
Dexamethasone Admin. [e]	X		X	X	X	X	X		X	X	X			
PEGPH20 Admin.	X		X	X	X	X	X		X	X	X			
NAB Admin.		X [f]		X [g]		X [g]			X [g]	X [g]	X [g]			
GEM Admin.		X [f]		X [g]		X [g]			X [g]	X [g]	X [g]			
Enoxaparin Admin. [h]	X													
Local Laboratory Assessments [i]	X													
Collection/Recording of SAEs, TE events, and AEs Leading to Discontinuation of Study Medication [j]	X												X	X
Long-term Follow-up [k]														X

Abbreviations: Admin. = administration; AE = adverse event; AG = placebo for PEGPH20 plus NAB and GEM; CT = computed tomography; D = study day; GEM = Gemcitabine; h = hour(s); ICF = informed consent form; IM = intramuscular; IV = intravenous(ly); MRI = magnetic resonance imaging; NAB = nab-Paclitaxel; PAG = PEGPH20 plus NAB and GEM; PD = progressive disease; PEGPH20 = pegylated recombinant human hyaluronidase; PO = orally; SAE = serious adverse event; SC = subcutaneous(ly); TE = thromboembolic; treat = treatment; Wk = study week.

(Table notes on next page)

Table 5 Notes:

[a] The procedures and dosing schedule for the Initial Cycle Post-final Analysis are only applicable to subjects who have chosen to switch from AG treatment to PAG treatment. Subjects continuing on PAG treatment post-final analysis will follow the dosing schedule for Subsequent Cycles Post-final Analysis.

[b] Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after treatment discontinuation of all study medications (PEGPH20, GEM, and NAB) and prior to initiation of subsequent anticancer therapy.

[c] Upon implementation of Protocol Amendment 6.

[d] CT/MRI scans will be performed locally at the Investigator's discretion.

[e] Dexamethasone 8 mg will be given preferably PO within 2 h prior to the start of and 8-12 h after completion of each infusion of PEGPH20 (total dose of 16 mg on dosing days). Subjects will self-administer dexamethasone PO unless given by study site personnel. Parenteral administration is allowed if the subject cannot tolerate oral dexamethasone. Additional doses of dexamethasone (PO, IM, or IV) may be given 24 hours prior to infusions of PEGPH20 or at any other time at the discretion of the Investigator based on tolerability.

[f] NAB and GEM will be administered on Day 2, 24 h (± 4 h) after completion of the Day 1 PEGPH20. NAB will be given first.

[g] NAB and GEM will be given 2 to 4 h after completion of the PEGPH20 infusion. NAB will be given first.

[h] All subjects will self-administer enoxaparin 1 mg/kg SC once a day during the Treatment Period. On dosing days, enoxaparin will either be self-administered by subjects or administered by study site personnel prior to the infusion of PEGPH20 (additional details in Section 10.1.1).

[i] Standard-of-care blood samples may be drawn at the Investigator's discretion and assessed at the local laboratory before NAB and GEM dosing.

[j] Details on SAE recording are provided in Section 10.3 and Section 10.5; details on TE event recording are provided in Section 10.4. Adverse events leading to discontinuation of any study medication (PEGPH20, NAB, or GEM) will be collected for 30 days after the last dose of study treatment as described for AEs in Section 10.5.

[k] After the End of Treatment Visit, subjects will enter long-term follow-up during which information on survival and subsequent anticancer therapy will be obtained by the site monthly until the subject dies, is lost to follow-up, or withdraws consent.

7. SELECTION AND WITHDRAWAL OF SUBJECTS AND STUDY TERMINATION

The study plans to randomize approximately 500 HA-high subjects with previously untreated Stage IV pancreatic cancer at study sites globally.

7.1. Inclusion Criteria

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

1. Signed, written Institutional Review Board/Ethics Committee-approved ICF.
2. Stage IV (PDA with histological or cytological confirmation of PDA.
3. Subjects must be determined to be HA-high based on archived or fresh tumor core biopsy or sample obtained after the subject has documented metastatic disease. Biopsies/samples must meet the following requirements:
    a. Pancreas tumor biopsies/samples obtained on or after the date that metastatic disease is documented or tumor biopsies/samples from a metastatic lesion are acceptable.
    b. Tumor biopsies or samples must meet the requirements provided in the Study Laboratory Manual with regard to tumor tissue architecture. Note: cytology samples from fine needle aspirates without maintained tissue architecture or brushing biopsies are not acceptable.
    c. Tumor tissue (formalin-fixed paraffin-embedded [FFPE] block preferred) must include enough tumor to make a minimum of 5-10 unstained, consecutive FFPE slides (10 slides are preferred) of 1 archival block that meet specific tissue sample requirements (see Study Laboratory Manual).
4. Radiographic confirmation of Stage IV PDA with at least 1 tumor metastasis measurable on CT scan or MRI per RECIST version 1.1 criteria, excluding the primary pancreatic lesion.
5. If a subject has had adjuvant/neoadjuvant therapy and/or therapy for locally advanced disease (chemotherapy for non-metastatic pancreatic cancer in combination with or without radiation therapy), tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of the aforementioned therapies, provided all toxicities have returned to baseline or ≤ Grade 1.
6. Eastern Cooperative Oncology Group Performance Status of 0 or 1.
7. Life expectancy ≥ 3 months.
8. Age ≥ 18 years.
9. A negative urine or serum pregnancy test within 7 days before Cycle 1, Day 1 (C1D1; first dose of study medication) if female subject is of childbearing potential.
10. Screening clinical laboratory values as follows (Section 8.2.7):
    a. Total bilirubin ≤ 1.5 times upper limit of normal (ULN) (subjects with Gilbert syndrome are eligible independent of bilirubin levels).

b. 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).
c. Serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 40 mL/min.
d. Serum albumin ≥ 2.5 g/dL.
e. Prothrombin time or international normalized ratio (INR) within normal limits (±15%), unless subject takes warfarin, in which case prothrombin time or INR result must be within therapeutic range.
f. Partial thromboplastin time (PTT) within normal limits (± 15%).
g. Hemoglobin ≥ 9 g/dL (transfusion and erythropoietic agents allowed).
h. Absolute neutrophil count ≥ 1,500 cells/mm^3.
i. Platelet count ≥ 100,000 /mm^3.

11. For women of childbearing potential (WOCBP) and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 1 month (WOCBP) or 6 months (men) after administration of the last dose of any study medication. Highly effective contraceptive methods consist of prior sterilization, intra-uterine device (IUD), intrauterine hormone-releasing system (IUS), oral or injectable contraceptives, barrier methods, and/or true sexual abstinence (Section 8.2.9).

7.2. Exclusion Criteria

Subjects are ineligible for enrollment if they meet any of the following exclusion criteria:

1. Clinical evidence of DVT, PE or other known TE event present during the screening period (see Section 8.2.11 and Section 8.2.12).
   a. Subjects with superficial vein thrombosis are eligible.
   b. Subjects with visceral/splanchnic vein thrombosis are still eligible if, in the opinion of the Investigator, the visceral/splanchnic vein thrombosis is primarily associated with the anatomic location of the underlying disease of metastatic pancreatic cancer (i.e., there must be primary or metastatic disease in reasonable proximity to the thrombosis, and the Investigator determines that the thrombosis is due to a local tumor event and not a coagulation issue).
2. Previous radiotherapy, surgery, chemotherapy, or investigational therapy for the treatment of metastatic disease.
   a. Palliative radiotherapy for pain control of metastatic bone lesions is allowed.
3. Known central nervous system involvement or brain metastases.
4. New York Heart Association Class III or IV cardiac disease (Appendix C) or myocardial infarction within the past 12 months.
5. History of cerebrovascular accident or transient ischemic attack.
6. Clinically significant pre-existing carotid artery disease.
7. Known infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C within the past 12 months.
8. Known allergy to hyaluronidase.

9. Current use of megestrol acetate or megestrol acetate-containing drugs (use within 10 days of Day 1).
10. Contraindication to heparin as per institutional guidelines.
11. Women currently pregnant or breastfeeding.
12. Intolerance to dexamethasone.
13. 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.
14. Any other disease, active, uncontrolled bacterial, viral or fungal infection requiring systemic therapy, 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.
15. Immunization with a live vaccine up to 2 weeks prior to Day 1.
16. Hypersensitivity to the active substance or ingredients of PEGPH20, gemcitabine, and nab-paclitaxel.
17. 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 protect the subject's welfare and may discontinue any study treatment at any time when this action appears to be in the subject's best interest. Whenever possible, the Investigator should contact the Medical Monitor prior to discontinuing the subject from study treatment. The reason for the subject's treatment discontinuation 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 as follows:
  - Disease progression documented by CT scan (or MRI) based on RECIST version 1.1 criteria, as determined by the CIV.
- Adverse event.
- 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 (e.g., subjects who permanently discontinue the LMWH treatment for any reason).

- Unambiguous clinical progression documented by the Investigator in the absence of radiological confirmation. The Investigator must review the latest CIV report for tumor assessments prior to discontinuing the subject from study treatment.
- The subject becomes pregnant (treatment must be discontinued immediately).

If all study medications (PEGPH20/placebo + NAB + GEM) have been permanently discontinued, then the subject will undergo the End of Treatment evaluations (refer to Section 8.1.2.3) and enter long-term follow-up (refer to Section 8.1.3).

If any study medication(s) has been interrupted for longer than 28 days (as calculated starting from Day 1 of the next planned Treatment Cycle), then the Investigator must consult the Medical Monitor to determine whether the subject may resume study treatment.

If randomized study medication (PEGPH20/placebo) has been discontinued in the absence of CIV-confirmed radiologic disease progression (e.g., due to unacceptable toxicity), the subject can continue to receive treatment with NAB and GEM, which is to be considered as continuation of the study regimen; therefore, all study assessments should continue according to the schedule specified in Table 2.

Subjects who discontinue all study medications for any reason should remain in the study for long-term follow-up assessments unless they withdraw consent, die, or become lost to follow-up. Long-term follow-up evaluations will be performed on a monthly basis, as detailed in Section 8.1.3.

7.3.2. Study Discontinuation

After the subject discontinues study treatment, the subject will be followed in long-term follow-up for survival and subsequent anticancer therapies (Section 8.1.3). 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 (e.g., per Investigator discretion if determined to be in the subject's best interest).

The Sponsor 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

The procedures to be performed during the study are listed by visit in the Study Schedule of Events (Table 1 and Table 2) and described in detail by visit in Section 8.1. Information on individual study assessments is provided in Section 8.2.

When duplicate evaluations are performed before study start, 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 up to 2 days 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 2 days when visits are twice a week). 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, when PEGPH20/placebo are administered twice per week, the twice weekly administrations should be separated by a minimum of 2 days (e.g., Monday and Thursday or Tuesday and Friday schedule). Where this is not possible because of extenuating circumstances (e.g., holidays), the administrations should be separated by at least 45 hours.

8.1. Study Procedures by Visit

8.1.1. Screening Visit(s)

Screening procedures should be performed as rapidly as possible within 28 days prior to C1D1 to facilitate subject entry requirements (note: per Section 8.2.1.1, tumor HA testing may be performed earlier if subject signs Prescreening ICF). In case of abnormal test values, retesting may be performed if medically indicated and within 28 days prior to C1D1.

If the following procedures were performed as part of standard-of-care prior to the subject signing the Main Study ICF, the results may be used for screening purposes providing they were performed within 28 days prior to C1D1, unless otherwise indicated: physical examination, vital sign measurements, height, weight/body surface area (BSA), and CT scans or MRI.

All subjects will be monitored for study procedure-associated SAEs starting from the time of Main Study ICF signature (or from the time of Prescreening ICF signature, if applicable [whichever is earlier]) as described in Section 10.2.

- Sign and date Main Study ICF (prior to screening procedures)
- Confirm availability and HA testing of tumor tissue – refer to Section 8.2.15.1 for additional details
- Subject registration, i.e., subject is entered into an Interactive Web Response System [IWRS] for screening
- Preliminary assessment of subject eligibility based on inclusion/exclusion criteria
- Medical history
- Prior medication history
- Physical examination

- Vital sign measurements
- Eastern Cooperative Oncology Group (ECOG) Performance Status
- Height
- Weight/BSA
- Disease assessment: obtain CT scan (or MRI if subject is intolerant to CT contrast agent) and send to the CIV (additional details in Section 8.2.11). In addition, chest CT scans should be read locally to screen for the presence of PE. These can be the same scans that are sent to the CIV. If subject has signs or symptoms of PE after the initial scan was completed, the chest scan should be repeated prior to randomization to assess for the presence of PE. If a PE is present, the subject will be considered a screening failure and will not be randomized.
- Doppler ultrasound of lower extremities
- Obtain samples for the following tests and send to local laboratory
  - Urine/serum pregnancy test (WOCBP) within 7 days before C1D1
- Obtain samples for the following tests and send to central laboratory:
  - Hematology
  - Blood chemistry (including C-reactive protein [CRP])
  - Urinalysis
  - Coagulation tests (prothrombin time [PT], PTT, INR) (thereafter, these tests will be performed upon determination of disease progression)
  - Serum CA19-9 levels
  - Plasma HA levels
  - Plasma sample for analysis of potential biomarkers of PEGPH20 activity
- Subject enrollment and randomization, within 4 days prior to C1D1and upon verification that subject meets all inclusion/exclusion criteria prior to randomization.

8.1.1.1. Re-screening

If medically indicated, subjects may be re-screened so long as they were not randomized into the study. In the event that a subject is to be re-screened, the only Screening procedures that must be performed again are those that would fall outside of the 28-day Screening window (i.e., more than -28 days prior to actual Cycle 1, Day 1 [C1D1] date), unless otherwise specified. Exceptions are detailed below.

The following details are applicable for subjects who want to re-screen and have already undergone tumor HA testing:

- HA-High: tumor HA testing does not need to be repeated for re-screening.
- HA-Low: re-screening is not allowed (subject is ineligible).

- Not evaluable: if subject had a sample that was not evaluable, another sample may be sent for HA testing (e.g., from repeat biopsy procedure, additional tissue from original biopsy sample).

For WOCBP, pregnancy testing must be performed within 7 days prior to actual C1D1 date.

In order to be enrolled in the study, a subject must be randomized within 4 days prior to C1D1.

8.1.2. Treatment Period

For all subjects, AEs and concomitant medications will be reviewed at each visit. The procedures listed below will be performed for all subjects:

- Standard-of-care blood samples should be drawn and assessed at the central laboratory before NAB and GEM dosing to confirm the subject meets the required criteria for dosing (see Section 8.3.2.3 and Section 8.2.7 for additional details).
- Premedications for chemotherapy are permitted per institutional guidelines.
- All subjects will self-administer enoxaparin 1 mg/kg SC once a day during the Treatment Period; on dosing days, enoxaparin will either be self-administered by subjects or administered by study site personnel prior to the infusion of randomized study medication. Enoxaparin treatment may be continued per Investigator's decision and standard-of-care when randomized study medication is permanently discontinued (Section 10.1.1)
- On dosing days, dexamethasone will be administered preferably PO prior to and after completion of each infusion of randomized study medication as specified in the following sections. Subjects will self-administer dexamethasone PO unless given by study site personnel.

Procedures by Cycle/Day listed in the following sections need not be performed in the listing order, unless otherwise specified.

8.1.2.1. Treatment Cycle 1

8.1.2.1.1. Cycle 1 Day 1

Prior to Randomized Study Medication Infusion

- Completion by subjects of EORTC QLQ-C30, EQ-5D, and NRS
- Physical examination
- Vital signs
- ECOG Performance Status
- Weight/BSA
- 12-lead ECG 3 times within a 5-minute period

- Blood sample collection for the following tests:
- – Hematology
  - – Blood chemistry (including CRP)
  - – Immunogenicity (PEGPH20 anti-drug antibodies [ADA] and neutralizing antibodies [NAb])
  - – Plasma PEGPH20 concentration (PK) anytime before the start of randomized study medication infusion
  - – Plasma HA levels anytime before the start of randomized study medication infusion
  - – Plasma sample for analysis of potential biomarkers of PEGPH20 activity
  - – Whole blood sample for pharmacogenetic analysis
- Dexamethasone administration within 2 hours prior to randomized study medication infusion

Randomized Study Medication Infusion

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

After Randomized Study Medication Infusion

- 12-lead ECG 3 times within a 5-minute period between 1 to 4 hours after completion of randomized study medication infusion
- Blood sample collection for plasma PEGPH20 concentration (PK) within 5 minutes after completion of randomized study medication infusion (actual collection times to be recorded)
- Dexamethasone administration 8 to 12 hours after completion of PEGPH20 or placebo infusion

8.1.2.1.2. Cycle 1 Day 2

Prior to NAB and GEM Infusions (PAG and AG Groups)

- Vital signs
- Blood sample collection for plasma PEGPH20 concentration (PK) and HA analyses immediately prior to the start of NAB infusion
- Plasma sample for analysis of potential biomarkers of PEGPH20 activity

NAB and GEM Infusions (PAG and AG Groups)

Administration of NAB and GEM 24 hours (± 4 hours) after completion of Day 1 randomized study medication infusion. NAB will be given first.

- NAB IV infusion over 30 to 40 minutes
- GEM IV infusion over 30 minutes, immediately after completion of NAB infusion

- Blood sample collection for plasma NAB and GEM concentration (PK) analysis immediately after the end of the NAB infusion and immediately after the end of the GEM infusion, respectively

8.1.2.1.3. Cycle 1 Day 4

Prior to Randomized Study Medication Infusion

- Vital signs
- Dexamethasone administration within 2 hours prior to randomized study medication infusion
- Plasma PEGPH20 concentration (PK) immediately prior to the start of randomized study medication infusion
- Plasma sample for analysis of potential biomarkers of PEGPH20 activity

Randomized Study Medication Infusion

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

After Randomized Study Medication Infusion

- Dexamethasone administration 8 to 12 hours after completion of randomized study medication infusion

8.1.2.1.4. Cycle 1 Day 8

Prior to Randomized Study Medication, NAB, and GEM Infusions

- Vital signs
- Blood sample collection for the following tests:
  - Hematology
  - Blood chemistry (including CRP)
  - Plasma sample for analysis of potential biomarkers of PEGPH20 activity
- Dexamethasone administration within 2 hours prior to the start of randomized study medication infusion

Randomized Study Medication, NAB, and GEM Infusions

- PEGPH20 or placebo IV infusion over 10 to 12 minutes (approximately 1 mL/min)
- NAB IV infusion over 30 to 40 minutes, 2 to 4 hours after completion of randomized study medication infusion
- GEM IV infusion over 30 minutes, immediately after completion of NAB infusion

After Randomized Study Medication, NAB, and GEM Infusions

- Dexamethasone administration 8 to 12 hours after completion of randomized study medication infusion

8.1.2.1.5. Cycle 1 Day 11

Prior to Randomized Study Medication Infusion

- Vital signs
- Dexamethasone administration within 2 hours prior to randomized study medication infusion
- Plasma sample for analysis of potential biomarkers of PEGPH20 activity

Randomized Study Medication Infusion

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

After Randomized Study Medication Infusion

- Dexamethasone administration within 8 to 12 hours after completion of randomized study medication infusion

8.1.2.1.6. Cycle 1 Day 15

Prior to Randomized Study Medication, NAB, and GEM Infusions

- Completion by subjects of EORTC QLQ-C30, EQ-5D, and NRS
- Vital signs
- 12-lead ECG 3 times within a 5-minute period
- Blood sample collection for the following tests:
  - Hematology
  - Blood chemistry (including CRP)
- Dexamethasone administration within 2 hours prior to randomized study medication infusion

Randomized Study Medication, NAB, and GEM Infusions

- PEGPH20 or placebo IV infusion over 10 to 12 minutes (approximately 1 mL/min)
- 12-lead ECG, 3 times within a 5-minute period between 1 to 4 hours after completion of randomized study medication infusion and before the NAB infusion
- NAB IV infusion over 30 to 40 minutes, 2 to 4 hours after completion of randomized study medication infusion
- GEM IV infusion over 30 minutes, immediately after completion of NAB infusion

After Randomized Study Medication, NAB, and GEM Infusions

- Dexamethasone administration within 8 to 12 hours after completion of randomized study medication infusion

8.1.2.1.7. Cycle 1 Day 18

Prior to Randomized Study Medication Infusions

- Vital signs
- Dexamethasone administration within 2 hours prior to randomized study medication infusion

Randomized Study Medication Infusion

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

After Randomized Study Medication Infusion

- Dexamethasone administration within 8 to 12 hours after completion of randomized study medication infusion

8.1.2.2. Treatment Cycles 2 and Beyond

For Treatment Cycles 2 and beyond, the following assessments may be performed up to 2 days prior to Days 1, 8, and/or 15: physical examination, vital signs, ECOG Performance Status, weight/BSA, and clinical laboratory tests (hematology and blood chemistry).

8.1.2.2.1. Cycles 2+, Day 1

Prior to Randomized Study Medication, NAB, and GEM Infusions

Completion by subjects of EORTC QLQ-C30, EQ-5D, and NRS

- Physical examination
- Vital signs
- ECOG Performance Status
- Weight/BSA
- Single 12-lead ECG (Cycles 2-6 only)
- Blood sample collection for the following tests:
  - Hematology
  - Blood chemistry (including CRP)
  - Serum CA19-9 level
  - Plasma HA, 1 sample either before the start of randomized study medication infusion or after completion of the GEM infusion
  - Plasma sample for analysis of potential biomarkers of PEGPH20 activity (every other cycle after Cycle 2)
  - Immunogenicity (PEGPH20 ADA, NAb)
- Local laboratory urine/serum pregnancy test (WOCBP)

- Dexamethasone administration within 2 hours prior to randomized study medication infusion

Randomized Study Medication, NAB, and GEM Infusions

- PEGPH20 or placebo IV infusion over 10 to 12 minutes (approximately 1 mL/minute)
- NAB IV infusion over 30 to 40 minutes, 2 to 4 hours after completion of randomized study medication infusion
- GEM IV infusion over 30 minutes, immediately after completion of NAB infusion

After Randomized Study Medication, NAB, and GEM Infusions

- Plasma NAB and GEM concentration (PK) analysis, immediately after the end of the NAB infusion and immediately after the end of the GEM infusion, respectively - in Cycle 2 and Cycle 3 only
- Plasma HA sample collection, 1 sample after completion of the NAB/GEM infusions if not collected prior to the randomized study medication infusion (see above)
- Dexamethasone administration within 8 to 12 hours after completion of randomized study medication infusion

8.1.2.2.2. Cycles 2+, Day 8

Prior to Randomized Study Medication, NAB, and GEM Infusions

- Vital signs
- Blood sample collection for the following tests:
  - Hematology
  - Blood chemistry (including CRP)
  - Plasma sample for analysis of potential biomarkers of PEGPH20 activity (every other cycle after Cycle 2)
- Dexamethasone administration within 2 hours prior to randomized study medication infusion

Randomized Study Medication, NAB, and GEM Infusions

- PEGPH20 or placebo IV infusion over 10 to 12 minutes (approximately 1 mL/min)
- NAB IV infusion over 30 to 40 minutes, 2 to 4 hours after randomized study medication infusion
- GEM IV infusion over 30 minutes, immediately after completion of NAB infusion

After Randomized Study Medication, NAB, and GEM Infusions

- Dexamethasone administration within 8 to 12 hours after completion of randomized study medication infusion

8.1.2.2.3. Cycles 2+, Day 15

Prior to Randomized Study Medication, NAB, and GEM Infusions

- Vital signs
- Blood sample collection for the following tests:
  - Hematology
  - Blood chemistry (including CRP)
- Dexamethasone administration within 2 hours prior to PEGPH20 or placebo infusion

Randomized Study Medication, NAB, and GEM Infusions

- PEGPH20 or placebo IV infusion over 10 to 12 minutes (approximately 1 mL/min)
- NAB IV infusion over 30 to 40 minutes, 2 to 4 hours after randomized study medication infusion
- GEM IV infusion over 30 minutes, immediately after completion of NAB infusion

After Randomized Study Medication, NAB, and GEM Infusions

- Dexamethasone administration within 8 to 12 hours after completion of randomized study medication infusion

8.1.2.2.4. Cycles 2+, Day 22

No study medications will be administered. The following assessment should be completed:

- Obtain CT scan (or MRI) and send to the CIV for disease assessment at the end of Cycle 2 and at the end of every subsequent second treatment cycle after the last dose or the following week (i.e., Days 15 to 28 of Cycles 2, 4, 6, 8, and beyond), to allow for enough time for the scan to be sent to and reviewed by the CIV prior to the start of subsequent cycles. The results should be interpreted and sent to the site before dosing in the next cycle begins. If the results are not received by the site before the next cycle begins, dosing should proceed; however, if the results (when received) indicate disease progression, study medication treatment will be discontinued.

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 treatment discontinuation of all study medications (PEGPH20/placebo, GEM, and NAB) and prior to initiation of subsequent anticancer therapy. Adverse events and concomitant medications will be reviewed at this visit, and the following assessments should be completed:

- Physical examination
- Vital signs
- ECOG Performance Status
- Weight/BSA

- Obtain CT scan (or MRI) and send to the CIV - CT scans (or MRI) must be obtained if radiologic disease progression was not documented in the previous CT scan (or MRI), unless the latter was performed within the last 14 days
- Blood sample collection for the following tests:
  - Hematology
  - Blood chemistry (including CRP)
  - Immunogenicity (PEGPH20 ADA, NAb)
  - Serum CA19-9 levels
  - Plasma sample for analysis of potential biomarkers of PEGPH20 activity
- Optional tumor sample collection upon determination of disease progression

8.1.3. Long-term Follow-up

After the End of Treatment Visit, subjects will enter long-term follow-up during which information on the subject's survival status and subsequent anticancer therapy will be obtained by the site monthly. Information may be collected by chart review, phone calls, clinic visits, or other means as appropriate. Long-term follow-up will continue until the subject dies, is lost to follow-up, or withdraws consent.

8.1.4. 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. When the subject returns to the clinic, all End of Treatment procedures should be performed (see Section 8.1.2.3).

8.2. Study Assessments

All assessments will be conducted as outlined in Table 1 and Table 2.

8.2.1. Main Informed Consent

The Investigator or designee must present and explain the study protocol to prospective study subjects before Screening. The Investigator or designee must:

- Be available to answer any questions the subject may have regarding the study protocol and procedures.
- 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, review and update the ICF(s) if necessary. In such a case, all subjects, including those already being treated, should be given the new information, given a copy of the revised ICF(s), and allowed to re-evaluate their consent to continue in the study.

- Provide a copy of the signed and dated ICF(s) to the subject. The original ICF(s) will be retained by the Investigator.

8.2.1.1. Prescreening Informed Consent

In accordance with local policies and institutional guidelines, subjects may provide consent for their tumor tissue to undergo HA testing on a separate, Prescreening ICF. *Note:* all ICF-related standards and procedures (e.g., those described above for Main Informed Consent, requirements specified in Sections 14.1 and 14.2) also apply to the Prescreening ICF.

Once the subject signs the Main Study ICF, s/he can continue to participate in the study and undergo the remaining screening procedures. The 28-day screening window begins when the subject signs the Main Study ICF (i.e., signature on a Prescreening ICF does not initiate the 28-day screening window).

8.2.2. Medical History and Concomitant Medications

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) should also be captured on the Medical History eCRF page.

Concomitant medications will be collected as specified in Section 10.12.

8.2.3. Adverse Events

Adverse events will be collected as described in Section 10.

8.2.4. Eastern Cooperative Oncology Group Performance Status

The subject's performance status will be assessed using the ECOG Performance Status criteria as described in Appendix D.

8.2.5. Vital Signs, Physical Examination, and Physical Measurements

Assessment of vital signs will include the measurement of blood pressure (systolic and diastolic), pulse, respiratory rate (number of breaths/min), 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.

Physical examinations will include ears/eyes/nose/throat/neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, central and peripheral nervous system, and dermatologic body systems.

Height will be recorded in cm, and weight will be recorded in kg. Body surface area will be calculated from the height and weight.

8.2.6. 12-Lead Electrocardiogram

Electrocardiograms will be performed during this study. Electrocardiograms will be performed in triplicate within a 5-minute period during Cycle 1, and as a single ECG in Cycles 2 to 6. The Investigator's evaluation of the ECGs as normal or as abnormal without or with clinical significance will be recorded in the eCRF.

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

Blood chemistry, hematology, coagulation parameters, and urinalysis will all be analyzed by the central laboratory. C-reactive protein levels will be measured as part of the blood chemistry panel.

Central laboratory assessments are listed below:

- 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), creatinine, and CRP (as indicated above).
- 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: PT, PTT, and INR.
- Urinalysis: protein, glucose, ketones, blood, specific gravity, nitrite, pH, leukocytes.

Central laboratory testing is mandatory and must be performed; however, if central laboratory results cannot be obtained, then local laboratory results may be used to determine subject eligibility prior to randomization. In such cases, results and reference ranges of the local laboratory will take precedence over those of the central laboratory (e.g., if a subject is eligible according to the local laboratory but ineligible according to the central laboratory, then that subject would still be considered qualified for study enrollment as per protocol). **Note:** even if local laboratory results are utilized for eligibility purposes, central laboratory testing remains mandatory; samples must still be sent to the central laboratory.

Standard-of-care blood samples will be drawn before NAB and GEM dosing to confirm the subject meets the criteria for dosing (see also Section 8.3.2.3). Coagulation tests after screening, including anti-Factor Xa testing (if done) or other tests if anti-Factor Xa is not available, may be performed as per institutional policy (see also Section 10.1). The standard-of-care tests for NAB and GEM dosing and optional coagulation tests should be performed at the central laboratory. When central laboratory results cannot be obtained, local laboratory results of standard-of-care blood sampling for NAB and GEM dosing and for optional coagulation tests may be used (samples must still be sent to the central laboratory).

The Investigator must evaluate all results outside the reference range and determine the clinical significance (clinically significant or not clinically significant).

8.2.8. Pregnancy Test

A serum or urine human chorionic gonadotropin test to determine whether a female subject is pregnant should be collected for all WOCBP. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. The pregnancy test will be performed by the local laboratory within

7 days before C1D1 (first dose of study medication). Pregnancy tests will be performed locally approximately every month at the beginning of each treatment cycle (Cycles 2 and Beyond) during the study. The results must be available prior to beginning of dosing for each cycle.

8.2.9. Contraception

Highly effective methods of contraception for participating WOCBP should be used during the study treatment and up to 1 month following the last dose of any study medication and include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- True sexual abstinence (defined as refraining from heterosexual intercourse if this is aligned with the preferred and usual lifestyle of the subject). Periodic abstinence, declaration of abstinence for the duration of the trial or withdrawal should not be considered as a highly effective method of contraception and therefore are not acceptable methods of contraception.

Participating men can be fertile or vasectomized. Fertile men are advised to use condoms as a contraceptive measure during the study and until 6 months after administration of the last dose of any study medication. Fertile men are advised to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to GEM and/or NAB therapy. In addition, if the female partner of the participating male subject is of childbearing potential, this female partner should apply contraception until 1 month after the study drug has been discontinued.

8.2.10. Immunogenicity

Blood samples will be collected from all subjects and analyzed for anti-PEGPH20 ADA and NAb, as appropriate (details in the Laboratory Manual). Initial testing will be done during the study; however, samples will be stored for possible re-analysis if deemed necessary.

8.2.11. Imaging/Radiologic Evaluation of Tumor Response and Progression

Computed tomography with contrast evaluations will be performed in accordance with imaging protocols provided by the CIV (must include venous phase chest, abdomen and pelvis contrast enhanced CT). In the event that the subject is intolerant to the CT contrast agent, either a non-contrast chest CT or an iodinated contrast enhanced MRI of the abdomen and pelvis is acceptable (refer to the Imaging Manual for full directives).

All scans will be sent to the blinded CIV for disease assessment based on RECIST version 1.1 criteria.

Submission of CT/MRI to the CIV is mandatory; however, local imaging results may be used to determine subject eligibility prior to randomization.

During the study, CT scans (or MRI) will be performed and sent to the blinded CIV at the end of Cycle 2 and at the end of every subsequent second treatment cycle after the last dose or the following week (i.e., Days 15 to 28 of Cycles 2, 4, 6, 8, and beyond), to allow time for reading of the scans by the CIV prior to the start of subsequent cycles. The results should be interpreted by the CIV and sent to the site before dosing in the next cycle begins. If the results are not received by the site before the next cycle begins, dosing should proceed; however, if the results (when received) indicate disease progression, study medication treatment will be discontinued.

For subjects who are going to be withdrawn from study treatment due to clinical disease progression, the Investigator must first review the latest CIV report for tumor assessments before making a decision regarding study treatment withdrawal for the subject, and a CT scan (or MRI) should be requested as soon as possible. Additionally, whenever possible, the Investigator should consult the Medical Monitor prior to treatment discontinuation for any reason other than radiologic disease progression by CIV evaluation.

At the End of Treatment Visit, a CT scan (or MRI) must be obtained if radiologic PD was not documented in the previous CT scan (or MRI), unless the latter was performed within the last 14 days.

8.2.11.1. Chest Computed Tomography to Screen for 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). These can be the same scans that are sent to the CIV. If a subject has signs and symptoms of PE after the initial screening scan was obtained, the scan should be repeated prior to randomization (refer to Section 8.1.1).

8.2.12. Doppler Ultrasound Scanning for Assessment of Deep Vein Thrombosis

Doppler ultrasound will be performed as per Section 10.1. Bilateral Doppler ultrasound scanning of the proximal and distal veins (Doppler of distal veins must be performed if feasible) is the current standard for routine clinical assessment of possible lower extremity DVT.

8.2.13. Hyaluronan

Plasma HA may be a potential biomarker indicator of tumor burden and tumor biology and is a pharmacodynamic marker of response to PEGPH20 treatment. Baseline and post-dose HA levels in plasma and in tumor biopsy samples (including tumor tissue collected at Screening and optional postdose tumor biopsy, if obtained) will be analyzed to evaluate the PEGPH20 treatment effect on tumor response. Plasma and biopsy tissue samples for HA analysis will be collected per the study Schedule of Events (see Section 3) and sent to the central laboratory for analysis.

8.2.13.1. Tumor-Associated Hyaluronan Investigational Use Only Assay

Tumor tissue collected at Screening and during the study will be sent to a central laboratory and tested for HA levels using an affinity histochemistry investigational use only (IUO) assay. Details will be provided in a separate Laboratory Manual. For screening purposes, the result for each subject screened (i.e., "HA-High" for eligible and "HA-Low" for ineligible based on HA levels) will be sent to the sites to determine eligibility of subjects to enter the study.

8.2.13.2. Total Hyaluronan Disaccharide Assay

Hyaluronan concentrations will be analyzed in blood plasma samples as total HA disaccharide using a validated liquid chromatography-tandem mass spectrometry (LC-MS-MS) assay at a contract laboratory (refer to the study Laboratory Manual).

8.2.14. CA19-9

CA19-9 (carbohydrate antigen 19-9 or sialylated Lewis(a) antigen) is a blood test from the tumor marker category. Serum samples will be collected from all subjects to assess the effect of treatment on CA19-9 levels and sent to the central laboratory for analysis.

8.2.15. Biomarker Assessments

This study will collect samples for biomarker assessments in all subjects (where not prohibited by local regulations). Sample types collected include tumor samples, whole blood samples, and plasma samples. Any sample or derivatives (such as deoxyribonucleic acid [DNA], ribonucleic acid [RNA], and protein) may be stored for up to 15 years after study completion to assist in any research related to PEGPH20 or cancer, and for potential diagnostic development.

In addition, biomarkers identified in other clinical studies may also be assessed in the biomarker samples collected from subjects enrolled in this study. The decision to perform other biomarker assessments may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Detailed instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Biomarker samples will be collected as specified in the Schedule of Assessments (Table 1 and Table 2).

8.2.15.1. Tumor Biopsy Tissue Samples

Available tumor tissue (FFPE block preferred) with enough tumor tissue to make a minimum of 5-10 unstained, consecutive FFPE slides (10 slides are preferred) of 1 archival block that meet specific tissue sample requirements (see Study Laboratory Manual) are required for eligibility determination. Archived or fresh tissue from the primary lesion or a metastatic lesion is required. Pretreatment (Screening) tumor biopsies will be used to determine tumor HA levels and study eligibility (see Section 8.2.13).

With the subject's consent, one tumor tissue sample may be optionally obtained upon determination of progression (one archival block or at least 10 unstained, consecutive slides of one archival block or a fresh-frozen biopsy).

All tumor samples may be used to assess the pharmacodynamic effects of PEGPH20 and to assess tumor-relevant pathway dysregulation (such as mutations, amplifications) that may be important in the development and progression of cancer as well as for potential use in diagnostic development.

8.2.15.2. Pharmacogenetic Sample

One blood sample will be collected from all subjects predose in Cycle 1 Day 1 to correlate individual subject DNA sequence variation (e.g., exploratory single nucleotide polymorphism [SNP] genotyping) with safety, tolerability, and potential clinical benefit.

The information obtained is solely used to further characterize drug effects and does not have clinical diagnostic or therapeutic implications for the individual subject. The Sponsor will be blinded as to the subject's identity and since the analysis is done for research purposes only, individual results will not be shared with the Investigator and/or subject or the subject's relatives. Any information obtained is not intended for inclusion in the medical record. This research will not change the care the subject receives in this study.

8.2.15.3. Plasma Samples

Plasma samples will be collected for potential analysis of biomarkers related to PEGPH20 mechanism of action as well as for exploratory studies to determine clinical response biomarkers. The types of biomarkers may be circulating proteins, tumor-derived DNA and/or tumor microRNA. Plasma sample collection is required in all subjects.

8.2.16. Pharmacokinetic Assessments

Pharmacokinetics of PEGPH20: Plasma samples will be collected from all subjects during the study to monitor the exposure-response relationship.

Pharmacokinetics of NAB and GEM: Plasma samples will be collected from all subjects during the study to evaluate the potential effect of PEGPH20 on the PK of NAB and GEM.

Postdose time points for PK samples should be relative to the stop time of study medication infusion. If samples are collected from a central line, the line should be flushed with saline prior to the collection of the PK samples. Postdose NAB and GEM PK samples should not be collected from the same line used to administer NAB and GEM.

8.2.17. Patient-Reported Outcomes

In this study, 3 PRO measures will be used to assess the impact of treatment on the following aspects of a subject's health status: health-t related quality of life using the EORTC QLQ-C30, general health outcome using the EQ-5D; and symptoms related to pancreatic cancer and treatment-associated toxicities using a Numerical Rating Scale (NRS). The individual PRO measures are briefly described below.

Subjects will complete the PRO measures using an electronic device. This data will be considered source data. Study-site personnel will be available to answer any questions that subjects may have during completion of the PRO measures.

EORTC QLQ-C30. The EORTC QLQ-C30 is a 30-item cancer-specific instrument to evaluate health-related quality of life comprising the following: 5 functional domain scales including Physical, Role, Emotional, Social, and Cognitive; an additional 2 items to evaluate global quality of life; 3 symptom scales to assess Fatigue, Pain, and Emesis; and 6 single items to assess other symptoms (Aaronson 1993). The recall period for items is the past 7 days. The total score for the instrument ranges from 0 to 100, with a high score for a functional scale representing a high/healthy level of functioning and a high score for a symptom scale or item representing a high level of symptomatology or problems (Fayers 2001).

EQ-5D. The EQ-5D is a generic measure of health outcome, and its use is a requirement of the National Institute for Health and Care Excellence (NICE). It consists of 6 items that cover 5 main domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; and a general visual analog scale (VAS) for health status. The recall period is "today." Domain scores range from 0 to 1, with a score of 0 indicating death and score of 1 indicating a perfect state; and the VAS is scored on a scale of 0 to 100, with higher scores signaling better health-related quality of life. EQ-5D scores have demonstrated to be significantly predictive of OS and clinical severity in pancreatic cancer patients (Pickard 2007, Pickard 2012, Romanus 2012).

NRS. The NRS is a non-standard unidimensional scale designed to capture symptoms related to pancreatic cancer and to treatment-associated toxicities that are not covered among the EORTC QLQ-C30 items and are deemed relevant based on a review of the literature. The NRS scale comprises 6 items: abdominal pain, neuropathy, taste alteration, peripheral edema, myalgia, and muscle spasms. The respondent selects a whole number (0-10 integers) that best reflects the outcome of interest.

8.3. Study Drug Administration

Randomized study medication (PEGPH20 or placebo for the PAG or AG treatment group, respectively) and NAB and GEM (both treatment groups) will be administered as specified in the Schedule of Events (Table 2) and in Table 3.

Missed or Held Doses of Study Medication

Guidelines regarding delayed and/or missed doses of study drugs are depicted schematically in Appendix E and outlined below.

- **Cycle 1**
  - **Day 1**: If dose of randomized study medication (PEGPH20/placebo) is delayed, Cycle 1 does not start. Cycle 1 starts when the subject receives the first dose of randomized study medication on Study Day 1 (C1D1). The Treatment Period of this study begins on C1D1 and the ±2 day Visit Window is based on the date of first dose administration.
  - **Day 2**: If one of the chemotherapy medications (NAB or GEM) is held, the other study medications may be given.
  - **Day 4, Day 11, or Day 18**: If PEGPH20/placebo is held, then cycle continues; NAB and/or GEM can be administered.
  - **Day 8 or Day 15**: see below ("Any Cycle").

- **Cycle 2 and Beyond**
  - **Day 1**:
    - If PEGPH20/placebo is held, then cycle continues; NAB and/or GEM can be administered.
    - If both NAB *and* GEM are held, then PEGPH20/placebo will also be held.
    - If only 1 of the chemotherapy drugs (NAB *or* GEM) is held, then PEGPH20/placebo can be administered.
  - **Day 8 or Day 15**: see below ("Any Cycle").

- **Any Cycle**
  - **Day 8 or Day 15**:
    - If PEGPH20/placebo is held, then cycle continues; NAB and/or GEM can be administered.
    - If one or both chemotherapy medications (NAB and/or GEM) is held, then the cycle continues; PEGPH20/placebo can be administered.

If both NAB and GEM are missed or held on Day 1 of Cycles 2+, randomized study medication must also be held; however, randomized study medication may be given alone or in combination with either or both NAB and GEM on Days 8 and 15 of any cycle.

If randomized study medication is held during any treatment cycle (except Cycle 1, Day 1), NAB and GEM may still be given according to the protocol-specified schedule if the subject meets all related criteria for dosing per current NAB and GEM Prescribing Information.

If one of the chemotherapy medications (NAB or GEM) is held, the other study medications may be given.

If NAB is held on Day 2 of Cycle 1, GEM should be administered 24 hours (± 4 hours) after administration of randomized study medication. 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 administration of randomized study medication.

If any dose (randomized study medication, NAB, and/or GEM) is missed on Day 8 or Day 15 of any cycle, the cycle will continue as scheduled with the subject having missed that dose or all doses skipped if medically necessary; this is also applicable for any doses missed on Day 4, Day 11, or Day 18 of Cycle 1.

Whenever possible, the Investigator should contact the Medical Monitor prior to discontinuing the subject from study treatment.

Refer to Section 7.3.1 for details regarding how to proceed if:

- all study medications have been permanently discontinued;
- any study medication(s) has been interrupted for longer than 28 days.

8.3.1. Randomized Study Medication

The PEGPH20 dose/placebo will be individually calculated at each dosing visit according to the subject's screening weight. When calculating the dose, there will be no downward adjustment to "ideal" body weight. Doses should be readjusted 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 unblinded study site pharmacist will prepare the doses of study medication per instructions provided in a separate Pharmacy Manual.

After completion of predose activities, randomized study medication 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 study staff. The volume and/or duration of randomized study medication administration may change at the discretion of the Sponsor, based upon safety information. The study nurse or designee will record the time the infusion was started and stopped. A saline flush should follow IV delivery of the complete randomized study medication infusion as per standard of care for flushing IV lines. Only a peripheral line should be used for the administration of randomized study medication. Heparin flushes should not be used on the same line as randomized study medication but 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, in which case the clinic staff should ensure the line is flushed with saline (minimum of 10 cc) prior to and after administering randomized study medication. The study site staff should ensure that randomized study medication is not administered 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 randomized study medication administration).

8.3.1.1. Hypersensitivity to Randomized Study Medication

In the event of a hypersensitivity reaction, the randomized study medication infusion should be stopped, and the symptoms should be treated as necessary. The Sponsor should be contacted immediately (see the Study Manual for contact information) so that blood draw timing and current knowledge of laboratory testing could be provided to the site. Blood should be drawn and analyzed at a laboratory which will be specified in separate instructions to the sites, to confirm the reaction (e.g., PEGPH20-specific immunoglobulin E [IgE] and serum tryptase levels).

At the Investigator's discretion and after discussion with the Sponsor, a rechallenge for the next visit may be performed 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 treatment and enter long-term follow up. 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 rechallenge should be performed after premedication with a combination of IV diphenhydramine, IV H2 blockers (such as famotidine), and IV dexamethasone. If the hypersensitivity reactions occur at the rechallenge, the subject should be discontinued from treatment and enter long-term follow up.

8.3.1.2. Randomized Study Medication Dose Modification Guidelines

Randomized study medication dose adjustments are allowed based on toxicities that are deemed related, possibly related, or probably related to blinded study medication. See Table 6 for guidelines.

Multiple times of dose reductions and rechallenges are allowed for the randomized study medication. The lowest dose level for dose reduction is 1.6 µg/kg.

Table 6: Randomized Study Medication Dose Adjustment and Toxicity Management Guidelines (HALO-109-301)

Event	Management/Action
Musculoskeletal Events	
Any Grade 1 MSEs	No change in dose of randomized study medication. May give additional dexamethasone, muscle relaxer, or pain medication.
Any Grade 2 intermittent muscle cramps or other types of MSEs	No change in dose of randomized study medication or dosing frequency required, but may reduce the dose to 1.6 µg/kg or decrease the dosing frequency of randomized study medication upon agreement with the Sponsor if the MSEs are persistent and resolve 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 with randomized study medication. If MSE resolve to ≤ Grade 2 within 14 days, may resume treatment at 1.6 µg/kg randomized study medication and/or decrease the dosing frequency of randomized study medication to once weekly (in Cycle 1) upon agreement with the Sponsor. For Grade 4 MSEs, continuation of treatment must be discussed with the Medical Monitor prior to restarting treatment at 1.6 µg/kg randomized study medication once weekly.
Any Grade 3 or 4 MSEs	Hold treatment if the MSEs do not resolve (as noted above) and remain Grade 3 or 4 for > 14 days. Treatment with randomized study medication may resume at 1.6 µg/kg upon agreement with the Sponsor if the MSEs resolve to ≤ Grade 2.
All Non-MSE Events (Except TE Events) Potentially Related to Randomized Study Medication	
Grade 1 or 2	No change.
Grade 3	Hold treatment with randomized study medication. Treatment may resume at the same dose level/volume if toxicity is resolved to baseline within 28 days. Treatment with randomized study medication may resume at 1.6 µg/kg or the dosing frequency may be reduced upon agreement with the Sponsor if toxicity is reduced to ≤ Grade 2 within 14 days.
Grade 4	Hold treatment with randomized study medication. If toxicity is resolved to ≤ Grade 2 or baseline, treatment may resume at 1.6 µg/kg or at a reduced dosing frequency, at the Investigator's discretion after discussion with the Sponsor.

Table 6: Randomized Study Medication Dose Adjustment and Toxicity Management Guidelines (HALO-109-301) (Continued)

Event	Management/Action
Thromboembolic Events (Regardless of Relatedness to Randomized Study Medication)	
Grade 1 Superficial Vein Thrombosis	No change.
Visceral/Splanchnic Vein Thrombosis (associated with underlying disease of metastatic pancreatic cancer)	No change.
Any Grade TE Event (Except: Superficial Vein Thrombosis; Visceral/Splanchnic Vein Thrombosis [associated with underlying disease of metastatic pancreatic cancer])	Discontinue randomized study medication treatment permanently and treat event per NCCN guidelines until documented resolution of event. Treatment with NAB and GEM may continue as deemed appropriate by the Investigator.

Abbreviation: MSEs = musculoskeletal events; NCCN = National Comprehensive Cancer Network; TE = thromboembolic.

8.3.2. Nab-paclitaxel and Gemcitabine

Premedications for chemotherapy are permitted per institutional guidelines.

The dose and schedule for NAB and GEM are per respective PI with the exception that the first doses of NAB and GEM will be given on Day 2 instead of Day 1 (Abraxane® US Prescribing Information 2015, Gemzar® US Prescribing Information 2017, Abraxane® EU Summary of Product Characteristics (SmPC) 2018, Gemcitabine EU SmPC 2016).

8.3.2.1. Nab-paclitaxel Administration

The NAB dose will be individually calculated for all infusion visits according to the subject's screening BSA. When 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. Refer to the Nab-paclitaxel PI for dosing administration directions.

NAB will be administered by IV infusion at a dose of 125 mg/m^2 over 30 to 40 minutes (study sites may follow standard-of-care dosing windows). NAB will be administered before GEM.

8.3.2.2. Gemcitabine Administration

The GEM dose will be individually calculated for all infusion visits according to the subject's screening BSA. When 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. Refer to the Gemcitabine PI for dosing administration directions.

GEM will be administered by IV infusion at a dose of 1000 mg/m^2 over 30 minutes (study sites may follow standard-of-care dosing windows). GEM will be administered immediately after completion of the NAB infusion.

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

Subjects should be monitored using standard-of-care central laboratory results prior to each NAB and GEM dose (additional details in Section 8.2.7). Dose reductions are permitted as outlined in Table 7; however these may be superseded by potential updates in the GEM or NAB PI or EU SmPC. Study treatment should be discontinued if a subject experiences toxicity that requires more than 2 dose reductions.

For the purpose of this study protocol, treatment with NAB and GEM should be modified according to the dose modification guidelines outlined in Section 8.3.2.3.1 and Section 8.3.2.3.2, although these may be superseded by updates in the NAB or GEM US PI and EU SmPC and notwithstanding potential differences in the NAB/GEM labels approved in other geographical regions. The guidelines provided in Table 7, Table 8, and Table 9 are derived from the Abraxane® US Prescribing Information 2015, Gemzar® US Prescribing Information 2017, Abraxane® EU SmPC 2018, and Gemcitabine EU SmPC 2016. For additional guidance, refer to the current NAB and GEM US PI and EU SmPC for current prescribing information and toxicity profiles.

Table 7: Nab-paclitaxel and Gemcitabine Dose Level Reductions (HALO-109-301)

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
First dose reduction	100	800
Second dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Source: Abraxane® US Prescribing Information 2015, Gemzar® US Prescribing Information 2017, Abraxane® EU SmPC 2018, and Gemcitabine EU SmPC 2016.

Dose re-escalations for NAB and GEM are allowed as per current NAB and GEM US Prescribing Information and EU SmPC and/or institutional guidelines.

8.3.2.3.1. Dose Modification Guidelines for Nab-paclitaxel and Gemcitabine (HALO 109-301)

Recommended dose modifications for subjects with adenocarcinoma of the pancreas are outlined in Table 8 for non-hematologic Adverse Drug Reactions and in Table 9 for hematologic Adverse Drug Reactions. Dose reductions are also allowed as per current NAB and GEM US Prescribing Information and EU SmPC and/or institutional guidelines.

Table 8: Dose Modification Guidelines for Non-Hematologic Adverse Drug Reactions for Subjects with Adenocarcinoma of the Pancreas (HALO-109-301)

Non-Hematologic Adverse Drug Reaction	Nab-paclitaxel Dose Modification	Gemcitabine Dose Modification
Febrile neutropenia Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1,500 cells/mm^3; resume at next lower dose level	
Peripheral neuropathy Grade 3 or 4	Withhold until toxicity improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous toxicity Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal toxicity Grade 3 mucositis or diarrhea	Withhold until toxicity improves to ≤ Grade 1; resume at next lower dose level	
Moderate to Severe hepatic impairment	Refer to current NAB US Prescribing Information and EU SmPC	Refer to current GEM US Prescribing Information and EU SmPC

Abbreviations: ANC = absolute neutrophil count; EU = European Union; GEM = gemcitabine; NAB = nab-paclitaxel; SmPC = Summary of Product Characteristics; US = United States.
Source: Abraxane® US Prescribing Information 2015, Gemzar® US Prescribing Information 2017, Abraxane® EU SmPC 2018, and Gemcitabine EU SmPC 2016.

Table 9: Dose Recommendation and Modification Guidelines for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle for Subjects with Adenocarcinoma of the Pancreas (HALO-109-301)

Cycle Day (any cycle)	ANC (cells/mm^3)		Platelets Count (cells/mm^3)	Nab-paclitaxel/Gemcitabine
Day 1	< 1,500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1,000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: if Day 8 doses were given without modification				
	500 to < 1,000	OR	50,000 to < 75,000	Treat with Day 8 dose level and follow with WBC growth factors OR Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: if Day 8 doses were reduced or given without modification				
	≥ 1,000	AND	≥ 75,000	Return to Day 1 dose levels and follow with WBC growth factors OR Treat with same doses as Day 8
	500 to < 1,000	OR	50,000 to < 75,000	Treat with Day 8 dose levels and follow with WBC growth factors OR Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: if Day 8 doses were withheld				
	≥ 1,000	AND	≥ 75,000	Return to Day 1 dose levels and follow with WBC growth factors OR Reduce 1 dose level from Day 1
	500 to < 1,000	OR	50,000 to < 75,000	Reduce 1 dose level and follow with WBC growth factors OR Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

Abbreviations: ANC = absolute neutrophil count; WBC = white blood cells.
Source: Abraxane® US Prescribing Information 2015, Gemzar® US Prescribing Information 2017, Abraxane® EU SmPC 2018, and Gemcitabine EU SmPC 2016.

8.3.2.3.2. Toxicity Management Guidelines

- Prophylaxis against sepsis: At the occurrence of fever >38.5°C (regardless of neutrophil count), the subjects should contact their physician and begin treatment with oral antibiotics per institutional guidelines (e.g., ciprofloxacin 500 mg PO twice per day or levofloxacin 500 mg PO once a day). It is advised that all subjects should be given a prescription for the appropriate antibiotics so they can immediately begin treatment with the first appearance of the fever.
- Colony stimulation factors: These should be given according to institutional guidelines and as outlined in Table 9.
- Interstitial pneumonitis: This can be seen with either NAB or GEM or the combination. Study medications should be immediately discontinued. If an infection etiology is ruled out, corticosteroids should be initiated.
- Posterior reversible encephalopathy syndrome (PRES): GEM should be permanently discontinued and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.
- Capillary leak syndrome: GEM should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy.

8.4. Excluded Concomitant Medications and Study Restrictions

Concurrent chronic use of IV heparin is prohibited; however, for acute TE events, IV heparin may be used.

Use of megestrol acetate and any megestrol acetate-containing drugs is prohibited. Live vaccines are prohibited during the study and for 4 weeks following the last study treatment administration.

Palliative radiotherapy is to be used with caution. Other radiotherapy is not allowed as per the exclusion criteria.

The metabolism of paclitaxel is catalyzed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

Any other anticancer 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 in long-term follow-up for survival/subsequent anticancer therapy).

8.5. Treatment Compliance

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

8.6. Randomization and Blinding

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 2:1 ratio to PAG or AG treatment. Randomization will be stratified by geographic region (North America, Europe, and Others).

Randomization will be performed using a centralized IWRS. At registration, the IWRS will assign a unique 9-digit subject identification number. The first 4 digits identify the study site and are followed by a hyphen; the last 5 digits represent the subject at that 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.

This study is double-blinded, i.e., the subjects, Sponsor, and Investigator and study site personnel, except the site pharmacist who will be preparing the doses of study medication, will be blinded to treatment during the treatment period of the study. Every effort should be made to ensure that subjects remain blinded to their treatment.

9. STUDY DRUG AND MATERIALS

9.1. Study Drug Description

9.1.1. PEGPH20 and Placebo

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/B or PEG) and rHuPH20. PH20 and PEG are covalently linked via a stable amide bond between PEG and the N-terminal amino group or the ε-amino groups present on lysine amino acid side chains of rHuPH20.

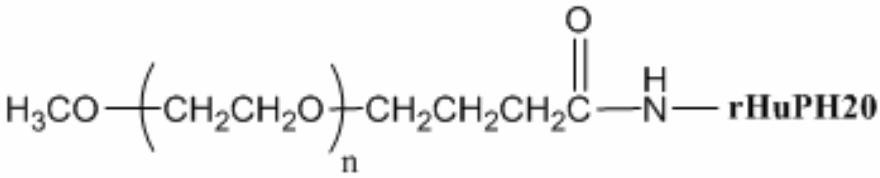
Chemical Name

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

Structural Formula

The structure of PEGPH20 is represented in Figure 3.

Figure 3: Structure of PEGPH20



PEGylated rHuPH20

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

Matching placebo for PEGPH20 will be a normal saline solution for IV administration. Refer to the Pharmacy Manual for additional information.

9.1.2. Nab-paclitaxel

Nab-paclitaxel (ABRAXANE®) is an albumin-bound form of paclitaxel, a microtubule inhibitor approved by FDA and other international regulatory agencies as a single agent for the treatment of metastatic breast cancer and locally advanced or metastatic non-small cell lung cancer; and in combination with GEM as a first-line treatment for metastatic adenocarcinoma of the pancreas.

Refer to the Nab-paclitaxel PI for a thorough description and indications of NAB.

9.1.3. Gemcitabine

Gemcitabine (GEMZAR®) is a nucleoside analogue that exhibits anti-tumor activity. It is approved by the FDA and other regulatory agencies as a single agent as first-line treatment for subjects with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. GEM is also indicated for patients previously treated with 5-FU. GEM is also indicated in combination with NAB as a first-line treatment for metastatic adenocarcinoma of the pancreas.

Refer to the Gemcitabine PI for a thorough description and indications of GEM.

9.2. Study Drug Packaging and Labeling

9.2.1. PEGPH20 and Placebo

PEGPH20 drug product 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 mL (0.3 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.

The current investigational PEGPH20 material will be administered initially in this study. When the commercial-scale material becomes available and after it has been deemed to have met all comparability criteria, it will be used in this study.

Placebo will be a normal saline solution and will be provided by the clinical study site.

9.2.2. Nab-paclitaxel

Nab-paclitaxel 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

Gemcitabine powder and gemcitabine concentrate, either generic or branded, are both acceptable for use in this study.

Gemcitabine powder. Gemcitabine powder is a white to off-white lyophilized powder for reconstitution with 0.9% Sodium Chloride Injection without preservatives. Gemcitabine powder is supplied in sterile single-use vials as follows:

- 200 mg white to off-white, lyophilized powder in 10-mL vials.

- 1 g white to off-white, lyophilized powder in 50-mL vials.

Gemcitabine concentrate. Gemcitabine concentrate will be provided as a sterile solution 1 g/26.3 mL (38 mg/mL) in a single-use glass vial per package. This sterile solution is concentrated and must be diluted before use.

9.3. Study Drug Storage

Temperature logs must be maintained for all study drugs (randomized study medication, NAB, and GEM).

9.3.1. PEGPH20

PEGPH20 drug product, 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 International Conference on Harmonisation (ICH) guidelines at 5°C ± 3°C, and concurrent stability evaluation is ongoing. The Sponsor will monitor drug stability and provide updates on an ongoing basis.

Placebo: not applicable.

9.3.2. Nab-paclitaxel

Nab-paclitaxel 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

Gemcitabine powder. Gemcitabine lyophilized powder should be stored at controlled room temperature from 20°C to 25°C (68°F to 77°F). Allowance for temperature excursions between 15°C and 30°C (59°F and 86°F) is noted in the respective package insert. Retain in the original package to protect from bright light.

Gemcitabine concentrate. Unopened vials of gemcitabine injection are stable until the expiration date indicated on the package when stored at 2°C to 8°C (36°F to 46°F). Do not freeze.

9.4. Study Drug Preparation

9.4.1. PEGPH20

PEGPH20, 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 PEGPH20 and placebo must be stored and kept for reconciliation by an unblinded study drug 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.

All doses of PEGPH20 and placebo will be prepared by the unblinded study site pharmacist. Refer to the Pharmacy Manual for additional information.

9.4.2. Nab-paclitaxel

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

9.4.3. Gemcitabine

Refer to the appropriate gemcitabine powder or gemcitabine concentrate PI for the most current drug preparation and handling guidelines.

9.5. Study Drug Accountability

The unblinded site pharmacist or qualified designee is responsible for making an inventory of study medication(s) upon their receipt. All used and unused study medication supplies should be retained until final reconciliation or as indicated by the Sponsor, or as per Institution policy. The study medications are 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 medications to be used other than as directed by this protocol. Although appropriate personnel may be designated to administer/dispense study medication and maintain drug accountability records, the Principal Investigator is ultimately responsible for all drug accountability.

The unblinded pharmacist must maintain accurate records of the receipt and disposition of study medication supplies. Documentation of drug disposition should identify the subject receiving the study medication, the amount and date of the dose, and any unused medication. These records will be reviewed by the unblinded study drug monitor. A copy of the reconciled drug inventory record will be provided to the Sponsor or its designee, and the study site will retain the original record.

After study medication is reconciled by the unblinded study drug monitor, medication 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 (PEGPH20 ADA, NAb), hematology, blood chemistry, coagulation, and urinalysis results; physical examination findings; vital signs; ECG results; pregnancy test results; and ECOG Performance Status.

10.1. Management of Thromboembolic Events

To minimize the occurrence of TE events, subjects will be managed proactively.

Doppler ultrasound of both legs (Section 8.2.12) and Chest CT (Section 8.2.11.1) will be performed during screening to exclude subjects with DVT and PE.

Low-molecular-weight heparin, specifically enoxaparin, will be administered to all subjects while they are receiving study treatment (see Section 10.1.1). If a subject is on a different LMWH or other anticoagulant (e.g., warfarin) prior to study entry, the subject should be switched over to enoxaparin. In the event the Investigator feels that an alternative LMWH is beneficial to the subject, the Investigator should obtain written pre-approval from the Sponsor or its designee, and if pre-approval is granted, this will not be considered a deviation from the protocol.

If a TE event, such as DVT or PE, is detected before the first dose of study treatment, randomized study medication will not be given; if a TE event is detected during study treatment, randomized study medication will be discontinued. In both cases, the subject may continue on chemotherapy alone per Investigator's decision. The exception is that superficial vein thrombosis or visceral/splanchnic vein thrombosis associated with underlying disease of metastatic pancreatic cancer (i.e., the primary or metastatic disease is in reasonable proximity to the thrombosis, and the Investigator determines that the thrombosis is due to a local tumor event and not a coagulation issue) do not require permanent discontinuation of randomized study medication (refer to Table 6 for further details).

The TE event should be managed per Investigator's decision and standard clinical practice (i.e., standard-of-care/current NCCN guidelines).

If randomized study medication is continued (in case of superficial vein thrombosis or visceral/splanchnic vein thrombosis associated with underlying disease of metastatic pancreatic cancer), then enoxaparin or other LMWH must be continued and may be increased to a therapeutic level. Alternatively, IV heparin may be used for acute management of the TE event, in which case randomized study medication should be held during IV heparin treatment and can be restarted once the IV heparin is stopped and LMWH is restarted.

Anti-Factor Xa testing may be performed at the central or a local laboratory pre-and postdose to verify that the dose of enoxaparin is correct at the Investigator's discretion per institutional guideline (Section 10.1.1).

Other tests may be performed as per institutional policy if anti Factor Xa is not available locally.

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

10.1.1. Enoxaparin Management

All subjects will self-administer enoxaparin SC at a dose of 1 mg/kg/day, as in Study 109-202 (see Section 4.4.4) and the study conducted by Riess et al. (see Section 4.3; Riess 2010). On dosing days, enoxaparin will either be self-administered by subjects or administered by study site personnel prior to the infusion of randomized study medication. The dosage of enoxaparin will be based on the subject's screening weight and should be modified if the subject's weight changes by 10%, or per Institution policy. Institution's rounding practices may be used when calculating the dose of enoxaparin. If prefilled syringes of enoxaparin are used, rounding may be performed. Efforts should be made to administer the dose as close to 1.0 mg/kg (± 10%) as possible; however, if prefilled syringes are used, the treating physician may use medical judgment regarding the appropriate prefilled syringe. If the difference between the rounded dose and the expected dose based on weight is greater than 20%, the Sponsor should be consulted. Refer to Table 10 for examples of rounding based on the expected enoxaparin dose.

Table 10: Enoxaparin Dosing (HALO-109-301)

Expected Enoxaparin Dose (mg)	Rounded Enoxaparin Dose (mg)	Syringes Dispensed
35-49	40	40 mg ×1
50-69	60	60 mg ×1
70-89	80	80 mg ×1
90-109	100	100 mg × 1
110-134	120	120 mg × 1
135-164	150	150 mg ×1

Hematology assessments will be performed weekly in the first 3 weeks of each cycle, and coagulation tests will be performed at baseline (Screening) and upon determination of disease progression (Section 8.1 and Table 2). Enoxaparin should be held if the platelet (plt) count is <50,000 plt/mm^3 and should be resumed once the platelet count is above 50,000 plt/mm^3. The 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. The Sponsor should be consulted if the Investigator does not feel the dose of enoxaparin should be restarted at a dose of 1.0 mg/kg.

Details on enoxaparin dosing/management for TE events are provided in Section 10.1.

In situations when enoxaparin is held, administration of randomized study medication should be stopped during the holding period. Abraxane and GEM therapy may continue per Investigator's decision.

Subjects who permanently discontinue enoxaparin therapy for any reason (refer to the enoxaparin PI) will be permanently withdrawn from study treatment with randomized study medication (See Section 7.3.1).

Enoxaparin treatment may be continued per Investigator's decision and standard-of-care when randomized study medication is permanently discontinued.

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 medication), whether or not considered related to the pharmaceutical product. The maximum severity grade of AEs or the worsening of a pre-existing medical condition occurring during the study should be recorded, regardless of relationship to study medication. See Section 10.5 for additional information.

The recording of AEs will begin at the start of the administration of the first dose of a study medication, with the exception of study procedure-associated SAEs. Any AE that occurs after the time of ICF signature (Main Study or Prescreening ICF, whichever is first) will be recorded as an SAE if the event is associated with a study procedure and meets criteria for seriousness, even if the subject has not yet received any study medication.

An 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 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 NCI CTCAE Version 4.03 (at time of study initiation) should be used when grading TE events. Table 11 denotes the most commonly reported TE events and the associated grading scale per CTCAE Version 4.03 (14 June 2010).

Table 11: 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 diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
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.					

Table 11: CTCAE Version 4.03 Grading for Thromboembolic Events (Continued)

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
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 replacement indicated	Deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Embolic event including pulmonary embolism or life threatening thrombus	Death
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Source: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 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 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, the event should be reported immediately to the safety contact and recorded as an AE or SAE.

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

10.5. Adverse Events

Events that occur before the first administration of study medication are not considered AEs, by definition (Section 10.2); these events will be recorded on the Medical History eCRF. However, as noted in Section 10.2, any study procedure-associated events occurring after the subject has

signed the Prescreening ICF and/or Main Study ICF (including prior to administration of study medication) should be recorded if the event is considered serious.

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 medication (except for study procedure-associated SAEs) and no later than 30 days after the last study medication dose. However, there is no limit on reporting SAEs considered reasonably related to study medication (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 medication 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, syndromes rather than individual signs or symptoms should be recorded, 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, individual clinical signs and symptoms should be recorded.

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, the Sponsor 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, whether or not serious, that result in permanent withdrawal from study treatment should be immediately reported to the Sponsor (Section 10.3).

The Sponsor will conduct reviews of all available AEs at a minimum of once every 3 months.

10.5.1. Classification of Adverse Events by Severity

The Investigator must categorize the severity of each AE using the CTCAE Version 4.03 (at time of study initiation).

It is 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 randomized study medication, NAB, and/or GEM. The Investigator should make this decision after careful consideration of the following:

- Does the AE follow a reasonable temporal sequence from administration of study medication?
- 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 medication or reduction in study medication 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 medication is re-administered?
- Does the AE follow an expected response pattern based on the established pharmacologic and toxicologic effects of the study medication?
- 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 medication administration.
- **Probably Related:** There is a high degree of certainty that the AE is related to study medication administration.
- **Possibly Related:** The AE could be related either to study medication administration or to concurrent disease/medication.
- **Unlikely Related:** There is a high degree of certainty that the AE is NOT related to study medication 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 medication may have interfered with the effectiveness of the contraceptive medication. Any pregnancy during the use of study medication and within 30 days of study medication 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 medication administration information. 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 medication 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 medication (or partner of a male subject who may become pregnant while the male subject is on study) until final resolution (delivery, miscarriage, or early termination of the pregnancy). Follow-up should occur monthly and should be documented in the study file. A follow-up Pregnancy Report Form must be completed for each follow-up contact with the subject (or partner of a male subject who may have become pregnant while the male subject is on study) 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

Randomized study medication, 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 must 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. **Contact the 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 of randomized study medication 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 respective PI.

Dosing details should be captured in the eCRF. If the subject receives a dose of a study medication 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 data to protect subject welfare and identify potential safety signals. Operational and logistical details will be provided in a separate DMC charter.

10.10. Unblinding

This study is double-blinded, i.e., the subjects, Sponsor, and Investigator and study site personnel, except the site pharmacist will be blinded to treatment during the treatment period of the study.

No member of the study team at Halozyme, the study sites, or any Contract Research Organization (CRO) handling data will have access to the subjects' treatment assignment until the time of final data analysis. Exceptions are relevant persons within the Sponsor's Clinical Trial Materials, Drug Safety & Pharmacovigilance, and Clinical Operations departments; within the CROs; and the pharmacists required to dispense the study drug at study sites.

In emergency situations that require a subject's treatment assignment to be disclosed in the interest of subject safety, the Investigator may break the treatment code to optimize the clinical management of the subject; the Investigator should contact the Medical Monitor to discuss the situation and, whenever possible, do so before breaking the treatment code. In this case, the treatment allocation shall only be shared if necessary, and if feasible, with personnel involved in the clinical management of the subject. Personnel exclusively involved in the clinical trial conduct, e.g., study coordinators, study nurses, and representatives from CRO/Sponsor, shall remain blinded to the treatment allocation.

The Sponsor will be notified via the Interactive Web Response System (IWRS) once the treatment code is broken and will remain blinded to the treatment allocation.

The DMC will be provided with unblinded data for their review, but the Sponsor's personnel (with the aforementioned exceptions) and Investigators directly involved in the conduct of the study will remain blinded.

10.11. Reporting Safety Information to the Regulatory Authorities and to the Institutional Review Board

The Sponsor will determine if SAEs are suspected unexpected serious adverse reactions (SUSARs), and if so will expedite reporting to Regulatory Authorities according to applicable Clinical Trials Regulations.

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 subjects receive during the study, other than a designated study medication (PEGPH20, placebo, NAB, and GEM), is regarded as concomitant medication. Study site personnel should record concomitant medications taken after the subject signs the ICF during the screening period prior to Study Day 1 through 30 days after the End of Treatment Visit on the Concomitant Medications eCRF.

Study site personnel should 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, they should ask subjects if there have been any changes in their prescription or nonprescription medications since their last visit.

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

Dexamethasone administered per protocol, as well as non-steroidal anti-inflammatory drugs, and/or cyclobenzaprine, which may be used for musculoskeletal symptoms, should be documented as concomitant medications. Enoxaparin, administered per protocol to minimize the occurrence of TE events, should also be documented as a concomitant medication. Granulocyte-colony stimulating factor is allowed, at the Investigator's discretion, for the treatment of hematologic toxicities including thrombocytopenia (Section 8.3.2.3.1 and Table 9).

10.12.1. Dexamethasone

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

Per protocol, dexamethasone 8 mg will be administered preferably PO within 2 hours prior to beginning each randomized study medication (PEGPH20 or placebo) infusion and 8 to 12 hours after completion of the randomized study medication infusion (total dose of 16 mg on dosing days). Subject will self-administer dexamethasone PO unless given by study site personnel. Parenteral administration is allowed if the subject cannot tolerate oral dexamethasone.

Additional doses of dexamethasone (PO, intramuscular [IM], or IV) may be given 24 hours prior to infusions of randomized study medication or at any other time at the discretion of the Investigator based on tolerability. The Investigator may adjust (increase or decrease) the dose and/or frequency of dexamethasone based on the clinical need (e.g., tapering off if subject is tolerating study medication).

10.12.2. Enoxaparin

Per protocol, enoxaparin will be administered SC at a dose of 1 mg/kg/day during the treatment period.

Refer to the current enoxaparin PI for prescribing information and toxicity profile and to Section 10.1.1 for additional details on enoxaparin management.

11. STATISTICS

11.1. Statistical Methods

In general, continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum (min), maximum (max), and quartiles). Categorical variables will be presented using frequencies and percentages. Results will be displayed for the 2 treatment groups as well as the 2 groups combined (total). All statistical analyses and data listings will be performed using SAS (Cary, NC).

11.1.1. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled, multicenter study.

Eligible subjects will be randomized in 2:1 ratio to receive either PAG or AG treatment. Randomization will be stratified by geographic region (North America, Europe, and Others).

The Sponsor, Investigator, study site personnel, and subjects will be blinded to the treatment that each subject will receive. To minimize bias to the PFS endpoint, disease progression will be based on the tumor assessment by the blinded CIV.

11.1.2. Sample Size

This study is event driven. Approximately 500 eligible subjects will be randomized to receive PAG or AG in 2:1 ratio. No interim efficacy analysis will be conducted. The study is powered for the final OS with 330 deaths. The statistical power and sample size calculations below are based on the comparison of treatment difference in OS between PAG and AG groups and obtained from East 6.3.1, Cytel Inc.

The median OS in the AG group is expected to be approximately 8.5 months (Von Hoff 2013). If PAG therapy improves median OS by 50% to 12.7 months with an HR of 0.67, the study will have 93% statistical power to show statistically significant improvement in OS at the significance level of 0.05 at the final OS analysis based on a 2-sided log-rank test after 330 deaths have been observed.

11.1.3. Analysis Populations

11.1.3.1. Intent-to-Treat (ITT) Population

All randomized subjects will be included in the ITT Population. The ITT population will be analyzed by treatment randomized. This population will be used for all efficacy analyses as well as for analyses of subject disposition, protocol deviations, and demographic and baseline characteristics.

11.1.3.2. Safety Population

All subjects who receive any study medication will be included in the Safety Population. The Safety population will be analyzed by treatment received. This population will be used for all safety analyses as well as for demographic and baseline characteristics.

11.1.3.3. PK Analysis Population

All subjects who receive any part of a dose of PEGPH20 and have at least 1 measurable PEGPH20 concentration will be included in the PK Analysis Population for the PK analysis of PEGPH20.

All subjects who receive any part of a dose of NAB and GEM in both treatment groups (PAG and AG) and have at least 1 measurable NAB and GEM concentration will be included in the PK Analysis Population for the PK analysis of NAB and GEM.

Blood samples for the aforementioned analyses deemed to be below the limit of quantitation (BLQ) will be included in the PK analyses, and the BLQ value will be handled accordingly by the modeling software.

11.1.4. Subject Disposition

Subject disposition data (including analysis populations) will be summarized for each treatment group and overall for all randomized subjects.

Subject disposition will be tabulated for number of subjects randomized, receiving any study treatment, on study treatment, discontinuing from treatment and reasons for discontinuing treatment, and discontinuing from the study and reasons for discontinuing from the study.

Enrollment by country and center, major protocol deviations, and the number of subjects randomized to each stratum will also be summarized.

In addition, the screening information will be summarized, including number of subjects screened, subjects with screening failure, and reasons of screening failure.

11.1.5. Analysis of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using both ITT and Safety Populations. The following demographic and baseline characteristics will be summarized by treatment group: age, race, ethnicity, country of residence, height, weight, BSA, ECOG Performance Status, medical history, disease characteristics, and treatment history.

11.1.6. Efficacy Analyses

The primary efficacy endpoint is OS, and the secondary efficacy endpoints are PFS, ORR, and DOR. All efficacy endpoints will be analyzed using the ITT population.

11.1.6.1. Type I Error Control

The overall family-wise type I error for the superiority tests of OS, PFS, and ORR will be controlled at the 2-sided 0.05 alpha level using the following fixed-sequence method (FDA Guidance 2017):

- The 2-sided alpha of 0.05 is assigned to OS.
- PFS will be tested at the 2-sided significance level of 0.05 only if OS is statistically significant.
- ORR will be tested at the 2-sided significance level of 0.05 only if both OS and PFS are statistically significant.

11.1.6.2. Analysis of the OS Efficacy Endpoint

Overall survival is defined as the time from randomization until death at any time from any cause. Subjects will be censored for OS at the time of the last "known alive" contact.

Median OS will be estimated using the Kaplan-Meier (KM) method. The median and its 95% confidence intervals (CIs), quartiles, and KM rates at Months 6, 9, 12, 18, and 24 will be presented by treatment group. The OS comparisons of the 2 treatment groups will be conducted at the 2-sided significance level of 0.05 using the stratified log-rank test stratified by the randomization stratification factor, which is geographic region (North America, Europe, and Others). The HR (and its 95% CI) for the treatment effect will be estimated using the stratified Cox proportional hazards regression model with Efron's method of handling ties, stratified by the randomization stratification factor.

11.1.6.3. Analysis of the PFS Efficacy Endpoint

Progression-free survival is defined as the time from randomization until the first occurrence of radiological disease progression, as determined by a blinded CIV based on RECIST version 1.1 criteria, or death from any cause during the treatment period. Because the dosing interval between treatment cycles is 14 days, the treatment period will include 14 days post-last dose of study treatment.

Subjects without radiological disease progression who die within 14 days of last dose of study treatment or randomization will be considered as having PFS events. Subjects with no PFS event will be censored for PFS on the date of the last post-baseline tumor assessment or on Day 1 if they have no post-baseline tumor assessments. The scheme of PFS events and censoring are presented in Table 12.

Table 12: Scheme of Events and Censoring for PFS (HALO-109-301)

Outcome	Situation	Date of Progression or Censoring
PFS Event	Radiological disease progression (determined by CIV based on RECIST 1.1) at scheduled or unscheduled visits or at end of treatment visit	First date of radiological disease progression
	Radiological disease progression after any missed scheduled visit	
	Death within 14 days of last dose or randomization with radiological disease progression	
	Death within 14 days of last dose or randomization without radiological disease progression	Death date
Censoring for PFS	No radiological disease progression by CIV or death within 14 days of last dose or randomization for subjects not dosed	Date of last adequate tumor assessment
	Discontinuation of treatment due to reasons other than radiological disease progression by CIV	
	Clinical disease progression determined by investigator with no radiological disease progression by CIV	
	Death after 14 days of last dose or randomization for subjects not dosed	
	No adequate tumor assessment by CIV at Baseline	Randomization date
	No adequate tumor assessment by CIV at post-Baseline	

Abbreviations: CIV = Central Imaging Vendor; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Median PFS will be estimated using the KM method. The median and its 95% CIs, quartiles, and KM rates at Months 6, 9, 12, 18, and 24 will be presented by treatment group. The PFS comparisons of the 2 treatment groups will be based on the stratified log-rank test stratified by the randomization stratification factor, which is geographic region (North America, Europe, and Others). The HR (and 95% CI) for the treatment effect will be estimated using the stratified Cox proportional hazards regression model with Efron's method of handling ties, stratified by the randomization stratification factor.

11.1.6.4. Analysis of Other Efficacy Endpoints

Objective Response Rate: ORR is defined as the percentage of subjects with a complete response [CR] or partial response [PR] as determined by the blinded CIV based on RECIST version 1.1 criteria. Treatment group differences in ORR will be analyzed using the Cochran-Mantel-Haenszel test using randomization stratification factor as the strata.

Duration of Response: DOR is defined as the time from the first objective response of CR/PR until disease progression or death within 14 days of last dose of study treatment or randomization. The DOR will be estimated using the KM method.

11.1.7. Analysis of Treatment Exposure

The study medication exposure will be summarized for each treatment group and overall using the Safety Population. Study medication exposure will include exposure duration, dosing cycles, dosing information for each study medication, such as number of does, dose intensity, and dose change.

11.1.8. Safety Analyses

All safety data will be summarized with descriptive statistics by treatment group using the Safety Population. No inferential statistical tests will be conducted for safety parameters.

Treatment-emergent AEs will be coded and tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and PT. Adverse events will also be analyzed by severity and relationship to study medication.

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

In addition, subjects who experience TE events will be summarized by Standard MedDRA Queries (SMQ) term and MedDRA PT by treatment group and grade.

Clinical laboratory data will be summarized using descriptive statistics. Shift tables will be presented for selected laboratory parameters. All AEs and laboratory parameters that can be graded will be graded using the CTCAE Version 4.03 (at time of study initiation).

Selected laboratory parameters, vital signs, and ECG results and the corresponding change from baseline over time will be summarized using descriptive statistics and data listings.

11.1.9. Pharmacokinetic and Population Pharmacokinetic Analysis

For PEGPH20, plasma exposure will be monitored in all subjects. The peak plasma concentration, concentration at 24 hours postdose on Day 1, and trough concentration on Day 4 of Cycle 1 will be compared to expected mean values. Descriptive statistics will be used to determine any deviations from expected exposure levels.

Plasma exposure levels of GEM and NAB will be evaluated in both treatment groups (with and without PEGPH20). Plasma concentrations immediately after GEM or NAB administration will be compared statistically or by PK modeling to delineate any potential effect of PEGPH20 on GEM and NAB plasma exposure.

11.1.10. Interim Analysis

No interim efficacy analysis will be conducted.

Interim safety data will be analyzed and evaluated periodically by an independent DMC, as described in a separate DMC charter.

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. Major protocol deviations are as follows:

- Violation of eligibility criteria.
- Dosing errors of study medication(s).
- Receiving excluded concomitant medications.
- Developed withdrawal criteria but not withdrawn from study treatment.
- Others reasons, as outlined in a separate Protocol Deviation Specification document.

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

Case Report Forms 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.

Completion of eCRFs is the Investigator's responsibility; it may be delegated to other study personnel and documented on the log for delegation of authority. The clinical monitoring staff will verify data recorded in the eCRF with source documents at the clinical study sites according

to the data management and study monitoring plan. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of all data reported on eCRFs 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, as defined by the ICH and in accordance with the ethical principles underlying European Union (EU) Directive 2001/20/EC and the US CFR, Title 21, Part 50 (21CFR50). All ethical and regulatory requirements are necessary to comply with the principles of GCP and must be followed. This includes inspection by the Sponsor, its representatives, health authority, or IRB/EC representatives at any time. Health authority is defined as any applicable government regulatory authority involved in granting approvals for the manufacturing, marketing, reimbursement and/or pricing of a Product in the Territory, including the FDA in the US, European Medicines Agency (EMA) in the EU, and Ministry of Health, Labour and Welfare (MHLW) in Japan. The Investigator must agree to the inspection of study-related records by the health authority, the Sponsor, and/or the Sponsor's representatives.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject ICF(s) will receive Institutional Review Board/Ethics Committee (IRB/EC) approval/favorable opinion prior to initiation of the study.

All serious breaches must be reported to Halozyme immediately. A serious breach is a breach of Section 14 and all ethical considerations incorporated therein in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks and shall be informed of their obligation to comply with the ethical considerations of the protocol. Compliance with these considerations will be the responsibility of the site and the Investigator at the site. The site and the Investigator will be liable for any breach of the ethical obligations.

14.1. Institutional Review Board/Independent Ethics Committee Review and Approval

In accordance with 21 CFR Parts 50 and 56, the Investigator agrees to obtain IRB/IEC approval of all appropriate material, including a copy of the protocol, ICF(s), Investigator’s Brochure, and subject recruitment materials/processes (e.g., advertisements) prior to the start of the study and/or prior to its use on the study.

Halozyme must be given an opportunity to review and approve any proposed ICF (s) and any proposed subject recruitment materials/processes. A copy of the IRB/IEC approval letter(s) for the protocol and ICF(s) must be supplied to Halozyme before subjects are screened.

The Investigator will supply Halozyme with the names, professions, and affiliations of IRB/IEC members, to demonstrate compliance with membership requirements. If the Investigator or a sub-Investigator is a routine voting member of the IRB/IEC, he or she may not vote on the study to avoid any potential or actual conflict of interest; Halozyme will be provided with a statement from the IRB/IEC that the Investigator/sub-Investigator did not vote on this study.

During the study, the Investigator is responsible for satisfying all IRB/IEC regulations for reporting study progress. Copies of all reports to and correspondence with the IRB/IEC 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/IEC. A copy of this report should be provided to Halozyme (Section 12.5).

The Investigator must maintain an IRB/IEC 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

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Halozyme will provide the Investigator with an appropriate (i.e., global or local) sample ICF. If the site provides the sample ICF, a copy of the proposed ICF must be submitted to Halozyme for review and comment before submission to the IRB/IEC. The ICF must be approved by the IRB/IEC and contain all elements required by all applicable regulatory and institutional regulations or policies including subject compensation information (if applicable), before it is used to obtain a subject's informed consent. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subject's signed ICF and, in the US, the subject's (and/or legally authorized representative's if the subject, for example, is a minor, mentally incompetent, or physically incapacitated, if applicable) signed Health Insurance Portability and Accountability Act of 1996 (HIPAA) Authorization. In the US, authorization to use or disclose personal health information in accordance with HIPAA requirements should be provided in the ICF, or in a separate document to be signed by the subject.

The consent form must also include a statement that Halozyme and regulatory authorities have direct access to subject records.

Each subject found eligible for the study must have voluntarily provided written informed consent, using the IRB/IEC-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.

16. REFERENCES

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17. APPENDICES

APPENDIX A. ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation	Term
ADA	Anti-drug antibody(ies)
AE	Adverse event
AG	Nab-paclitaxel plus gemcitabine
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle
CFR	Code of Federal Regulations
CI	Confidence interval
CIV	Central Imaging Vendor
CR	Complete response
CRO	Contract Research Organization
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DVT	Deep vein thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Term
eCRF	Electronic case report form
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EQ-5D	European Quality of Life-5 Dimensions Scale
EU	European Community
FFPE	formalin-fixed paraffin-embedded
5-FU	Fluorouracil
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEM	Gemcitabine
HA	Hyaluronan
IA	Interim analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
INR	International normalized ratio
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intra-uterine device
IUO	Investigational use only
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
IWRS	Interactive Web Response System
KM	Kaplan-Meyer
LMWH	Low-molecular-weight heparin
min	Minutes
MHLW	Ministry of Health, Labour and Welfare
MRI	Magnetic resonance imaging
MSE	Musculoskeletal event

Abbreviation	Term
MTD	Maximum tolerated dose
NAB	Nab-paclitaxel, ABRAXANE®
NAb	Neutralizing antibodies
NaCl	Sodium chloride
NCI	National Cancer Institute
NRS	Numerical Rating Scale
ORR	Objective response rate
OS	Overall survival
PAG	PEGPH20 in combination with nab-paclitaxel plus gemcitabine
PD	Progressive disease
PDA	Pancreatic ductal adenocarcinoma
PE	Pulmonary embolism
PEGPH20	PEGylated Recombinant Human Hyaluronidase
PFS	Progression-free survival
PI	Prescribing Information
PK	Pharmacokinetic(s)
plt	platelet(s)
PO	By mouth
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
PY	Patient years
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	Recombinant human hyaluronidase PH20
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Stable disease

Abbreviation	Term
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvate transaminase
SmPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TE	Thromboembolic
TME	Tumor microenvironment
U	Unit
ULN	Upper limit of normal
US	United States
VTE	Venous thromboembolic event
WOCBP	Woman of childbearing potential

APPENDIX B. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1

Target Lesion Evaluation:

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Non-Target Lesion Evaluation:

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

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.

APPENDIX D. ECOG PERFORMANCE STATUS

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group (Oken 1982).
Note: Shaded grades represent acceptable status for enrollment in Study HALO-109-301.

APPENDIX E. DOSE MODIFICATION SCHEMATIC