CLINICAL STUDY PROTOCOL

Title:	**A Phase 1b Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Combined with Pembrolizumab in Subjects with Selected Hyaluronan-High Solid Tumors**
Phase	**1b**
Protocol Number:	**HALO-107-101**
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Protocol Amendment 3 Date:	**21 November 2016**
Protocol Amendment 4 Date:	**06 November 2017**
IND:	**102770**
Sponsor:	**Halozyme, Inc.** 11388 Sorrento Valley Road San Diego, CA 92121 Office: [redacted]

[Approval Signature Page to be Inserted here]

1. SYNOPSIS

Sponsor/Company

Halozyme, Inc.

Protocol Number

HALO-107-101

Study Title

A Phase 1b Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Combined with Pembrolizumab in Subjects with Selected Hyaluronan-High Solid Tumors

Study Objectives

Dose Escalation

Primary:

- To assess the safety and tolerability of PEGylated recombinant human hyaluronidase (PEGPH20) combined with pembrolizumab (Keytruda®) (PEGPEM) in subjects with relapsed/refractory non-small cell lung cancer (NSCLC) and relapsed/refractory gastric adenocarcinoma.
- To determine the recommended Phase 2 dose (RP2D) of PEGPH20 when administered with pembrolizumab in subjects with relapsed/refractory NSCLC and relapsed/refractory gastric adenocarcinoma.

Secondary:

- To assess the pharmacokinetics (PK) of PEGPH20 when given in combination with pembrolizumab in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.
- To obtain an early assessment of the antitumor activity of PEGPEM, as assessed by objective response rate (ORR), duration of response (DOR), disease control rate (DCR) and progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and overall survival (OS) in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.

Exploratory:

- To assess the PK of pembrolizumab when given in combination with PEGPH20 in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.

Dose Expansion

Note: The objectives described below will be evaluated in hyaluronan-high (HA-high) subjects with relapsed/refractory NSCLC and HA-high subjects with relapsed/refractory gastric adenocarcinoma.

Primary:

- To evaluate the efficacy of PEGPEM as assessed by ORR based on RECIST v1.1

Secondary:

- To evaluate the efficacy of PEGPEM as assessed by DOR, DCR and PFS based on RECIST v1.1, and OS
- To evaluate the efficacy of PEGPEM as assessed by ORR, DOR, DCR and PFS based on immune-response related criteria (irRC)
- To characterize the PK of PEGPH20 when given in combination with pembrolizumab
- To evaluate the safety and tolerability profile of PEGPEM

Exploratory:

- To evaluate the efficacy of PEGPEM, as assessed by ORR, DOR, DCR and PFS based on RECIST v1.1 criteria and irRC, by programmed death-ligand 1 (PD-L1) expression levels
- To assess the treatment effect of PEGPEM as follows:
  - Based on HA levels in plasma and tumors, or other potential biomarkers.
  - Based on tumor blood flow and metabolic activity as assessed by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and positron emission tomography (PET)/computed tomography (CT) scans, respectively.
- To assess the PK of pembrolizumab when given in combination with PEGPH20

Study Design

This Phase 1b study of PEGPEM will consist of 2 portions:

- A Dose Escalation portion in subjects with relapsed/refractory Stage IIIB or IV NSCLC after failing at least 1 previous platinum-based chemotherapy regimen (refer to Inclusion Criterion #2) and subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma after failing at least 1 previous chemotherapy regimen for locally advanced or metastatic disease.
- Followed by a Dose Expansion portion in:
  - Previously untreated, HA-high subjects with Stage IIIB or IV NSCLC
  - Previously treated, HA-high subjects with relapsed/refractory Stage IIIB or IV NSCLC having failed no more than 1 previous platinum-based chemotherapy regimen (refer to Inclusion Criterion #3) for locally advanced or metastatic disease and

- HA-high subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens for locally advanced or metastatic disease.

Note: In Dose Expansion, subjects will be selected for enrollment whose tumors are HA-high, using a co-developed investigational diagnostic assay. Subjects will be tested retrospectively for PD-L1 expression levels.

Since PEGPH20 has not been evaluated in clinical studies in combination with pembrolizumab, this study will have a Dose Escalation portion to evaluate the safety and tolerability of PEGPEM treatment before the Dose Expansion portion is initiated. The Dose Escalation portion will also be used to determine the dose of PEGPH20 to be evaluated in the Dose Expansion portion.

The treatment period will consist of 21-day cycles.

In Dose Escalation, PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle (i.e. 3 doses/cycle) and pembrolizumab (2 mg/kg every 21 days) on Day 1 of each cycle (i.e. 1 dose/cycle), 4-6 hours after the completion of PEGPH20 administration (per Protocol Amendment 2).

In Dose Expansion, 200 mg of pembrolizumab will be administered every 21 days (per Protocol Amendment 3 [see Section 4.6.4 for additional details]) and the dosing schedule will be as follows:

- PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle (i.e. 3 doses/cycle) and pembrolizumab (200 mg every 21 days) on Day 1 of each cycle (i.e. 1 dose/cycle), 4-6 hours after the completion of PEGPH20 administration.

In Dose Expansion, an independent data monitoring committee (DMC) will review all available safety data from the first 3 NSCLC subjects and first 3 gastric adenocarcinoma subjects who have completed Cycle 1, to determine if the safety and tolerability profile of the PEGPEM combination is acceptable (refer to the DMC charter for additional details). The DMC will also continue to periodically review safety data to protect subject welfare and identify potential safety signals.

Treatment in both portions of the study will continue until death, withdrawal of consent from the study, disease progression, or unacceptable toxicity; however, subjects with asymptomatic disease progression will be allowed to continue the study treatment at the Investigator's discretion despite evidence of increasing tumor burden or appearance of new lesions for up to 6 weeks if the subject is "clinically stable." Clinically stable is defined as:

- Absence of symptoms and signs indicating clinically significant progressive disease (PD) (including worsening of laboratory values) indicating disease progression;
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status; and
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Dose interruptions and modifications of study treatment are permitted.

In single-agent studies of PEGPH20 and the combination study with gemcitabine (GEM), the dose-limiting toxicity (DLT) was musculoskeletal events (MSEs) of myalgia and muscle cramping. In clinical studies HALO-109-102, HALO-109-201 and HALO-109-202, dexamethasone was administered per protocol to attenuate the severity of MSEs. Since this study uses an immunotherapeutic agent and dexamethasone may suppress an immune response, it should only be used when prescribed by the Investigator and following a discussion with the Sponsor.

Piroxicam and toradol have been investigated in an animal model of MSEs and may be helpful in decreasing the severity of MSEs in subjects (internal Halozyme report). Piroxicam (20 mg) will be administered at least 1-2 hours prior to PEGPH20 administration on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience) to minimize the severity of MSEs. Prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or over-the-counter [OTC] equivalent).

Toradol may be given for severe pain as recommended in the Toradol Prescribing Information. Toradol should not be administered concurrently with piroxicam as per the Prescribing Information, as it is contraindicated to administer toradol simultaneously with other nonsteroidal anti-inflammatory drugs (NSAIDs) because of the cumulative risk of inducing serious NSAID-related side effects.

To help minimize MSEs, prescribed medication such as narcotics, muscle relaxants and other analgesics (with the exceptions of steroids), OTC drugs and physical therapy can be used at the Investigator's discretion.

All NSCLC subjects will be given enteric-coated 81 mg of aspirin/day and all gastric adenocarcinoma subjects will be given enoxaparin 40 mg/day (pre-filled syringes of enoxaparin are allowed), for prophylaxis of thromboembolic (TE) events, given the high incidence seen in these tumor types. Subjects who experience any TE event requiring full-dose anticoagulants while on study will discontinue treatment with PEGPH20. Treatment with pembrolizumab, however, may continue at the Investigator's discretion.

In gastric adenocarcinoma subjects, if enoxaparin is discontinued for any reason, PEGPH20 will also be discontinued. Treatment with pembrolizumab, however, may continue at the Investigator's discretion.

Subjects who discontinue PEGPH20 and pembrolizumab treatment will have an End of Treatment Visit and enter long-term follow-up for survival.

Subjects will be assessed for adverse events (AEs) and clinical laboratory evaluations as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

In both portions of the study, tumor response and progression will be assessed by the Investigator at the end of Cycle 2, Cycle 4 and then at the end of every fourth treatment cycle thereafter (i.e., Week 3 of Cycles 2, 4, 8, 12, 16 and beyond) based on RECIST v 1.1 criteria (Eisenhauer 2009; Appendix C) and irRC (Nishino 2013; Nishino 2014; Appendix E). Tumor assessment scans (CT/MRI of chest, abdomen, pelvis, and other areas of known or newly suspected disease) should be performed at Screening (within 28 days prior to first dose of study drugs) and obtained any

time on or after Day 15 (of Cycles 2, 4, 8, 12, 16 and every fourth treatment cycle thereafter) to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit.

A CT/MRI brain scan must be performed at Screening (within 28 days prior to first dose of study drugs), to assess potential central nervous system disease and/or metastases.

For the duration of the study (i.e., post-baseline), CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a complete response (CR). For NSCLC subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points.

To determine the best overall response, a confirmatory scan must be performed no sooner than 28 days after the initial scan that showed a response (Partial Response [PR] or Complete Response [CR]) based on RECIST v1.1 and irRC. A confirmatory scan should also be performed to confirm disease progression based on irRC no sooner than 28 days after the initial scan that showed progression.

Phase 1b Dose Escalation Portion

This portion of the study is a single-arm, dose escalation study of PEGPH20 in combination with pembrolizumab. Using a standard 3+3 dose escalation design, approximately 3 to 6 subjects in each cohort will receive PEGPH20 + pembrolizumab. PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle to consecutive cohorts in increasing dose levels (1.6, 2.2, 2.6, 3.0, and 4.0 µg/kg). Pembrolizumab will be administered on Day 1 of each cycle, 4-6 hours after the dose of PEGPH20. If the maximum tolerated dose (MTD) is not reached at 4.0 µg/kg, higher doses may be evaluated. If ≥2 subjects experience a DLT at the 1.6 µg/kg dose level, Cohort -1 will be opened and subjects will be dosed at 1.0 µg/kg on Day 1, Day 8, and Day 15 of each 21-day cycle. The RP2D of PEGPH20 will be the MTD determined in Dose Escalation or the Sponsor may decide to choose a dose lower than the MTD and which has completed evaluation in Dose Escalation and is found to be safe and tolerable to evaluate in Dose Expansion.

The number of cohorts studied and number of subjects exposed to a given dose level will depend on the doses tested. It is anticipated that up to 5 dose levels will be studied for a total of approximately 30 subjects exposed to study medication. The dose allocation for 5 cohorts of subjects assigned to the 5 preselected dose levels and the -1 cohort assigned to the preselected dose of 1.0 µg/kg (if ≥2 subjects experience a DLT at 1.6 µg/kg dose level) is shown as an example in Table S-1. The study medication dosing and treatment schedule are shown in Table S-2.

Safety data from all subjects dosed will be reviewed to determine the RP2D. Dose escalation will be guided by safety data from each subject during the 21 days following their first dose of PEGPH20. Intra-subject dose escalation to the next PEGPH20 dose studied may be allowed if the Investigator deems it in the best interest of the subject and after discussion with the Sponsor and provided the next PEGPH20 dose studied has been determined not to have exceeded the MTD.

- If none of 3 subjects in a given cohort experience a DLT within 21 days of starting treatment, enrollment and dosing may proceed at the next planned dose level.

- If 1 of 3 initial subjects at a given dose level experiences a DLT within the first 21 days of treatment, 3 additional subjects will be enrolled and dosed at the same dose level. If ≤1 of 6 subjects experiences a DLT, dose escalation may continue to the next planned higher dose.
- If ≥2 subjects at a given dose level experience a DLT within the first 21 days of treatment, that dose level will be considered to have exceeded the MTD and dose escalation will be stopped. If the previous dose level did not already have 6 subjects treated with ≤1 DLT, enrollment and dosing will then resume in the previous dose level with additional subjects up to a total of 6 subjects. The highest dose level at which no more than 1 of 6 evaluable subjects has experienced a DLT in the first 3 weeks of treatment will be considered the MTD for the PEGPEM combination. The RP2D will be based on the overall safety profile.
- If ≥2 subjects at the 1.6 µg/kg dose level experience a DLT within the first 21 days of treatment, Cohort -1 will be opened at a lower dose level of 1.0 µg/kg.

Note: Additional subjects may be enrolled in each cohort to further assess the tolerability of PEGPEM and determine an acceptable safety profile prior to the enrollment in the next dose level and expansion portion of the study.

Definition of DLT

DLTs will be assessed for each subject during the 21 days following their first PEGPH20 dose and will be defined as any of the following:

- Any treatment-emergent Grade ≥3 toxicity that is considered related to either PEGPH20 or pembrolizumab or the combination of PEGPH20 and pembrolizumab (nausea, vomiting, musculoskeletal events and diarrhea will be considered DLTs only if they reach ≥ Grade 3 despite adequate supportive care measures).
- Grade 3 MSEs are considered DLTs only if they do not reduce to ≤ Grade 2 within 48 hours despite therapeutic intervention.
- Hypersensitivity/infusion reactions related to PEGPH20 or pembrolizumab dosing will not be considered DLTs (hypersensitivity reactions are generally not related to the dose level of a drug since they can occur even upon a low level of exposure).

To be considered evaluable for DLT assessment, subjects must receive 1 of the 3 full planned doses of PEGPH20 and 1 complete dose of pembrolizumab in Cycle 1. Subjects who experience a DLT within the first 21 days of treatment and withdraw from the study will be considered evaluable for DLT and will not be replaced. Subjects who withdraw within the first 21 days for reasons other than a DLT will be considered not evaluable and will be replaced. Any PEGPH20 treatment-related AE that results in interruption or reduction of either PEGPH20 or pembrolizumab may be considered a DLT at the Investigator's discretion.

The Sponsor and the participating investigators will meet as soon as practical, post completion of a cohort, and no more than 10 business days after the end of the last cohort to determine an acceptable dose for the Dose Expansion portion after reviewing all available safety data from Cycle 1 from all subjects in the Dose Escalation portion.

Table S-1: Dose Allocation and Cohort Schedule - Dose Escalation Portion

Cohort	PEGPH20 µg/kg	Pembrolizumab mg/kg
-1	1.0	2
1	1.6	2
2	2.2	2
3	2.6	2
4	3.0	2
5	4.0[a]	2

Abbreviations: PEGPH20 = PEGylated Recombinant Human Hyaluronidase
Note: Each treatment cycle is 21 days. Dose interruption and modifications are permitted.
[a] If the MTD is not reached at 4.0 µg/kg, higher doses may be evaluated.

Phase 1b Dose Expansion Portion

Approximately 51 HA-high subjects will be studied in the Dose Expansion portion at the RP2D identified in the Dose Escalation portion:

- Approximately 30 subjects with Stage IIIB or IV NSCLC, previously untreated or treated and having failed no more than 1 previous platinum-based chemotherapy (refer to Inclusion Criterion #3)
- Approximately 21 subjects with relapsed/refractory gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens.

The study medication dosing and treatment schedule are shown in Table S-2.

Table S-2: Study Medication Dosing and Treatment Schedule – Dose Escalation and Dose Expansion

Time point	PEGPEM Treatment
Subjects with NSCLC or Gastric Adenocarcinoma	
Cycle 1 and Beyond (Each Cycle 21 Days)	
Week 1	
Day 1	PEGPH20 Pembrolizumab (4-6 hours after PEGPH20)
Week 2	
Day 8	PEGPH20
Week 3	
Day 15	PEGPH20

Abbreviations: PEGPEM = PEGPH20 in combination with pembrolizumab; PEGPH20 = PEGylated Recombinant Human Hyaluronidase; NSCLC = non-small cell lung cancer

Notes: Dose interruption and modifications are permitted.
On Days 1, 8, and 15 of Cycle 1 and Day 1 of Cycle 2, measurements of total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (as part of blood chemistry) must be obtained prior to dosing (within 48 hours is acceptable). Dosing can only take place if total bilirubin, ALP AST, and ALT values are within the ranges specified in the Inclusion Criteria. If a subject has any of these values outside the specified ranges on Day 1 of Cycle 2, the Investigator should discuss further dosing plans for the subject with the Sponsor.
Visit window is ±2 days of the specified times.

Study Population

Males and females aged 18 years and above.

Phase 1b Dose Escalation: Subjects with relapsed/refractory Stage IIIB or IV NSCLC after failing at least 1 previous platinum-based chemotherapy regimen (refer to Inclusion Criterion #2) and subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma after failing at least 1 previous chemotherapy regimen for locally advanced or metastatic disease.

Phase 1b Dose Expansion: Subjects with HA-high Stage IIIB or IV NSCLC, previously untreated or treated and having failed no more than 1 previous platinum-based chemotherapy regimen, and who have tissue available for HA-selection and PD-L1 testing; and HA-high subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens for locally advanced or metastatic disease and who have tissue available for HA-selection and PD-L1 testing.

Inclusion Criteria

For both portions of the study (unless otherwise specified), subjects must satisfy all of the following inclusion criteria to be enrolled in the study:

1. Written Institutional Review Board/Ethics Committee-approved Informed Consent form, signed by subject or legally authorized representative.
2. **Dose Escalation portion** - Histologically confirmed and documented, previously treated stage IIIB or IV NSCLC having failed at least 1 previous platinum-based chemotherapy regimen for locally advanced or metastatic disease, or relapsed/refractory locally advanced or metastatic gastric adenocarcinoma having failed at least 1 previous chemotherapy regimen for locally advanced or metastatic disease. Subjects with NSCLC who are known to be epidermal growth factor receptor (EGFR)-mutation positive must have received an EGFR inhibitor and subjects known to be anaplastic lymphoma kinase (ALK)-mutation positive must have received an ALK inhibitor (subject's documented EGFR/ALK mutation status and/or confirmation reports/molecular pathology/analysis reports should be included in the subject's medical records and made available for Sponsor/Sponsor representative[s] review).
    a. Subjects with gastroesophageal junction (GEJ) tumors are eligible.
    b. For subjects with either NSCLC or gastric cancer, prior treatment administered in the adjuvant setting is permitted provided it was administered at least 6 months prior to first-line therapy for metastatic disease.
    c. For subjects with NSCLC, prior first-line treatment with bevacizumab (AVASTIN®) or biosimilars is allowed.
    d. For subjects with NSCLC, prior maintenance treatment with bevacizumab, pemetrexed (ALIMTA®), or erlotinib (TARCEVA®) is allowed.

e. For subjects with human epidermal growth factor receptor 2 positive (HER2+) gastric cancer, prior treatment with trastuzumab (HERCEPTIN®) is required (subject's documented HER2 status and/or confirmation reports/molecular pathology/analysis reports should be included in the subject's medical records and made available for Sponsor/Sponsor representative[s] review).

3. **Dose Expansion portion - NSCLC subjects:** Histologically confirmed and documented, previously untreated or treated stage IIIB or IV NSCLC. Previously treated subjects must have failed no more than 1 previous platinum-based chemotherapy regimen for locally advanced or metastatic disease. Previously treated subjects with NSCLC who are known to be EGFR-mutation positive must have received an EGFR inhibitor and subjects who are known to be ALK-mutation positive must have received an ALK inhibitor (subject's documented EGFR/ALK mutation status and/or confirmation reports/molecular pathology/analysis reports should be included in the subject's medical records and made available for Sponsor/Sponsor representative[s] review). **Gastric adenocarcinoma subjects:** histologically confirmed and documented previously treated relapsed/refractory locally advanced or metastatic gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens for locally advanced or metastatic disease.

   a. Subjects with GEJ tumors are eligible.
   b. For subjects with either NSCLC or gastric cancer, prior treatment administered in the adjuvant setting is permitted provided it was administered at least 6 months prior to first-line therapy for metastatic disease.
   c. For previously treated subjects with NSCLC, prior treatment with or without bevacizumab (AVASTIN®) or bevacizumab biosimilars is allowed.
   d. For previously treated subjects with NSCLC, prior maintenance treatment with bevacizumab, pemetrexed (ALIMTA®), or erlotinib (TARCEVA®) is allowed.
   e. For subjects with HER2+ gastric cancer, prior treatment with trastuzumab (HERCEPTIN®) is required (subject's documented HER2 status and/or confirmation reports/molecular pathology/analysis reports should be included in the subject's medical records and made available for Sponsor/Sponsor representative[s] review).

4. Prior to enrollment, confirmation of the following must be obtained:

   a. **Dose Escalation portion** - Available tumor tissue in a formalin-fixed paraffin-embedded (FFPE) block or 5-10 unstained consecutive core biopsy slides from 1 tumor tissue block that meet specific tissue sample requirements are preferred but not mandatory for enrollment in this portion of the study. **Note:** Fine needle aspirates or brushing biopsies will not be acceptable.
   b. **Dose Expansion portion -** Available tumor tissue in FFPE block or 10-15 unstained consecutive tumor tissue slides from 1 tumor tissue block that meet specific tissue sample requirements are mandatory. **Note:** Fine needle aspirates or brushing biopsies will not be acceptable. Archived resection specimens from the primary tumor without radiologic evidence of metastasis at the time of resection are not suitable to establish histological confirmation and require new tumor tissue of a metastatic site.

5. To be eligible for the Dose Escalation portion, subjects need only have evaluable disease (details in Section 8.2.15); to be eligible for the Dose Expansion portion, subjects must

have measurable disease per RECIST v1.1. Previously irradiated tumors may be eligible if they have clearly progressed in size.

6. ECOG Performance Status of 0 or 1.
7. Life expectancy ≥3 months.
8. Males and females aged ≥18 years.
9. Resolution of all acute toxic effects of prior therapy or surgery to baseline.
10. Screening clinical laboratory values are as follows:
    a. Total and indirect bilirubin ≤1.5 × upper limit of normal (ULN), except for Gilbert's syndrome
    b. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤2.5 × ULN (<5 × ULN is allowed if liver metastases are present)
    c. Serum creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥40 mL/min
    d. Serum albumin ≥3.0 g/dL
    e. Hemoglobin ≥10 g/dL (transfusion and erythropoietic agents allowed)
    f. Absolute neutrophil count ≥1500 cells/mm^3
    g. Platelet count ≥100,000/mm^3
11. Female participants of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test within 7 days before Day 1 (first dose of study medication).
12. For WOCBP and for men, agreement to use an effective contraceptive method from the time of screening throughout the study until 4 months (WOCBP) or 3 months (men) after administration of the last dose of any study medication. Highly effective contraceptive methods consist of prior sterilization, intrauterine device (IUD), intrauterine hormone releasing system (IUS), oral or injectable contraceptives, and/or barrier methods. Abstinence alone is not considered an adequate contraceptive measure for the purposes of this study.
13. Subjects must also satisfy the following inclusion criterion to be enrolled in the Dose Expansion portion of the study:
    a. Subjects (NSCLC and gastric adenocarcinoma) must be determined to have HA-high levels from their tumor biopsies. Tumor samples must meet the requirements noted in the Inclusion Criterion #4.
    b. NSCLC and gastric adenocarcinoma subjects must have tissue available for HA-selection and PD-L1 testing. Tumor samples must meet the requirements noted in the Inclusion Criterion #4.

Exclusion Criteria

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

1. Previous treatment with pembrolizumab, nivolumab, or other programmed cell death-1 antibody (anti- PD-1) or PD-1 ligand 1 antibody (anti-PD-L1) agents.
2. New York Heart Association Class III or IV (Appendix D) cardiac disease or myocardial infarction within the past 12 months before screening, or preexisting atrial fibrillation.

3. History of cerebrovascular accident or transient ischemic attack.
4. NSCLC subjects with known brain metastases (exception below).
    a. Subjects with treated brain metastases who meet all of the following criteria are eligible:
        i. Stable brain metastases for at least 1 month,
        ii. No evidence of progression or hemorrhage after treatment,
        iii. No ongoing requirement for corticosteroids.
5. Gastric adenocarcinoma subjects with brain metastases.
6. History of active bleeding within the last 3 months requiring transfusion.
7. Anti-angiogenic therapy within the last month.
8. Known interstitial fibrosis or interstitial lung disease.
9. History of pulmonary embolism or pulmonary embolism found on screening exam.
10. Pre-existing carotid artery disease.
11. History of DVT with contraindications to pharmacologic anticoagulation.
12. History of:
    a. Pneumonitis that requires oral or IV steroids;
    b. Or known cases of hepatobiliary diseases (e.g., primary biliary cholangitis, primary sclerosing cholangitis, history of immune-mediated cholangitis);
        i. Subjects with cholangitis attributed to infectious etiology (e.g., ascending cholangitis, bacterial cholangitis) are eligible if the infection has been fully resolved prior to the screening visit.
    c. Or known cases of drug-induced hepatobiliary toxicities.
13. NSCLC subjects with hypersensitivity to aspirin.
14. Gastric adenocarcinoma subjects with contraindications to enoxaparin.
15. Autoimmune diseases:
    a. Active autoimmune disease requiring systemic treatment within the past 3 months
    b. Documented history of clinically severe autoimmune disease (e.g., colitis, Crohn's disease)*
16. Active, uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
17. Known infection with human immunodeficiency virus, active infection with hepatitis B, or hepatitis C.
18. Known allergy to hyaluronidase.
19. Hypersensitivity to the active substance or ingredients of PEGPH20 and pembrolizumab.
20. Known allergy to piroxicam or other NSAIDs.

21. Current use of megestrol acetate (within 10 days of Day 1).
22. Chronic use of steroids for pain or emesis management.
23. Women currently pregnant or breastfeeding.
24. History of another primary cancer within the last 3 years that required treatment, with the exception of non-melanoma skin cancer, early-stage prostate cancer, or curatively treated cervical carcinoma in situ.
25. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that lead to reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the subject at high risk for treatment complications.
26. Subject inability to comply with study and follow-up procedures, as judged by the Investigator.

*Any relevant diseases that are not listed as examples of exclusionary diseases are to be discussed with the Sponsor.

Study Medication

For this study, study medication will include PEGPH20 and pembrolizumab.

PEGPH20: PEGPH20 drug product is supplied as an aqueous solution containing 0.3 mg/mL PEGPH20 with 10 mM succinic acid, 130 mM NaCl and 10 mM methionine at pH 6.2. Each vial contains 1.2 mL (0.36 mg) of PEGPH20 drug product. PEGPH20 drug product is provided as a refrigerated formulation and should be stored at 2°C to 8°C before use.

PEGPH20 mixing instructions will be provided to sites in the pharmacy manual. PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle as an intravenous (IV) infusion over 10 minutes, approximately 1 mL/minute (a window of +2 minutes is allowed, i.e., infusion can be 10 to 12 minutes). The dose for the escalation portion will depend on the escalation process. The PEGPH20 dose for the expansion portion will be the MTD established in the escalation portion or a dose lower than the MTD and which has completed evaluation in Dose Escalation and found to be safe and tolerable.

Pembrolizumab: In Dose Escalation, pembrolizumab 2 mg/kg will be administered as an IV infusion over 30 minutes every 21 days on Day 1 of each cycle, 4-6 hours after the completion of PEGPH20 administration (Keytruda® US Prescribing Information 2015). In Dose Expansion, 200 mg of pembrolizumab will be administered as an IV infusion over 30 minutes every 21 days on Day 1 of each cycle, 4-6 hours after the completion of PEGPH20 administration (see Section 4.6.4 for additional details).

Refer to pembrolizumab Prescribing Information for a description of the drug (Keytruda® US Prescribing Information 2017).

Study Duration

The study will consist of an optional prescreening period for HA-testing in Dose Expansion (per Protocol Amendment 3), a screening period of up to 28 days, a treatment period (21-day cycles), a 30-day post-treatment period (after last dose) for collection of AEs and long-term follow-up.

Subjects will be allowed to continue treatment on study until unacceptable toxicity or disease progression. Subjects with asymptomatic disease progression however, will be allowed to continue the study treatment at the Investigator's discretion despite evidence of increasing tumor burden or appearance of new lesions for up to 6 weeks if the subject is clinically stable.

Clinically stable is defined as:

- Absence of symptoms and signs indicating clinically significant PD (including worsening of laboratory values) indicating disease progression;
- No decline in ECOG performance status; and
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Disease progression will be defined by the presence of 1 or both of the following, based on the Investigator's assessment:

- Disease progression documented by CT scan/MRI scan based on RECIST v1.1.
- Clinical tumor-related progression that is well documented in the absence of radiological scans demonstrating disease progression.

Investigators may also discontinue study treatment if it is no longer in the best interest of the subject.

Subjects who discontinue treatment with PEGPH20 and pembrolizumab will be followed every 12 weeks for survival until death, withdrawal of consent, or lost to follow-up.

Criteria for Evaluation

Study Endpoints

Dose Escalation

Primary:

- Dose-limiting toxicity, MTD, and RP2D.

Secondary:

- PK parameters of PEGPH20: maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), terminal elimination half-life ($T_{1/2}$), area-under-the-concentration time curve (AUC), volume of distribution (V_D) and clearance (CL).
- ORR, DOR, DCR, and PFS based on RECIST v1.1.
- OS.

Exploratory:

- PK parameters of pembrolizumab: C_{max}, C_{min}, $T_{1/2}$, AUC, V_D and CL.

Dose Expansion

Primary:

- ORR based on RECIST v1.1

Secondary:

- DOR, DCR and PFS based on RECIST v1.1, and OS
- ORR, DOR, DCR, and PFS based on irRC
- PK parameters of PEGPH20: C_{max}, C_{min}, $T_{1/2}$, AUC, V_D and CL.
- Incidence of AEs
- Changes in clinical safety laboratory values
- Changes in cardiovascular parameters (electrocardiogram [ECG]) and vital signs

Exploratory:

- ORR, DOR, DCR, and PFS based on RECIST v1.1 criteria and irRC by PD-L1 expression levels.
- Changes from pre-treatment in plasma HA and tumor HA (when available).
- Correlation between plasma HA levels pre-dose, post-dose and any pharmacodynamic response.
- Changes in tumor blood flow as measured by DCE-MRI.
- Changes in tumor metabolism as measured by PET/CT.
- Correlation of biomarkers in plasma and tumor biopsy to study endpoints.
- PK parameters of pembrolizumab: C_{max}, C_{min}, $T_{1/2}$, AUC, V_D and CL.

Safety Assessments

The safety and tolerability of PEGPEM will be assessed by evaluation of serious and non-serious AEs, clinical monitoring, concomitant medications, dose modification / interruption / discontinuation of study treatment, clinical laboratory tests (hematology, blood chemistry thyroid function tests), blood glucose (either as part of chemistry or single assessment), 12-lead ECGs, vital sign measurements, and PEGPH20 anti-drug antibodies, as specified in the Study Schedule of Events.

Efficacy Assessments

Subjects will be evaluated for efficacy endpoints ORR, DOR, DCR and PFS per both RECIST v 1.1 and irRC criteria that are based on radiological assessments of the disease; see the Study Schedule of Events. Subjects may be evaluated for efficacy endpoints ORR, DOR, DCR and PFS based on RECIST v1.1 criteria and irRC, by PD-L1 expression levels.

Pharmacokinetic Assessments

Plasma PEGPH20 and serum pembrolizumab concentrations will be measured as specified in the Study Schedule of Events.

Biomarker and Pharmacodynamic Assessments

The treatment effect of PEGPEM will be evaluated based on pre- and post-treatment measurement of HA in plasma and tumor as well as change in potential biomarkers of pembrolizumab and/or PEGPH20 activity in plasma and tumor biopsies, blood flow as measured by DCE-MRI, and tumor metabolism as measured by PET/CT.

Statistical Methods

Planned Total Sample Size

In the dose escalating portion, there may be up to 5 dose levels for a total of approximately 30 subjects.

In the Dose Expansion portion, approximately 51 subjects will be enrolled (approximately 30 with HA-high tumors in NSCLC cohort and approximately 21 with HA-high tumors in the gastric adenocarcinoma cohort).

KEYNOTE-001 study data presented at the American Society of Clinical Oncology 2016 (Hui 2016) showed that when treated with pembrolizumab alone, treatment naïve subjects who had evaluable PD-L1 Tumor Proportion Score [TPS] levels had an ORR of 29% and previously treated subjects who had evaluable PD-L1 TPS levels had an ORR of 21%. Under the assumption that no more than 40% of the subjects enrolled in this study will be treatment naïve, ORR in the combined NSCLC population is expected to be approximately 24% when treated with pembrolizumab alone. A 20% improvement in ORR is considered clinically meaningful when PEGPH20 is added to pembrolizumab. Under these conditions, 30 NSCLC subjects would provide approximately 80% power at the hypothesized ORR of 44% when the null hypothesis H0: ORR ≤24% is tested against H1: ORR >24% using an exact one-sided binomial test at a 10% significance level.

KEYNOTE-012 study data showed that the ORR in PD-L1 positive gastric cancer subjects is about 22% (Muro 2016). Since subjects will not be selected based on PD-L1 expression levels prospectively in this study, in order to accommodate all subjects (irrespective of PD-L1 expression levels), a conservative ORR of 15% is assumed with pembrolizumab treatment alone and it is further assumed that the addition of PEGPH20 to pembrolizumab will lead to a clinically meaningful improvement of 20% in ORR to 35%. Under these assumptions, 21 subjects will provide approximately 80% power at the hypothesized ORR of 35% when the null hypothesis H0: ORR ≤15% tested against H1: ORR >15% using an exact one sided binomial test at a 10% significance level.

Analysis Populations

Safety Population: All subjects who receive any study medication. The Safety Population will be used for subject disposition, demographics and safety analyses.

DLT Evaluable Population: All subjects who receive at least 1 of the 3 full planned doses of PEGPH20 and 1 complete dose of pembrolizumab in Cycle 1 and have been followed for the first 21 days of treatment or have experienced a DLT during the initial 21 days (Cycle 1) of the study. The DLT Evaluable Population will be used for DLT analysis.

PK Analysis Population: All subjects who receive any PEGPH20 and have measurable PEGPH20 concentrations in at least 1 sample collected for PK analysis. PK Analysis Population will be used for PK analysis.

Efficacy Evaluable Population: All HA-high subjects who receive at least 1 dose of the RP2D of PEGPH20 and at least 1 dose of pembrolizumab. The efficacy evaluable population will be used for all efficacy analyses.

Tumor Response Evaluable Population: Subjects in the Efficacy Evaluable Population who have at least one post-baseline tumor assessment. Tumor Response Evaluable Population will also be used for overall tumor response analysis.

Analyses

Analysis of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using safety population by dose level for subjects in the Dose Escalation portion and separately for all subjects in the Dose Expansion portion. The following demographic and baseline characteristics will be summarized: age, race, height, weight, medical history, disease characteristics, and treatment history.

Efficacy Analyses

All efficacy analyses will be conducted using the Efficacy Evaluable Population. ORR and DOR will also be analyzed using Tumor Response Evaluable population.

The primary efficacy endpoint of the study is PEGPEM treatment effect on ORR based on RECIST v1.1. The statistical hypothesis tests for the primary endpoint are as follows:

- NSCLC cohort: H_0: ORR ≤23%; H_1: ORR >23%
- Gastric adenocarcinoma cohort: H_0: ORR ≤15%; H_1: ORR >15%

The hypothesis tests will be conducted using the one-sided exact binomial test at the significance level of 0.1.

ORR will be calculated as the number of subjects with a confirmed CR or PR divided by the number of subjects in the analysis population multiplied by 100. The exact 80% confidence interval of ORR will also be constructed. DCR and its exact 80% CI will be calculated. Median DOR, PFS and OS and their corresponding 80% confidence intervals will be estimated using the Kaplan-Meier method.

Safety Analyses

All safety parameters will be summarized using the Safety Population.

All AEs will be presented in incidence tables coded by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term and System Organ Class. Additionally, separate AE incidence tables, coded by MedDRA term, will be presented by: 1) toxicity grade (severity) graded by the CTCAE and 2) relationship to study medication (PEGPH20 and pembrolizumab).

All AEs, serious adverse events, AEs leading to treatment discontinuation, and deaths occurring during the study will be summarized.

Laboratory parameters and vital signs and the corresponding change from baseline over time will be summarized using descriptive statistics.

Pharmacokinetic and Pharmacodynamic Analyses

For PEGPH20 noncompartmental and compartmental PK modeling will be performed. The AUC, the C_{max} and $T_{1/2}$ will be summarized from noncompartmental analysis along with descriptive statistics. Other PK analyses may be performed and population PK parameters including $T_{1/2}$, V_D, and CL will be evaluated and reported if the data are sufficient. For plasma HA, descriptive statistics will be used to summarize the measured plasma concentrations.

Exploratory Analyses

Descriptive summaries will be provided for all exploratory endpoint analyses.

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3. STUDY SCHEDULES OF EVENTS

Table 1: Study Schedule of Events: Screening (Dose Escalation and Expansion)

Tests and Assessments	Screening
	≤28 Days Prior to Day 1
Sign and Date Informed Consent (Subject may provide consent for HA testing of tumor tissue on a separate, prescreening ICF in Dose Expansion [details in Section 8.2.1.1])[a]	X
Study Procedure-Associated SAE Recording	X
Inclusion/ Exclusion Criteria	X
Medical History	X
Prior Medication History	X
Confirm and Retrieve Tumor Tissue[b]	X
Disease Assessment (CT scan/MRI scan of chest, abdomen, pelvis, and other areas of known or newly suspected disease)[c]	X
CT/MRI Brain scan to assess potential CNS disease and/or metastases	X
PET/CT[d]	X
DCE-MRI[d]	X
12-Lead ECG	X
Subject Registration into Interactive Web Response System following signing of ICF/prescreening ICF (if used in Dose Expansion)	X
Physical Examination[c]	X
Vital Signs[c]	X
ECOG Performance Status	X
Height[c]	X

Table 1: Study Schedule of Events: Screening (Dose Escalation and Expansion) (Continued)

Tests and Assessments	Screening
	≤28 Days Prior to Day 1
Weight[c]	X
Urine/Serum Pregnancy Tests (WOCBP) (Local Laboratory)[e]	X
Central Laboratory Assessments	
Plasma HA Level and Exploratory Biomarkers	X
Hematology, Chemistry (Including Glucose), Urinalysis	X
Thyroid Function Tests[f]	X
Coagulation Tests	X

Abbreviations: CT = computed tomography; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HA = hyaluronan; PET = positron emission tomography; T3 = triiodothyronine; T4 = total thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential; CNS = Central Nervous System; ICF = Informed Consent Form; SAE = Serious Adverse Event

Note: Each treatment cycle is 21 days. Dose interruption and modifications are permitted.

[a] The 28-day screening window will begin when the subject signs the study ICF (i.e., signature on the prescreening ICF does not initiate the screening window).

[b] In Dose Escalation – Available tissue from the primary or a metastatic lesion is required. A formalin-fixed paraffin-embedded (FFPE) block or 5-10 unstained, consecutive core biopsy slides of 1 tumor tissue block (refer to Inclusion Criterion #4 for more details) are required to send to the central laboratory. **Note:** Fine needle aspirates or brushing biopsies will not be acceptable.

In Dose Expansion – Available tissue from the primary or a metastatic lesion is required. An FFPE block or 10-15 unstained, consecutive tumor tissue slides of 1 tumor tissue block (refer to Inclusion Criterion #4 for more details) are required to send to the central laboratory. **Note:** Fine needle aspirates or brushing biopsies will not be acceptable. Archived resection specimens from the primary tumor without radiologic evidence of metastasis at the time of resection are not suitable to establish histological confirmation and require new tumor tissue of a metastatic site. Tumor tissue must be sent to central laboratory to assess HA status for eligibility into the Dose Expansion portion of the study.

[c] If these procedures are performed as part of standard-of-care prior to the subject's signing of the Informed Consent Form, the results may be used for screening purposes provided the procedures were performed within the screening window.

[d] Optional procedure. PET/CT and DCE-MRI scans will be sent to the Central Imaging Vendor for analysis if they are conducted. DCE-MRI scans must be obtained within 14 days prior to Day 1 (first dose of study medication).

[e] To be performed within 7 days prior to Day 1 (first dose of study medication).

[f] Blood samples will be collected for baseline testing of thyroid hormones (free T3, free T4; and TSH).

Table 2: Study Schedule of Events: PEGPH20 Plus Pembrolizumab Treatment (Cycles 1 and Beyond)

Tests and Assessments[a]	Treatment Cycle 1 (3 Weeks)					Treatment Cycle 2 and Beyond (Repeats Every 3 Weeks)				28 Day Confirmatory CT Scan/MRI Scan	End of Treatment[b]	Long-Term Follow-up[c]
	Wk 1		Wk 2	Wk 3		Wk 1		Wk 2	Wk 3			
	D1	D2	D8	D15	D18	D1	D2	D8	D15			
Confirm Eligibility Based on Inclusion/ Exclusion Criteria	X											
Physical Examination											X	
Vital Signs[d]	X		X	X		X		X	X		X	
ECOG Performance Status	X					X					X	
Weight	X					X						
12-Lead ECG[e]											X[e]	
Disease Assessment – CT/MRI Scan[f]									X[f]		X[g]	
Response Confirmation Scan										X[h]		
CT/MRI Brain scan[i]									X[i]			
PET/CT Scan[j] (Optional at Selected Sites)					X				X			

Table 2: Study Schedule of Events: PEGPH20 Plus Pembrolizumab Treatment (Cycles 1 and Beyond) (Continued)

Tests and Assessments[a]	Treatment Cycle 1 (3 Weeks)					Treatment Cycle 2 and Beyond (Repeats Every 3 Weeks)				28 Day Confirmatory CT Scan/MRI Scan	End of Treatment[b]	Long-Term Follow-up[c]
	Wk 1		Wk 2	Wk 3		Wk 1		Wk 2	Wk 3			
	D1	D2	D8	D15	D18	D1	D2	D8	D15			
DCE-MRI[k] (Optional at Selected Sites)		X			X							
Urine/serum pregnancy test (local laboratory) before Dosing (WOCBP)						X						
Central Laboratory Assessments												
Hematology	X		X	X		X		X	X		X	
Blood Chemistry (Includes Glucose)	X[l]		X[l]	X[l]		X[l]					X	
Blood Glucose								X	X			
Thyroid Function Tests[m]						X						
Coagulation Tests	X					X					X	
Immunogenicity[n]	X					X					X	
PK, HA and Other Biomarker Analyses	Refer to Table 3 for schedule of PK and biomarker sampling time points											
Optional Post-dose Tumor Biopsy					X[o]							

Table 2: Study Schedule of Events: PEGPH20 Plus Pembrolizumab Treatment (Cycles 1 and Beyond) (Continued)

Tests and Assessments[a]	Treatment Cycle 1 (3 Weeks)					Treatment Cycle 2 and Beyond (Repeats Every 3 Weeks)				28 Day Confirmatory CT Scan/MRI Scan	End of Treatment[b]	Long-Term Follow-up[c]
	Wk 1		Wk 2	Wk 3		Wk 1		Wk 2	Wk 3			
	D1	D2	D8	D15	D18	D1	D2	D8	D15			
Piroxicam and Proton Pump Inhibitor Administration[p]	X		X	X		X		X	X			
PEGPH20 Administration[q]	X		X	X		X		X	X			
Enteric-coated Aspirin Administration for NSCLC subjects[r]	X	X	X	X	X	X	X	X	X			
Enoxaparin Administration for Gastric adenocarcinoma subjects[r]	X	X	X	X	X	X	X	X	X			
Pembrolizumab Administration	X[q]					X[q]						
Concomitant Therapy/Procedure Recording	X									X	X	
Adverse Event Recording	X									X	X	
Long-Term Follow-up[c]												X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PEG = PEGylated Recombinant Human Hyaluronidase; CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group;

PET = positron emission tomography; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; DVT = deep vein thrombosis; HA = hyaluronan; PD = progressive disease; PEGPEM = PEGPH20 + pembrolizumab; PK = pharmacokinetics; T3 = triiodothyronine; T4 = total thyroxine; TSH = thyroid stimulating hormone; Wk = Week; NSCLC = non-small cell cancer.

Note: Visit window is ±2 days of the specified times.

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

[b] Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after determination of PD or within 7 days after treatment discontinuation of PEGPH20 and pembrolizumab for other reasons.

[c] After the End of Treatment Visit, subjects will enter long-term follow-up during which information on the subject's survival and subsequent anti-cancer therapy will be obtained by the site every 12 weeks. Long term follow-up will continue until the subject dies, is lost to follow-up, or withdraws consent.

[d] Vital signs will be done pre dose on Day 1, Day 8 and Day 15 of all cycles and End of Treatment Visit. On all other days, vital signs will be collected for clinically significant AEs.

[e] 12-lead ECG will be done at end of treatment and on an as needed basis when clinically indicated.

[f] Tumor assessment scans (CT/MRI of chest, abdomen, pelvis, and other areas of known or newly suspected disease) will be obtained and evaluated locally for response evaluation based on Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 criteria and irRC at the end of Cycle 2, Cycle 4 and then at the end of every fourth treatment cycle thereafter (i.e., Week 3 of Cycles 2, 4, 8, 12, 16 and beyond). Scans will also be sent to the Central Imaging Vendor (CIV) to be stored for possible central review at a later date, if needed. Scans may be obtained any time on or after Day 15 (of Cycles 2, 4, 8, 12, 16 and every fourth treatment cycle thereafter) to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit. For subjects who are withdrawn from the study due to clinical disease progression, a CT/MRI scan should be requested as soon as possible after clinical progression is determined.

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

[h] A confirmatory scan should be performed no sooner than 28 days after the initial scan that showed a response based on RECIST v1.1 (PR or CR) or irRC. A confirmatory scan should also be performed to confirm disease progression based on irRC no sooner than 28 days after the initial scan that showed progression.

[i] CT/MRI of the brain will be performed for the duration of the study (i.e., post-baseline), if clinically indicated, and within a target of 1 week after a subject achieves a complete response (CR). For NSCLC subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points.

[j] Optional PET/CT will be performed at selected sites. The CIV will analyze PET/CT scans if they are conducted.

[k] Optional DCE-MRI will be performed at selected sites. The CIV will analyze PET/CT and DCE-MRI scans if they are conducted.

[l] On Days 1, 8, and 15 of Cycle 1 and Day 1 of Cycle 2, measurements of total bilirubin, ALP, AST, and ALT (as part of blood chemistry) must be obtained prior to dosing (within 48 hours is acceptable). Local laboratories may be used for these measurements. Dosing can only take place if total bilirubin, ALP, AST and ALT values are within the ranges specified in the Inclusion Criteria. If a subject has any of these values outside the specified ranges on Day 1 of Cycle 2, the Investigator should discuss further dosing plans for the subject with the Sponsor.

[m] Blood samples will be collected for testing of thyroid hormones (free T3, free T4, and TSH]) on Day 1 of Cycle 2 and every third cycle thereafter (i.e., Day 1 of Cycles 2, 5, 8, 11, 14, 17, 20, etc.).

[n] Plasma samples for PEGPH20 immunogenicity will be drawn prior to PEGPH20 dosing on day 1 of every cycle and end of treatment.

[o] Optional post-dose tumor biopsy should be done at the end of Cycle 1 (on or after Day 18) but prior to 1st PEGPH20 dose in Cycle 2.

[p] Piroxicam (20 mg) will be administered at least 1-2 hours prior to PEGPH20 administration on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience), to minimize the severity of MSEs. Prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or over-the-counter [OTC] equivalent).

[q] PEGPH20 will be given in increasing doses (1.6, 2.2, 2.6, 3.0 and 4.0 µg/kg) in combination with 2 mg/kg pembrolizumab in the Dose Escalation portion of the study. If ≥2 subjects experience a DLT at the 1.6 µg/kg dose level, Cohort -1 will be opened and subjects will be dosed at 1.0 µg/kg. In the Dose Expansion portion of the study, PEGPH20 will be given at the RP2D identified in the Dose Escalation portion of the study with 200 mg pembrolizumab.

[r] All NSCLC subjects will be given enteric-coated 81 mg of prophylactic aspirin/day and all gastric adenocarcinoma subjects will be given prophylactic enoxaparin 40 mg/day (pre-filled syringes of enoxaparin are allowed), for prophylaxis of TE events, given the high incidence seen in these tumor types.

Table 3: Study Schedule of Events: Immunogenicity, Pharmacokinetic, Plasma HA, and Exploratory Biomarker Sample Collection

Sampling	Draw Number	Time Point	Screen	Treatment Cycle 1 (21 days)		Treatment Cycles 2+ (Repeats Every 21 days)		End of Treatment
				Week 1		Week 1		
				D1	D2	D1	D2	
Plasma Hyaluronan Exploratory Biomarkers	HA	Screening	X	-	-	-	-	-
PEGPH20 Pharmacokinetics	1	Pre PEGPH20 Dose (within 2 hours prior to dosing)	-	X	-	-	-	-
Plasma Hyaluronan Exploratory Biomarkers Immunogenicity[a]	1HAI	Pre PEGPH20 Dose (within 2 hours prior to dosing)	-	X	-	X	-	-
PEGPH20 Pharmacokinetics	2	15 minutes Post PEGPH20 Dose (±5 minutes)	-	X	-	X	-	-
PEGPH20 Pharmacokinetics	3	1 hour Post PEGPH20 Dose (±15 minutes)	-	X	-	-	-	-
PEGPH20 Pharmacokinetics Plasma Hyaluronan Exploratory Biomarkers	4	2-4 hours Post PEGPH20 Dose	-	X	-	-	-	-
Pembrolizumab Pharmacokinetics	5	Pre PEM Dose (within 2 hours prior to dosing)	-	X	-	X	-	-
PEGPH20 Pharmacokinetics	6	6-8 hours Post PEGPH20 Dose	-	X	-	X	-	-
Plasma Hyaluronan Exploratory Biomarkers	6HA	6-8 hours Post PEGPH20 Dose	-	X	-	-	-	-
Pembrolizumab Pharmacokinetics	7	0-2 hours Post PEM Dose	-	X	-	X	-	-

Table 3: Study Schedule of Events: Immunogenicity, Pharmacokinetic, and HA Sample Collection (Continued)

Sampling	Draw Number	Time Point	Screen	Treatment Cycle 1 (21 days)		Treatment Cycles 2+ (Repeats Every 21 days)		End of Treatment
				Week 1		Week 1		
				D1	D2	D1	D2	
PEGPH20 Pharmacokinetics	8	24-26 hours Post PEGPH20 Dose	-	-	X	-	X	-
Plasma Hyaluronan Exploratory Biomarkers	8HA	24-26 hours Post PEGPH20 Dose	-	-	X	-	-	-
PEGPH20 Pharmacokinetics	9	28-32 hours Post PEGPH20 Dose	-	-	X	-	X	-
Pembrolizumab Pharmacokinetics	10	24-28 hours Post PEM Dose	-	-	X	-	X	-
Immunogenicity[a]	99	End of Treatment	-	-	-	-	-	X
PEGPH20 Pharmacokinetics Immunogenicity Plasma Hyaluronan Exploratory Biomarkers Pembrolizumab Pharmacokinetics	U#	Unscheduled	X	X	X	X	X	X

Abbreviations: D = day; HA = hyaluronan; PEM = pembrolizumab.

[a] PEGPH20 Immunogenicity.

Notes: Pembrolizumab PK samples will be collected and analyzed when a validated assay is available. If a subject discontinues PEGPH20 therapy, PEGPH20 PK samples will not be collected from that subject. However, if that subject continues on pembrolizumab therapy at the discretion of the Investigator, pembrolizumab PK samples must be collected.

Plasma samples are required for PEGPH20 PK, plasma hyaluronan, biomarker, and PEGPH20 immunogenicity analysis; serum samples are required for pembrolizumab PK analysis.

4. BACKGROUND AND RATIONALE

4.1. Non-Small Cell Lung Cancer

Lung cancer accounts for about 27% of all cancer deaths and is by far the leading cause of cancer death among both men and women. An estimated 158,040 deaths (86,380 in men and 71,660 in women) are expected to occur in 2015 in the United States (US) alone. Although the incidence rate has been declining in recent times for both men and women, the American Cancer Society's estimates that 221,200 new cases of lung cancer (115,610 in men and 105,590 in women) will be diagnosed in the US in 2015 (American Cancer Society 2015).

Lung cancers are broadly classified into two types: small cell lung cancers (13%) and non-small cell lung cancers (NSCLC) (83%) for the purposes of treatment (American Cancer Society 2015). NSCLC, which arises from the epithelial cells of the lung of the central bronchi to terminal alveoli, is the most common type of lung cancer. The main types of NSCLC are adenocarcinoma (approximately 50% of cases), squamous cell (approximately 30% of cases), large cell (approximately 10% of cases) and bronchial alveolar carcinoma (now classified as adenocarcinoma in situ).

The prognosis for NSCLC is poor (Jemal 2011), and at least 50% of patients treated for early stage disease will go on to experience progression or relapse to advanced disease (Sculier 2009). Seventy percent of patients present with advanced stage disease, for which the response rate to current standard combination chemotherapy is only 20% to 25%, and median survival is 10 to 12 months (Gupta 2014). Clearly a plateau has been reached with traditional chemotherapy and further progress will depend upon identifying novel methods to target tumor cells.

Harnessing the human immune system to target lung cancer could result in the development of effective treatment options against lung cancer and potentially enhance the effect of cytotoxic chemotherapy.

4.2. Gastric adenocarcinoma

Gastric cancer was the world's third leading cause of cancer mortality in 2012 and was responsible for 723,000 deaths worldwide that year (Bass 2014). Although its incidence and mortality has declined since then, the American Cancer Society estimates that there will be 24,590 new cases of gastric cancer reported in the US in 2015 along with 10,720 deaths (American Cancer Society 2015). Gastric adenocarcinoma is a malignant epithelial tumor, originating from glandular epithelium of the gastric mucosa. Ninety percent of all tumors of the stomach are malignant, and gastric adenocarcinoma comprises 95% of the total number of malignancies (Dicken 2005).

The survival rates for gastric cancer are among the worst of any solid tumor (Yang 2011). For early-stage cancer, surgical resection remains the mainstay of curative-intent treatment (Wang 2015). Despite the success of modern chemotherapy in the treatment of large bowel cancers, the 5-year survival of patients with advanced gastric cancer is 3.1%. The role of surgery is also limited in advanced gastric cancer as only 23% of stage IV gastric cancer patients receiving a palliative gastrectomy are alive one year after surgery (Yang 2011).

Current management strategies and treatments are limited primarily by lack of specificity to the cancer cells and by general treatment toxicities that limit full delivery of anticancer agents (Wang 2015). For these reasons, novel therapeutic strategies are urgently needed.

4.3. Hyaluronan and Malignancy

Hyaluronan (HA) is a high-molecular-mass polysaccharide found in the extracellular matrix of tumors. Accumulation of HA in several malignant diseases is associated with aggressive tumor type, cancer progression/metastasis, and poor prognosis (Toole 2008; Sironen 2011). Interaction of pericellular HA and CD44 has been shown to influence drug resistance (Misra 2003). Local aberrations of HA metabolism have been reported in many solid tumor malignancies, where elevated levels of HA frequently correlate with poor prognosis in tumors such as pancreatic (Kultti 2012; Whatcott 2011), breast (Auvinen 2000), gastric (Setälä 1999), colorectal (Ropponen 1998), ovarian (Anttila 2000), prostate (Bharadwaj 2009) and lung carcinoma (Chow 2010). Further information about HA in lung cancer is provided in Section 4.6.3.

4.4. PEGylated Recombinant Human Hyaluronidase PH20

Halozyme, Inc. (Halozyme) has developed an investigational new molecular entity, PEGylated recombinant human hyaluronidase PH20 (PEGPH20), which uses a novel mechanism of action to systemically target tumors that accumulate HA. In preclinical models, both tumor xenografts in immunocompromised mice and autochthonous tumors from genetically engineered $^{KrasLSL\text{-}G12D/þ}$; $Trp53^{LSL\text{-}R172H/þ}$; Cre (KPC) mice, depletion of HA from the tumor microenvironment (TME) has been shown to inhibit the growth of tumors characterized by accumulation of HA (Thompson 2010; Jiang 2012; Provenzano 2012; Jacobetz 2013).

The PH20 recombinant human hyaluronidase (rHuPH20) enzyme is a soluble domain of the endogenous human PH20 glycoprotein, devoid of its carboxy-terminal, lipid anchor attachment site. To increase the plasma half-life and enable systemic therapeutic exposure not possible with existing recombinant human PH20 (rHuPH20), Halozyme developed a PEGylated version of PH20. Like rHuPH20, PEGPH20 removes HA from the extra cellular matrix by depolymerizing the substrate (Thompson 2010). 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 accumulation (Jiang 2012). PEGPH20 has a terminal plasma half-life of approximately 3.2 hours in rodents and 50 hours in monkeys. In humans, data from 2 subjects dosed with 50 µg/kg PEGPH20 in Study HALO-109-101 demonstrated a plasma half-life of 2.5 to 4.8 hours for the initial phase and 26 to 49 hours (1 to 2 days) for the terminal phase (as compared with <5 min for rHuPH20 intravenous (IV) hyaluronidase [Wolf 1982]). The increased plasma half-life of PEGPH20 makes sustained depletion of tumor-associated HA feasible.

4.4.1. PEGPH20 and Chemotherapy

Enzymatic HA depletion from the TME, with PEGPH20 either alone or in combination with chemotherapy, represents an innovative potential treatment that could provide improved therapeutic outcomes for patients (Pillwein 1998; Baumgartner 1998; Klocker 1998), based on a reduction in interstitial fluid pressure, and the subsequent vascular decompression, increased blood volume, and concomitantly enhanced drug penetration into HA-rich tumors (Spruss 1995, Brekken 1998; Eikenes 2005; Thompson 2010), and on the reduction of tumor HA levels, which

was reported to reduce in vitro tumor cell proliferation, motility, and invasion, and to reduce the growth of implanted tumors (Shuster 2002; Simpson 2002; Kim 2004; Nishida 2005; Udabage 2005; Li 2007; Thompson 2010; Provenzano 2012; Jacobetz 2013).

In the autochthonous KPC pancreatic model, PEGPH20 treatment induced fenestrations and interendothelial junctional gaps in pancreatic endothelia (Jacobetz 2013). Independent studies in the same model reported that the increased vascular perfusion observed when PEGPH20 is given in combination with gemcitabine (GEM) persisted for weeks after therapy ceased, suggesting that the TME was permanently remodeled following PEGPH20 treatment (Provenzano 2012; Provenzano 2013). In mouse pancreatic xenografts, PEGPH20 treatment induced translocation of E-cadherin and β-catenin to the plasma membrane of cancer cells, suggesting at least a partial reversal of the classic epithelial-mesenchymal transition (EMT) observed during the progression of malignancy (Kultti 2014). Finally, in NSCLC patient-derived xenografts (PDx) the antitumor effect of PEGPH20 in combination with docetaxel (Doc) (Taxotere®) was evaluated (Halozyme Report 13036). In HA-high PDx tumors, PEGPH20 enhanced the effect of Doc, increasing tumor growth inhibition from 52.5% for Doc alone to 115% for PEGPH20 plus Doc, while concomitantly increasing survival by 50% (35d for Doc alone vs 70d for PEGPH20 plus Doc).

4.5. Clinical Experience with PEGPH20 and Clinical Development Plan

PEGPH20 is being developed as an investigational, novel therapeutic agent for use in combination with chemotherapy or other agents for the treatment of patients with cancers that accumulate HA. As of 13 February 2016, approximately 238 subjects had been exposed to at least 1 dose of PEGPH20 in 6 Sponsor clinical studies: in 2 Phase 1 studies as a single agent (HALO-109-101 and HALO-109-102), in combination with chemotherapy in a Phase 1b study in pancreatic cancer (HALO-109-201), in combination with chemotherapy in a Phase 2 study in pancreatic cancer (HALO-109-202), in combination with chemotherapy in a Phase 1b study in lung cancer (HALO-107-201) and in combination with an immunotherapeutic drug pembrolizumab in this Phase 1b study in lung cancer (HALO-107-101). The clinical development program also includes an ongoing Phase 3 study of PEGPH20 in combination with chemotherapy in HA-high subjects with pancreatic cancer.

4.5.1. Phase 1 Study HALO-109-101

This study enrolled 14 subjects with advanced malignancies (including one subject with NSCLC) who experienced disease progression after previous therapy. This study was amended due to the observation of severe musculoskeletal events (MSEs) and was closed due to these events and inability to dose escalate.

4.5.2. Phase 1 Study HALO-109-102

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

26 subjects enrolled in this study, six were treated at 3.0 µg/kg once weekly and 15 received 3.0 µg/kg twice weekly schedule. The maximum tolerated dose (MTD) was determined to be 3.0 µg/kg once or twice weekly.

4.5.3. Phase 1b Study HALO-109-201

This study was initiated to identify the recommended Phase 2 dose (RP2D) of PEGPH20 in combination with GEM (Gemzar®) in subjects with metastatic pancreatic cancer. A total of 28 subjects were treated with PEGPH20 administered by IV infusion twice per week for the first 4 weeks, then weekly for three weeks, followed by one week rest. GEM was administered at 1000 mg/m^2 intravenously over 30 minutes once per week for 7 weeks followed by one week rest. Dexamethasone was used 1 hour pre and 8 hours post PEGPH20 dosing. From Cycle 2 onward, PEGPH20 and GEM were administered once weekly for three weeks in a 4-week cycle.

4.5.4. Phase 2 Study HALO-109-202

This is an ongoing Phase 2 multicenter, open-label, randomized study which enrolled/randomized a total of 279 subjects with Stage IV previously untreated pancreatic ductal adenocarcinoma (PDA) who are receiving either PEGPH20 combined with nab-paclitaxel (NAB) plus GEM (PAG treatment) or NAB plus GEM (AG treatment). The study is blinded to the Sponsor.

In April 2014, the HALO-109-202 Data Monitoring committee (DMC) reported an imbalance in TE events with a higher incidence in subjects treated with PAG than AG therapy alone (28.4% vs. 14.8%, respectively). Based on these findings, the study was placed on a temporary clinical hold. All 29 ongoing subjects in the PAG group stopped PEGPH20 therapy and remained on AG therapy alone. In June 2014, the temporary clinical hold was lifted and the study protocol was amended to: (1) include concomitant use of prophylactic enoxaparin for all subjects, (2) requirement to discontinue PEGPH20 permanently after a TE event occurred, and (3) exclude subjects with evidence of DVT or pulmonary embolism as well as those subjects determined to be at high risk of TE events s. Stage 1 of this study includes subjects who were enrolled prior to the clinical hold (N = 146 randomized). Stage 2 is ongoing and includes subjects enrolled after the clinical hold and subsequent protocol amendment (N = 133 randomized).

A data analysis was performed as of a data cut of 16 December 2016. Interim safety and efficacy data from this study are presented in Section 4.5.7 Safety and Section 4.5.8 Efficacy.

4.5.5. Phase 1b Study HALO-107-201

This was a Phase 1b/2, randomized, multicenter study of PEGPH20 in subjects with recurrent previously treated locally advanced or metastatic NSCLC receiving either PEGPH20 combined with Doc or Doc alone.

The study was designed to have a Phase 1b Dose Escalation portion and a Safety Evaluation portion, in all comers (i.e., subjects not selected based on HA status), and a Cohort Expansion portion in prospectively selected HA-high subjects followed by a Phase 2 portion.

In the Phase 1b Dose Escalation portion, approximately 3 to 6 subjects/ cohort were to receive PEGPH20 at each increasing dose level (1.6, 2.2, 2.8 and 3.0 µg/kg) once/cycle in combination with standard dosing of docetaxel (75 mg/m^2 every 21 days). Additional Safety Evaluation (in up

to 20 subjects) and Cohort Expansion portions (in up to 50 subjects) were to further evaluate the safety and tolerability of PEGPH20 in combination with docetaxel (PDoc) treatment before initiating Phase 2. Safety and preliminary pharmacokinetic (PK) results from all subjects dosed in Phase 1b were to be used to determine the RP2D for the Phase 2 portion. In Phase 2, approximately 188 subjects prospectively selected for high HA levels were planned to be randomized in a 1:1 ratio to receive PDoc at the PEGPH20 dose selected in Phase 1b or docetaxel alone (Doc; 75 mg/m^2 once in each 21-day cycle).

This study was terminated during the Dose Escalation portion due to evolving standard-of-care in the NSCLC treatment landscape. At the time of termination, 16 subjects had been enrolled in the Dose Escalation portion, of which 15 were dosed at 3 different dose levels of PEGPH20 (1.6, 3.0, and 2.2 µg/kg). Results are pending analysis at the time of writing this protocol amendment. TE event data are given in Section 4.5.7.2. Additional information is provided in the PEGPH20 Investigator's Brochure.

4.5.6. Phase 3 Study HALO-109-301

This is an ongoing randomized, double-blind, placebo-controlled, multicenter study of PEGPH20 (3.0 µg/kg) in combination with NAB (125 mg/m^2) plus GEM (1000 mg/m^2) (PAG treatment) compared with placebo plus NAB and GEM (AG treatment) in 420 and up to 570 subjects with HA-high Stage IV previously untreated PDA.

Eligible subjects are randomized in a double-blind fashion to 1 of 2 treatment groups in a 2:1 ratio for PAG:AG. Randomization is stratified by geographic region (North America, Europe, and Others).

The Treatment Period consists of 4-week treatment cycles (28 days), with Week 4 of every cycle being a rest week (i.e., no treatment is given). PEGPH20 or placebo is administered as an 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 is administered as IV infusions once weekly for Weeks 1 to 3 of all treatment cycles.

4.5.7. Safety

In more than approximately 238 subjects exposed to PEGPH20, either in the monotherapy or combination setting in Sponsor clinical studies, the most frequently reported adverse events (AEs) are fatigue, cytopenia (anemia, thrombocytopenia, neutropenia), gastrointestinal events (nausea, vomiting, and diarrhoea), and peripheral oedema. In addition to these common AEs, both MS events (primarily muscle spasms and myalgias) and thromboembolic (TE) events are considered identified risks of PEGPH20. Each of these AEs remain manageable with supportive therapy, considering the low rate (14%) of discontinuation due to any study drug related AE. Please refer to the Investigator's Brochure for additional safety information.

4.5.7.1. Musculoskeletal Events

Prior to the initiation of study HALO-109-102, MSEs had been as severe as Grade 3/4; however, since the use of pre- and post-dose prophylaxis with dexamethasone in studies of PEGPH20 in combination with chemotherapy, the majority are Grade 1/2 in severity and, in general, have not led to treatment discontinuations. Since this study uses an immunotherapeutic agent and

dexamethasone may suppress an immune response, it should only be used when prescribed by the Investigator and following a discussion with the Sponsor.

Piroxicam and toradol have been investigated in an animal model of MSEs and may be helpful in decreasing the severity of MSEs in subjects (internal unpublished Halozyme report). In this study, piroxicam will therefore be administered to decrease the severity of MSE's; toradol may be given for severe pain as recommended in the Prescribing Information (see Section 10.12 for additional details).

4.5.7.2. Thromboembolic Events

Thromboembolic events and their sequelae have been observed in clinical studies evaluating PEGPH20 monotherapy and combination therapies.

In the 2 completed Phase 1 studies of PEGPH20 monotherapy in subjects with advanced solid tumors (HALO-109-101 and HALO-109-102; N = 40), TE events were observed in 1 subject who experienced embolism.

In the Phase 1b Study HALO-107-201 in NSCLC, which was discontinued early by the Sponsor in August 2016 due to the changing treatment landscape for NSCLC, up to the date of study discontinuation, 4 of 15 (27%) treated subjects experienced a TE event, including deep vein thrombosis (DVT) and superficial thrombophlebitis.

In completed Study HALO-109-201 of PEGPH20 in combination with gemcitabine in pancreatic cancer, the incidence of TE events was approximately 28%, the majority being of venous origin.

Regarding the Phase 2 Study HALO-109-202 in pancreatic cancer, as discussed in Section 4.5.4, an imbalance was observed in the rate of TE events between the PAG and AG treatment arms (28.4% vs. 14.8%) in Stage 1 of the study that led to the implementation of risk mitigation measures, including the exclusion of high-TE event risk subjects and the administration of enoxaparin prophylaxis in all subjects. The majority of the TE events were of venous origin (DVT and pulmonary embolism); however, arterial events were also reported. Itis widely accepted that pancreatic cancer is a tumor type with a high TE event background rate. Published studies have reported a TE event incidence in these patients ranging from 17% to 57.7% (Khorana 2004; Bapat 2016).

Since the implementation of the aforementioned measures in Stage 2 of HALO-109-202, the incidence of TE events has decreased considerably compared with that observed in Stage 1. Based on an analysis as of a data cutoff of 16 December 2016, the TE rate in the PAG and AG groups, respectively, decreased from 43% and 25% in Stage 1 (no enoxaparin prophylaxis) to 10% and 6% in Stage 2 (with enoxaparin 1 mg/kg/day prophylaxis). Additional details are provided in the PEGPH20 Investigator's Brochure.

While the rate of TE events in pancreatic cancer is reported to be highest among malignancies (Pelzer 2015), rates of TE events in NSCLC and gastric cancer have also been reported to be elevated (Chew 2008 and Khorana 2012, respectively). Based on these data, the following safety measures will be taken to safeguard subjects:

1. Subjects with a history of or presence of a pulmonary embolism at baseline will be excluded from this trial.

2. All NSCLC subjects will be given enteric-coated 81 mg of prophylactic aspirin/day and all gastric adenocarcinoma subjects will be given prophylactic enoxaparin 40 mg/day for TE event prophylaxis, given the high incidence seen in these tumor types, and closely monitored. PEGPH20 will be discontinued for subjects who experience any TE requiring full-dose anticoagulation while on study. Treatment with pembrolizumab, however, may continue as deemed appropriate by the Investigator.
3. In gastric adenocarcinoma subjects, if enoxaparin is discontinued for any reason, PEGPH20 will also be discontinued. Treatment with pembrolizumab, however, may continue as deemed appropriate by the Investigator.
4. Sites will report any TE event to the Sponsor immediately and no later than 24 hours of awareness.

4.5.8. Efficacy

In the Phase 1b study (HALO-109-201) in subjects with pancreatic cancer, responses were assessed by an independent central radiologist. Partial Response (PR) was reported in 10 of the 24 subjects who received PEGPH20 at either the 1.6 or 3.0 µg/kg dose level. In addition, subjects who had HA high in tissue biopsies experienced better responses (5/6 subjects), which correlated with prolonged progression-free survival (PFS; 219 days) and overall survival (OS; approximately 395 days). PRs were seen in 4 of the 11 subjects who had lower HA in tissue biopsies. The PFS and OS in the low-HA group were 108 days and 174 days, respectively (Hingorani 2015). Further details about efficacy in early studies are provided in the PEGPH20 Investigator's Brochure.

Halozyme has developed, in collaboration with a leading diagnostic company, Ventana Medical Systems, Inc., a novel co-developed investigational diagnostic assay (VENTANA HA RxDx assay [RxDx]) to identify subjects who might benefit most, based on HA tumor content, from the administration of PEGPH20 in conjunction with other cancer therapeutics. This assay uses an affinity-histochemistry-based staining method to evaluate HA levels in tumor biopsies.

For Phase 2 HALO-109-202, a data analysis was performed as of a data cut of 16 December 2016. Tumor samples from were collected and analyzed in a prospective-retrospective fashion using the RxDx assay. As of the data cutoff date, of the 279 subjects comprising the ITT Population, 97% (270/279) of subjects in the Stage 1 + Stage 2 combined were off treatment. Efficacy results for the combined Stage 1 + Stage 2 ITT HA-high Population (n = 84 [49 PAG, 35 AG]) indicate a statistically significant 77% improvement in PFS, with a median of 9.2 months for PAG vs. 5.2 months for AG (HR: 0.51; p-value: 0.048). Despite the limitations of the Stage 1 data set due to the clinical hold (e.g., subjects discontinuing PEGPH20 and continuing on AG alone), there was a 35% improvement in median OS which was 11.5 months with PAG 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 have a worse prognosis when treated with the standard of care AG therapy, suggesting that high levels of HA are a potential 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. Additional details are provided in the PEGPH20 Investigator's Brochure.

4.5.9. Clinical Pharmacokinetics

Subjects enrolled in the Phase 1 studies received PEGPH20 at doses ranging from 0.5 to 50 µg/kg with or without dexamethasone. Blood samples were collected at scheduled time points, and plasma was analyzed for PEGPH20 concentrations. PK analysis suggests that a linear PK model adequately described the available PEGPH20 plasma concentration versus time profiles. The maximum plasma concentrations were estimated to be between 0.4 and 1.0 hours after dosing. Subjects dosed with 50 µg/kg PEGPH20 in Study HALO-109-101 demonstrated a plasma half-life of 2.5 to 4.8 hours for the initial phase and 26 to 49 hours (1 to 2 days) for the terminal phase. Estimates for initial distribution volume were consistent with expectations for therapeutic macromolecules. The prolonged plasma half-life of PEGPH20 makes sustained depletion of tumor-associated HA feasible. Clinical experience to date (largely involving combination therapy with GEM) indicates that the linear PK characteristics of PEGPH20 given alone are maintained in combination therapy. Details of the PK characteristics of PEGPH20 are provided in the PEGPH20 Investigator's Brochure.

4.6. Study Rationale

Therapy with mAbs directed against multiple check-point receptors involved in the immune response (e.g. cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], programmed cell death‑1 [PD-1] and PD-1 ligand 1 [PD-L1]) has changed the treatment paradigm for advanced melanoma and NSCLC. However, when used as single agents, in advanced previously treated NSCLC patients, these compounds have lower response rates (<25%) and may have considerable systemic toxicity (Brahmer 2012; Brahmer 2014; Garon 2015). These compounds are currently either approved or in development by pharmaceutical companies for numerous indications including NSCLC, renal cell cancer, head and neck cancer and lymphoma. The rationale for combining PEGPH20 with such immunotherapies is based on nonclinical data indicating that addition of PEGPH20 to such therapies leads to increased accessibility of natural killer (NK) cells to HA-high tumor cells *in vitro* and *in vivo*, increased accessibility of antibodies to HA-high tumor cells (e.g. trastuzumab [Herceptin®]), increased antibody-dependent killing of HA-high tumor cells *in vitro* (e.g. trastuzumab and cetuximab [Erbitux™], increased antibody- and NK-dependent tumor growth inhibition in xenograft models (Singha 2015), increased tumor growth inhibition of anti-CTLA4 in a syngeneic murine colon cancer model (unpublished internal report) and increased accumulation of a salmonella-based therapeutic and neutrophils in orthotopic pancreatic tumors (Manuel 2014).

This Phase 1b study will test the safety and early biological activity of PEGPH20 combined with the immunotherapeutic mAb pembrolizumab (Keytruda®) (the combination is hereafter referred to as PEGPEM) in subjects with HA-high solid tumors.

4.6.1. Pembrolizumab for Treatment of NSCLC

Platinum-based chemotherapy, with or without maintenance therapy, subsequently followed by second-line cytotoxic chemotherapy, is standard treatment for most patients with advanced non-small cell lung cancer, with a median survival of approximately 1 year. One hallmark of cancer is immune evasion, in which the immune system does not mount an effective antitumor

response. PD-1 is a negative costimulatory receptor expressed primarily on the surface of activated T-cells. The binding of PD-1 to one of its ligands, PD-L1 or PD-L2, can inhibit a cytotoxic T-cell response. Tumors can co-opt this pathway to escape T-cell–induced antitumor activity. Pembrolizumab, a highly selective, humanized monoclonal IgG4 kappa isotype antibody against PD-1, can disrupt the engagement of PD-1 with its ligands and impede inhibitory signals in T-cells, with resultant tumor recognition by cytotoxic T-cells.

The efficacy and safety of PD-1 inhibition with pembrolizumab was assessed in patients with advanced NSCLC in a Phase 1 study in which 495 patients were assigned to receive pembrolizumab at a dose of either 2 mg or 10 mg per kg of body weight every 3 weeks or 10 mg per kg every 2 weeks (Garon 2015). The primary objectives of the study were to evaluate the safety, side-effect profile, and antitumor activity of pembrolizumab. The study also sought to define and validate an expression level of the PD-L1 that is associated with the likelihood of clinical benefit.

Among all the patients, the ORR observed was 19.4%, and the median duration of response (DOR) was 12.5 months. The median PFS was 3.7 months, and the median OS was 12.0 months. PD-L1 expression in at least 50% of tumor cells was selected as the cutoff. Among patients with a proportion score of at least 50% the response rate was 45.2%. Among all the patients with a proportion score of at least 50%, median PFS was 6.3 months; median OS was not reached. Common side effects attributed to pembrolizumab were fatigue, pruritus, and decreased appetite.

In conclusion, pembrolizumab had an acceptable side-effect profile and showed antitumor activity in patients with advanced non-small-cell lung cancer. PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab.

4.6.2. Pembrolizumab for Treatment of Gastric Adenocarcinoma

Treatment choices for gastric cancer depend on tumor type and stage. The only hope for cure currently rests on removal of the malignant tissue either endoscopically or by surgical resection. For advanced disease, treatment is largely palliative and consists of a combination of surgery, chemotherapy, and radiation. Overall, the results of current therapy for advanced disease are poor with low 5 years survivals. Immunotherapy provides another dimension to the prevention and management of gastric cancer and offers hope of breaking through current constraints (Matsueda 2014).

The safety and efficacy of pembrolizumab was assessed in a phase 1b study in patients with advanced gastric cancer in KEYNOTE-012 (Clinicaltrials.gov identifier NCT01848834). Using a prototype immunohistochemistry assay, PD-L1 expression was assessed in archival tumor samples from patients with recurrent/metastatic adenocarcinoma of the stomach or gastroesophageal junction. Eligible patients with PD-L1 staining in stroma or ≥1% of tumor cells were enrolled and treated with pembrolizumab 10mg/kg every 2 weeks for up to 24 months or until complete response (CR), disease progression or unacceptable toxicity. AEs were monitored and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE c4.0). Radiographic imaging was performed every 8 weeks. Primary efficacy endpoint was ORR assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Of the 162 patients screened, 65 (40%) were PD-L1 positive. Of these 65 patients, 39 enrolled. The number of prior therapies for advanced disease ranged from 0 to 5; 67% received ≥2 prior therapies. Median follow-up duration was 8.8 months (range 6.2-12.6); 13 patients (33%) remain

on therapy. Four patients experienced 5 total grade 3-5 drug-related adverse events: peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis (n = 1 each). There was 1 drug-related death (hypoxia). ORR was 22% (95% CI 10-39) by central review and 33% (95% CI 19-50) by Investigator review. Median time to response was 8 weeks (range 7-16), with a median response duration of 24 weeks (range 8+ to 33+). PD-L1 expression level was associated with ORR (1-sided P = 0.10). The 6-month PFS rate was 24%. The 6-month OS rate was 69%.

In conclusion, pembrolizumab demonstrated manageable toxicity and promising antitumor activity in advanced gastric cancer patients selected for PD-L1 expression using a prototype immunohistochemistry assay. These results support the ongoing development of pembrolizumab for gastric cancer (Muro 2015).

The safety and efficacy of nivolumab, another anti-PD-1 antibody was assessed in 7 patients with advanced gastric cancer, unselected for PD-L1 expression, in a multicenter phase 1 trial. No objective responses were observed in the gastric cancer patients (Brahmer 2012).

4.6.3. Use of PEGPH20 in HA-high Tumors

The degradation of tumor-associated HA is hypothesized to increase the ability of anti-cancer agents to penetrate tumor tissue and, therefore increase cytotoxic activity in tumors. In tumors that are rich in HA, as is the case for NSCLC and gastric cancer, tumor tissue may be especially sensitive to the HA-degradation by PEGPH20 and thus responsive to an increase in the immunotherapeutic effects of pembrolizumab. Modifying the extracellular environment to increase the penetration and efficacy of immunotherapeutics represents a novel approach to treating NSCLC and gastric adenocarcinoma in a setting that has demonstrated preliminary therapeutic efficacy.

In addition to increasing tumor perfusion, and subsequently increasing the accumulation of therapeutics, PEGPH20-mediated HA removal alone has been shown in preclinical models to significantly inhibit tumor growth; the magnitude of the PEGPH20 antitumor activity correlating with the magnitude of tumor HA accumulation (Thompson 2010; Jiang 2012). Further, HA removal appears to be associated with sustained changes in tumor vascular architecture and a reduction of EMT tumor markers (Provenzano 2012; Jacobetz 2013; Kultti 2014).

In an investigation of the HA accumulation profile in human lung cancer using commercially available human tissue microarray (n=117, US Biomax), high levels of HA accumulation were found in 29% of NSCLC cancer tissues with the highest levels of (41%) of HA in squamous tumor type (HA high accumulation [HA-high] was found in 33% of large cell carcinomas and 11% of adenocarcinomas; Jiang 2011). In an investigation of human tissue microarray of gastric adenocarcinoma, high levels of HA accumulation were found in 42% of the gastric adenocarcinoma tissues (Jacobetz 2013).

In an investigation of the antitumor activity of PEGPH20 (single-agent and in combination with therapeutically relevant drug regimens) in NSCLC HA-high expressing human tumor explant models, the antitumor activity of PEGPH20 corresponded to the extent of HA in the tumor, and tumor growth inhibition responses were 97% for HA-high tumors, 44% for medium-HA tumors, and 16% for low-HA tumors (Jiang 2012).

In an animal study combining PEGPH20 with cisplatin and GEM (indicated for the first-line treatment of patients with inoperable, locally advanced [Stage IIIA or IIIB], or metastatic [Stage IV] NSCLC (GEMZAR® Product Insert), in HA-high patient-derived xenograft models of NSCLC, PEGPH20 administered 24 hours before combination chemotherapy inhibited tumor growth by 76.6% ($\Delta T/\Delta C$=23.4%, $p < 0.01$), whereas the combination of cisplatin and GEM alone was not significant. In an animal study combining PEGPH20 with Doc (indicated for patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy (Joshi 2014; TAXOTERE® Product Insert), co-administration of PEGPH20 with Doc increased Doc growth inhibition from 52% ($p < 0.01$) to 116% ($p < 0.0001$), and increased the median survival time 2-fold (35 days with Doc alone compared with 70 days with Doc plus PEGPH20). Further details of these studies are provided in the PEGPH20 Investigator's Brochure.

4.6.4. Rationale for Dose Selection

Rationale for PEGPH20 Dose Selection

A dose of 3.0 µg/kg was identified as the MTD for PEGPH20 as either a single agent or in combination with GEM in 3 separate trials (2 Phase 1 and 1 Phase 1b clinical study). In the phase 1 trial Study HALO-109-101, PEGPH20 was administered once every 21 days. In the phase 1 trial, Study HALO-109-102, PEGPH20 was administered twice per week for the first 4 weeks followed by once a week for the following 4-week cycles (no washout in week 4). In the phase 1b trial, Study HALO-109-201, PEGPH20 was administered twice weekly for the first 4 weeks, then once weekly for 3 of every 4 weeks for the duration of subject participation.

In an ongoing randomized Phase 2 study in subjects with advanced PDA, PEGPH20 is being administered at 3.0 µg/kg twice weekly for 3 weeks during the 1st 4-week cycle, then weekly for 3 of 4 weeks in subsequent cycles in combination with nab-paclitaxel at 125 mg/m^2/week for 3 of 4 weeks and GEM at 1000 mg/m^2 weekly for 3 of 4 weeks.

Since PEGPH20 has not been evaluated in clinical studies in combination with pembrolizumab, this study will have a Dose Escalation portion in which PEGPH20 will be administered to consecutive cohorts in increasing doses (1.6, 2.2, 2.6, 3.0, and 4.0 µg/kg) selected based on clinical judgment, to evaluate the safety and tolerability of PEGPEM treatment before the Dose Expansion portion is initiated. The Dose Escalation portion will also be used to determine the dose of PEGPH20 to be evaluated in the Dose Expansion portion.

Rationale for Pembrolizumab Dose Selection in Dose Escalation

Standard dosing of pembrolizumab (2 mg/kg) will be administered every 3 weeks in the Dose Escalation portion per the Pembrolizumab Prescribing Information (Keytruda® US Prescribing Information 2015) (Protocol Amendment 2).

Rationale for Pembrolizumab Dose Selection in Dose Expansion

A dose of 200 mg pembrolizumab will be administered every 3 weeks to NSCLC subjects in the Dose Expansion portion, per the Pembrolizumab Prescribing Information (Keytruda® US Prescribing Information 2017). The same dosage of pembrolizumab (200 mg every 3 weeks) will also be administered to gastric adenocarcinoma subjects as it is being used in Phase 2 and Phase 3 gastric adenocarcinoma trials evaluating pembrolizumab as a single agent or in combination

with other chemotherapeutics (KEYNOTE-59 [Clinicaltrials.gov identifier NCT02335411], KEYNOTE-061 [Clinicaltrials.gov identifier NCT02370498]).

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Dose Escalation

Primary Objectives

- To assess the safety and tolerability of PEGPEM in subjects with relapsed/refractory NSCLC and relapsed/refractory gastric adenocarcinoma.
- To determine the RP2D of PEGPH20 when administered with pembrolizumab in subjects with relapsed/refractory NSCLC and relapsed/refractory gastric adenocarcinoma.

Secondary Objectives

- To assess the PK of PEGPH20 when given in combination with pembrolizumab in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.
- To obtain an early assessment of the antitumor activity of PEGPEM, as assessed by ORR, DOR, disease control rate (DCR) and PFS based on RECIST v1.1, and OS in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.

Exploratory Objective:

- To assess the PK of pembrolizumab when given in combination with PEGPH20 in subjects with relapsed/refractory NSCLC or relapsed/refractory gastric adenocarcinoma.

5.1.2. Dose Expansion

Note: The objectives described below will be evaluated in HA-high subjects with relapsed/refractory NSCLC and HA-high subjects with relapsed/refractory gastric adenocarcinoma.

Primary Objective

- To evaluate the efficacy of PEGPEM as assessed by ORR based on RECIST v1.1

Secondary Objectives

- To evaluate the efficacy of PEGPEM as assessed by DOR, DCR and PFS based on RECIST v1.1, and OS
- To evaluate the efficacy of PEGPEM as assessed by ORR, DOR, DCR and PFS based on immune-response related criteria (irRC)

- To characterize the PK of PEGPH20 when given in combination with pembrolizumab
- To evaluate the safety and tolerability profile of PEGPEM

Exploratory Objectives

- To evaluate the efficacy of PEGPEM, as assessed by ORR, DOR, DCR, and PFS based on RECIST v1.1 criteria and irRC, by PD-L1 expression levels
- To assess the treatment effect of PEGPEM as follows:
  - Based on HA levels in plasma and tumors, or other potential biomarkers.
  - Based on tumor blood flow and metabolic activity as assessed by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and positron emission tomography (PET)/computed tomography (CT) scans, respectively.
- To assess the PK of pembrolizumab when given in combination with PEGPH20

5.2. Study Endpoints

5.2.1. Dose Escalation

Primary Endpoint

- Dose-limiting toxicity, MTD, and RP2D.

Secondary Endpoints

- PK parameters of PEGPH20: maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), terminal elimination half-life ($T_{1/2}$), area-under the-concentration-time curve (AUC), volume of distribution (V_D) and clearance (CL).
- ORR, DOR, DCR and PFS based on RECIST v1.1.
- OS.

Exploratory Endpoint

- PK parameters of pembrolizumab: C_{max}, C_{min}, $T_{1/2}$, AUC, V_D and CL.

5.2.2. Dose Expansion

Primary Endpoint

- ORR based on RECIST v1.1.

Secondary Endpoints

- DOR, DCR and PFS based on RECIST v1.1, and OS.
- ORR, DOR, DCR and PFS based on irRC.
- PK parameters of PEGPH20: C_{max}, C_{min}, $T_{1/2,}$ AUC, V_D and CL.
- Incidence of AEs.
- Changes in clinical safety laboratory values.

- Changes in cardiovascular parameters (electrocardiogram [ECG]) and vital signs.

Exploratory Endpoints

- ORR, DOR, DCR, and PFS based on RECIST v1.1 criteria and irRC by PD-L1 expression levels.
- Changes from pre-treatment in plasma HA and tumor HA (when available).
- Correlation between plasma HA levels pre-dose, post-dose and any pharmacodynamic response.
- Changes in tumor blood flow as measured by DCE-MRI.
- Changes in tumor metabolism as measured by PET/CT.
- Correlation of biomarkers in plasma and tumor biopsy to study endpoints.
- PK parameters of pembrolizumab: C_{max}, C_{min}, $T_{1/2}$, AUC, V_D and CL.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan: Description

This Phase 1b study of PEGPEM will consist of 2 portions:

- A Dose Escalation portion in subjects with relapsed/refractory Stage IIIB or IV NSCLC after failing at least 1 previous platinum-based chemotherapy regimen (refer to Inclusion Criterion #2) and subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma after failing at least 1 previous chemotherapy regimen for locally advanced or metastatic disease.
- Followed by a Dose Expansion portion in:
  - Previously untreated or treated HA-high subjects with Stage IIIB or IV NSCLC. Previously treated subjects must have failed no more than 1 previous platinum-based chemotherapy regimen for locally advanced or metastatic disease (refer to Inclusion Criterion #3).
  - HA-high subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens for locally advanced or metastatic disease.

Note: In Dose Expansion, subjects will be selected for enrollment whose tumors are HA-high, using a co-developed investigational diagnostic assay (details in Section 8.2.17.1.3). Subjects will be tested retrospectively for PD-L1 expression levels.

The study design is depicted in Figure 1.

Since PEGPH20 has not been evaluated in clinical studies in combination with pembrolizumab, this study will have a Dose Escalation portion to evaluate the safety and tolerability of PEGPEM treatment before the Dose Expansion portion is initiated. The Dose Escalation portion will also be used to determine the dose of PEGPH20 to be evaluated in the Dose Expansion portion.

The treatment period will consist of 21-day cycles.

In Dose Escalation, PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle (i.e. 3 doses/cycle) and pembrolizumab (2 mg/kg every 21 days) on Day 1 of each cycle (i.e. 1 dose/cycle), 4-6 hours after the completion of PEGPH20 administration.

In Dose Expansion, 200 mg of pembrolizumab will be administered every 21 days (per Protocol Amendment 3 [see Section 4.6.4 for additional details]) and the dosing schedule will be as follows:

- PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle (i.e. 3 doses/cycle) and pembrolizumab (200 mg every 21 days) on Day 1 of each cycle (i.e. 1 dose/cycle), 4-6 hours after the completion of PEGPH20 administration.

In Dose Expansion, an independent DMC will review all available safety data from the first 3 NSCLC subjects and first 3 gastric adenocarcinoma subjects who have completed Cycle 1, to determine if the safety and tolerability profile of the PEGPEM combination is acceptable (refer to the DMC charter for additional details). The DMC will also continue to periodically review safety data to protect subject welfare and identify potential safety signals.

Treatment in both portions of the study will continue until death, withdrawal of consent from the study, disease progression, or unacceptable toxicity; however, subjects with asymptomatic disease progression will be allowed to continue study treatment at the Investigator's discretion despite evidence of increasing tumor burden or appearance of new lesions for up to 6 weeks if the subject is "clinically stable." Clinically stable is defined as:

- Absence of symptoms and signs indicating clinically significant PD (including worsening of laboratory values) indicating disease progression;
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status; and
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Dose interruptions and modifications of study treatment are permitted.

In the single-agent studies of PEGPH20 and the combination study with GEM, the DLTs were MSEs of myalgia and muscle cramping. In clinical studies HALO-109-102, HALO-109-201 and HALO-109-202, dexamethasone was administered per protocol to attenuate the severity of MSEs. Since this study uses an immunotherapeutic agent, and dexamethasone may suppress an immune response, it should only be used when prescribed by the Investigator and following a discussion with the Sponsor (Section 10.12.4).

Piroxicam and toradol have been investigated in an animal model of MSEs and may be helpful in decreasing the severity of MSEs in subjects (internal unpublished Halozyme report). Piroxicam (20 mg) will be administered at least 1-2 hours prior to PEGPH20 administration on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience), to minimize the severity of MSEs. The prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or over-the-counter [OTC] equivalent).

Toradol may be given for severe pain as recommended in the Toradol Prescribing Information (Section 10.12.1). Toradol should not be administered concurrently with piroxicam as it is contraindicated in the Prescribing Information to administer toradol simultaneously with other

nonsteroidal anti-inflammatory drugs (NSAIDs) because of the cumulative risk of inducing serious NSAID-related side effects.

To help minimize MSEs, prescribed medication such as narcotics, muscle relaxants and other analgesics (with the exceptions of steroids), OTC drugs and physical therapy can be used at the Investigator's discretion.

All NSCLC subjects will be given enteric-coated 81 mg of prophylactic aspirin/day and all gastric adenocarcinoma subjects will be given prophylactic enoxaparin 40 mg/day (pre-filled syringes of enoxaparin are allowed), for prophylaxis of TE events, given the high incidence seen in these tumor types (Section 10.12.2). PEGPH20 will be discontinued for subjects who experience any TE requiring full-dose anticoagulation while on study. Treatment with pembrolizumab, however, may continue as deemed appropriate by the Investigator.

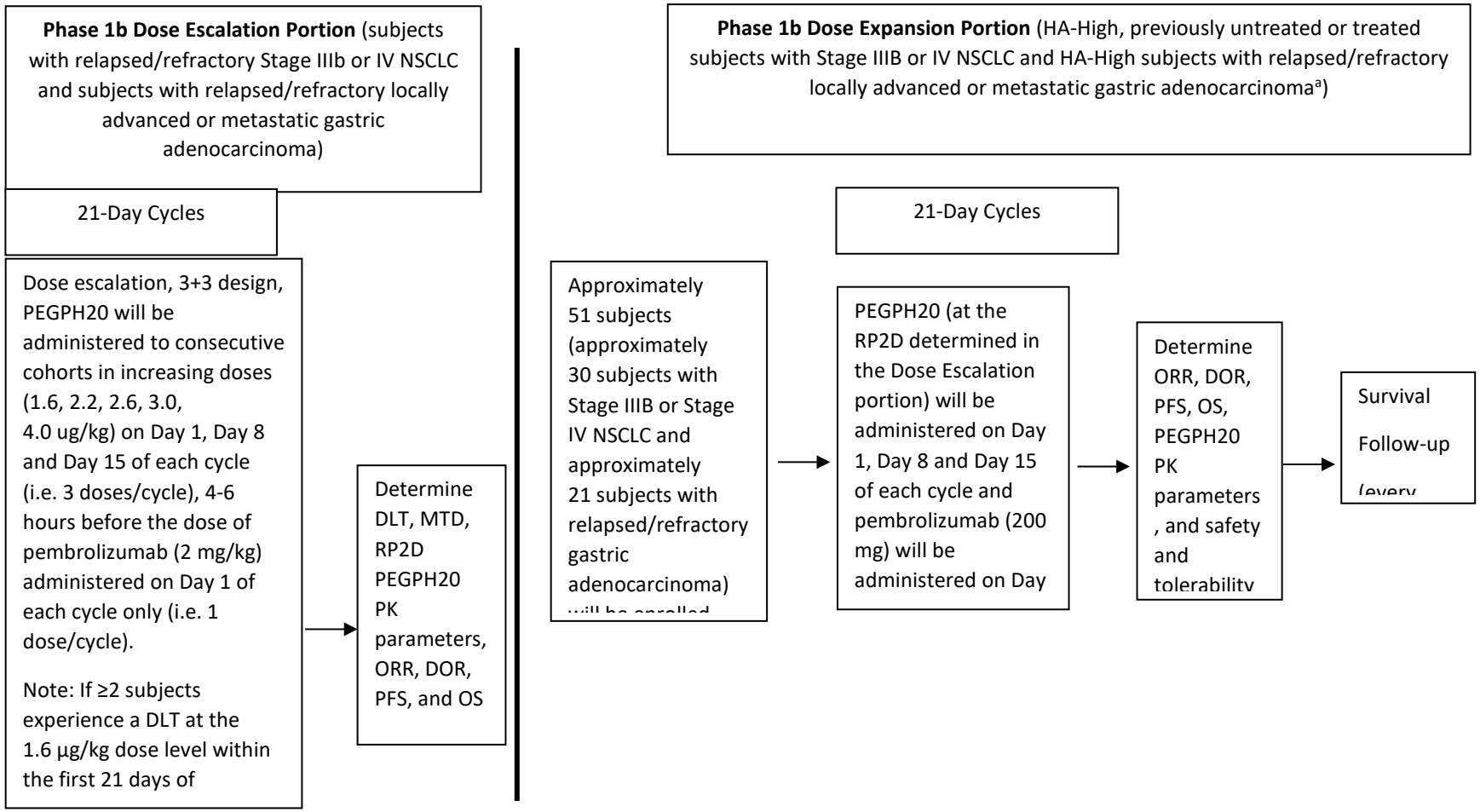
In gastric adenocarcinoma subjects, if enoxaparin is discontinued for any reason, PEGPH20 will also be discontinued. Treatment with pembrolizumab, however, may continue as deemed appropriate by the Investigator.

After discontinuing study treatment (PEGPH20 and pembrolizumab), subjects will have an End of Treatment Visit and will enter the long-term follow-up for survival.

Subjects will be assessed for AEs and clinical laboratory evaluations as graded by the CTCAE v 4.03.

In both portions of the study, tumor response and progression based on RECIST v 1.1 criteria (Eisenhauer 2009; Appendix C) and irRC (Nishino 2013; Nishino 2014; Appendix E) will be assessed by the Investigator at the end of Cycle 2, Cycle 4 and then at the end of every fourth treatment cycle thereafter (i.e., Week 3 of Cycles 2, 4, 8, 12, 16 and beyond). Scans may be obtained any time on or after Day 15 (of Cycles 2, 4, 8, 12, 16 and every fourth treatment cycle thereafter) to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit. A confirmatory scan must be performed no sooner than 28 days after the initial scan that showed a response (PR or CR) based on RECIST v1.1 (to determine the best overall response) and irRC. A confirmatory scan should also be performed to confirm disease progression based on irRC no sooner than 28 days after the initial scan that showed progression.

Figure 1: Study Design - Phase 1b Dose Escalation and Dose Expansion (HALO-107-101)



Abbreviations: NSCLC = Non-Small Cell Lung Cancer; PEGPH20 = PEGylated Recombinant Human Hyaluronidase; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose; PK = pharmacokinetic; ORR = objective response rate; HA = hyaluronan; DOR = duration of response; PFS = progression-free survival; OS = overall survival

[a] In Dose Expansion, subjects will be selected for enrollment whose tumors are HA-high, using a co-developed investigational diagnostic assay. Subjects will be tested retrospectively for PD-L1 expression levels

6.1.1. Phase 1b Dose Escalation

This portion of the study is a single-arm, dose escalation study of PEGPH20 in combination with pembrolizumab subjects with relapsed/refractory NSCLC after failing at least 1 previous platinum-based therapy (refer to Inclusion Criterion #2) and subjects with relapsed/refractory gastric adenocarcinoma after failing at least 1 previous chemotherapy regimen. Using a standard 3+3 dose escalation design, approximately 3 to 6 subjects in each cohort will receive PEGPH20 + pembrolizumab. PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle to consecutive cohorts in increasing dose levels (1.6, 2.2, 2.6, 3.0, and 4.0 µg/kg). Pembrolizumab will be administered on Day 1 of each cycle, 4-6 hours after the dose of PEGPH20. If the MTD is not reached at 4.0 µg/kg, higher doses may be evaluated. If ≥2 subjects experience a DLT at the 1.6 µg/kg dose level, Cohort -1 will be opened and subjects will be dosed at 1.0 µg/kg on Day 1, Day 8 and Day 15 of each 21-day cycle. The RP2D of PEGPH20 will be the MTD determined in Dose Escalation or the Sponsor may decide to choose a dose lower than the MTD and which has completed evaluation in Dose Escalation and is found to be safe and tolerable to evaluate in Dose Expansion.

The number of cohorts studied and number of subjects exposed to a given dose level will depend on the doses tested. It is anticipated that up to 5 dose levels will be studied for a total of approximately 30 subjects exposed to study medication. The dose allocation for 5 cohorts of subjects assigned to the 5 preselected dose levels and 1 cohort assigned to the preselected dose of 1.0 µg/kg (if ≥2 subjects experience a DLT at 1.6 µg/kg dose level) is shown as an example in Table 4. The study medication dosing and treatment schedule are shown in Table 5.

Safety data from all subjects dosed will be reviewed to determine the RP2D. Dose escalation will be guided by safety data from each subject during the 21 days following their first dose of PEGPH20. Intra-subject dose escalation to the next PEGPH20 dose studied may be allowed if the Investigator deems it in the best interest of the subject and after discussion with the Sponsor and provided the next PEGPH20 dose studied has been determined not to have exceeded the MTD.

- If none of 3 subjects in a given cohort experience a DLT within 21 days of starting treatment, enrollment and dosing may proceed at the next planned dose level.
- If 1 of 3 subjects at a given dose level experiences a DLT within the first 21 days of treatment, 3 additional subjects will be enrolled and dosed at the dose level at which the DLT occurred. If ≤1 of 6 subjects experience a DLT, dose escalation will continue to the next planned higher dose.
- If ≥2 subjects at a given dose level experience a DLT within the first 21 days of treatment, that dose level will be considered to have exceeded the MTD and dose escalation will be stopped. If the previous dose level did not already have 6 subjects treated with ≤1 DLT, enrollment and dosing will then resume in the previous dose level with additional subjects up to a total of 6 subjects. The highest dose level at which no more than 1 of 6 evaluable subjects has experienced a DLT in the first 3 weeks of treatment will be considered the MTD for the PEGPEM combination. The RP2D will be based on the overall safety profile.

- If ≥2 subjects at the 1.6 µg/kg dose level experience a DLT within the first 21 days of treatment, Cohort -1 will be opened at a lower dose level of 1.0 µg/kg.

Note: Additional subjects may be enrolled in each cohort to further assess the tolerability of PEGPEM and determine an acceptable safety profile prior to the enrollment in the next dose level and expansion portion of the study.

Definition of DLT

DLTs will be assessed for each subject during the 21 days following their first PEGPH20 dose and will be defined as any of the following:

- Any treatment-emergent Grade ≥3 toxicity that is considered related to either PEGPH20 or pembrolizumab or the combination of PEGPH20 and pembrolizumab (nausea, vomiting, musculoskeletal events and diarrhea will be considered DLTs only if they reach ≥ Grade 3 despite adequate supportive care measures).
- Grade 3 MSEs are considered DLTs only if they do not reduce to ≤ Grade 2 within 48 hours despite therapeutic intervention.
- Hypersensitivity/infusion reactions related to PEGPH20 or pembrolizumab dosing will not be considered DLTs (hypersensitivity reactions are generally not related to the dose level of a drug since they can occur even upon a low level of exposure).

To be considered evaluable for DLT assessment, subjects must receive 1 of the 3 full planned doses of PEGPH20 and 1 complete dose of pembrolizumab in Cycle 1. Subjects who experience a DLT within the first 21 days of treatment and withdraw from the study will be considered evaluable for DLT and will not be replaced. Subjects who withdraw within the first 21 days for reasons other than a DLT will be considered not evaluable and will be replaced. Any PEGPH20 treatment-related AE that results in interruption or reduction of either drug (PEGPH20 or pembrolizumab) may be considered a DLT at the Investigator's discretion.

The Sponsor and the participating Investigators will meet as soon as practical, post completion of a cohort, and no more than 10 business days after the end of the last cohort to determine an acceptable dose for the Dose Expansion portion after reviewing all available safety data from Cycle 1 from all subjects in the Dose Escalation portion.

Table 4: Dose Allocation and Cohort Schedule - Dose Escalation Portion

Dose Level	PEGPH20 µg/kg	Pembrolizumab mg/kg
-1	1.0	2
1	1.6	2
2	2.2	2
3	2.6	2
4	3.0	2
5	4.0[a]	2

Abbreviations: PEGPH20 = PEGylated Recombinant Human Hyaluronidase.
Note: Each treatment cycle is 21 days. Dose interruption and modifications are permitted.
[a] If the MTD is not reached at 4.0 µg/kg, higher doses may be evaluated.

6.1.2. Phase 1b Dose Expansion

Approximately 51 HA-high subjects will be studied in the Dose Expansion portion at the RP2D identified in the Dose Escalation portion:

- Approximately 30 subjects with Stage IIIB or IV NSCLC, previously untreated or treated and having failed no more than 1 previous platinum-based chemotherapy (refer to Inclusion Criterion #3)
- Approximately 21 subjects with relapsed/refractory gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens.

The study medication dosing and treatment schedule are shown in Table 5.

Table 5: Study Medication Dosing and Treatment Schedule - Dose Escalation and Dose Expansion

Time point	PEGPEM Treatment
Subjects with NSCLC or Gastric Adenocarcinoma	
Cycle 1 and Beyond (Each Cycle 21 Days)	
Week 1	
Day 1	PEGPH20 Pembrolizumab (4-6 hours after PEGPH20)
Week 2	
Day 8	PEGPH20
Week 3	
Day 15	PEGPH20

Abbreviations: PEGPEM = PEGPH20 in combination with pembrolizumab; PEGPH20 = PEGylated Recombinant Human Hyaluronidase; NSCLC = non-small cell lung cancer.
Notes: Dose interruption and modifications are permitted; refer to Section 8.3 for further guidance.
Visit window is ±2 days of the specified times.

6.1.3. Study Duration

The study will consist of a Screening period of up to 28 days, a treatment period (21-day cycles), a 30-day post-treatment period (after last dose) for collection of AEs and a long-term follow-up. Subjects will be allowed to continue treatment on study until disease progression (as defined in Section 6.1.4) or unacceptable toxicity. Subjects with asymptomatic disease progression however, will be allowed to continue the study treatment at the Investigator's discretion despite evidence of increasing tumor burden or appearance of new lesions for up to 6 weeks if the subject is clinically stable.

Investigators may also discontinue study treatment if it is no longer in the best interest of the subject. Subjects who discontinue treatment with PEGPH20 and pembrolizumab will be followed every 12 weeks for survival until death, withdrawal of consent, or lost to follow-up.

6.1.4. Disease Progression

Disease progression will be defined as presence of 1 or both of the following:

Disease progression documented by CT scan/MRI scan based on RECIST v1.1 (Eisenhauer 2009; Appendix C) as determined by the Investigator.

Clinical tumor-related progression that is well documented in the absence of scans demonstrating radiographic disease progression.

Radiographic disease progression is based on the analysis of CT/MRI scans by the Investigator. Investigators should continue study treatment until disease progression (not including asymptomatic disease progression in clinically stable subjects [see Section 6.1 for definition of clinically stable]) has occurred, but may discontinue study treatment if there is documented clinical disease progression and/or unacceptable toxicity and/or study treatment is no longer in the best interest of the subject. Subjects who discontinue treatment with PEGPH20 and pembrolizumab will be followed every 12 weeks for survival until death, withdrawal of consent, or lost to follow-up.

7. SELECTION AND WITHDRAWAL OF SUBJECTS AND STUDY TERMINATION

The Dose Escalation portion of the study will enroll subjects with relapsed/refractory Stage IIIB or IV NSCLC after failing at least 1 previous platinum-based chemotherapy regimen (refer to Inclusion Criterion #2) and subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma after failing at least 1 previous chemotherapy regimen for locally advanced or metastatic disease.

The Dose Expansion portion of the study will enroll:

- HA-high subjects with Stage IIIB or IV NSCLC, previously untreated or treated and having failed no more than 1 previous platinum-based chemotherapy (refer to Inclusion Criterion #3), who have tissue available for HA-selection and PD-L1 testing

and

- HA-high subjects with relapsed/refractory locally advanced or metastatic gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens for locally advanced or metastatic disease, who have tissue available for HA-selection and PD-L1 testing.

7.1. Inclusion Criteria

For both portions of the study (unless otherwise specified), subjects must satisfy all of the following inclusion criteria to be enrolled in the study:

1. Written Institutional Review Board (IRB)/Ethics Committee (EC) -approved Informed Consent form (ICF), signed by subject or legally authorized representative.
2. Dose Escalation portion - Histologically confirmed and documented, previously treated stage IIIB or IV NSCLC having failed at least 1 previous platinum-based chemotherapy regimen for locally advanced or metastatic disease, or relapsed/refractory locally

advanced or metastatic gastric adenocarcinoma having failed at least 1 previous chemotherapy regimen for locally advanced or metastatic disease. Subjects with NSCLC who are known to be epidermal growth factor receptor (EGFR)-mutation positive must have received an EGFR inhibitor and subjects known to be anaplastic lymphoma kinase (ALK)-mutation positive must have received an ALK inhibitor (subject's documented EGFR/ALK mutation status and/or confirmation reports/molecular pathology/analysis reports should be included in the subject's medical records and made available for Sponsor/Sponsor representative[s] review).

a. Subjects with gastroesophageal junction (GEJ) tumors are eligible.
b. For subjects with either NSCLC or gastric cancer, prior treatment administered in the adjuvant setting is permitted provided it was administered at least 6 months prior to first-line therapy for metastatic disease.
c. For subjects with NSCLC, prior first-line treatment with bevacizumab (AVASTIN®) or biosimilars is allowed.
d. For subjects with NSCLC, prior maintenance treatment with bevacizumab, pemetrexed (ALIMTA®), or erlotinib (TARCEVA®) is allowed.
e. For subjects with human epidermal growth factor receptor 2 positive (HER2+) gastric cancer, prior treatment with trastuzumab (HERCEPTIN®) is required (subject's documented HER2 status and/or confirmation reports/molecular pathology/analysis reports should be included in the subject's medical records and made available for Sponsor/Sponsor representative[s] review).

3. Dose Expansion portion - **NSCLC subjects:** Histologically confirmed and documented, previously untreated or treated stage IIIB or IV NSCLC. Previously treated subjects must have failed no more than 1 previous platinum-based chemotherapy regimen for locally advanced or metastatic disease. Previously treated subjects with NSCLC who are known to be EGFR-mutation positive must have received an EGFR inhibitor and subjects who are known to be ALK-mutation positive must have received an ALK inhibitor (subject's documented EGFR/ALK mutation status and/or confirmation reports/molecular pathology/analysis reports should be included in the subject's medical records and made available for Sponsor/Sponsor representative[s] review). **Gastric adenocarcinoma subjects:** histologically confirmed and documented previously treated relapsed/refractory locally advanced or metastatic gastric adenocarcinoma having failed no more than 2 previous chemotherapy regimens for locally advanced or metastatic disease.

a. Subjects with GEJ tumors are eligible.
b. For subjects with either NSCLC or gastric cancer, prior treatment administered in the adjuvant setting is permitted provided it was administered at least 6 months prior to first-line therapy for metastatic disease.
c. For previously treated subjects with NSCLC, prior treatment with or without bevacizumab (AVASTIN®) or bevacizumab biosimilars is allowed.
d. For previously treated subjects with NSCLC, prior maintenance treatment with bevacizumab, pemetrexed (ALIMTA®), or erlotinib (TARCEVA®) is allowed.
e. For subjects with HER2+ gastric cancer, prior treatment with trastuzumab (HERCEPTIN®) is required (subject's documented HER2 status and/or confirmation reports/molecular pathology/analysis reports should be included in the subject's medical records and made available for Sponsor/Sponsor representative[s] review).

4. Prior to enrollment, confirmation of the following must be obtained:
    a. **Dose Escalation portion** - Available tumor tissue in a formalin-fixed paraffin-embedded (FFPE) block or 5-10 unstained consecutive core biopsy slides from 1 tumor tissue block that meet specific tissue sample requirements are preferred but not mandatory for enrollment in this portion of the study. **Note:** Fine needle aspirates or brushing biopsies will not be acceptable.
    b. **Dose Expansion portion -** Available tumor tissue in FFPE block or 10-15 unstained consecutive tumor tissue slides from 1 tumor tissue block that meet specific tissue sample requirements are mandatory. **Note:** Fine needle aspirates or brushing biopsies will not be acceptable. Archived resection specimens from the primary tumor without radiologic evidence of metastasis at the time of resection are not suitable to establish histological confirmation and require new tumor tissue of a metastatic site.
5. To be eligible for the Dose Escalation portion, subjects need only have evaluable disease (details in Section 8.2.15); to be eligible for the Dose Expansion portion, subjects must have measurable disease per RECIST v1.1. Previously irradiated tumors may be eligible if they have clearly progressed in size.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix B).
7. Life expectancy ≥3 months.
8. Males and females aged ≥18 years.
9. Resolution of all acute toxic effects of prior therapy or surgery to baseline.
10. Screening clinical laboratory values are as follows:
    a. Total and indirect bilirubin ≤1.5 × upper limit of normal (ULN), except for Gilbert's syndrome
    b. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤2.5 × ULN (<5 × ULN is allowed if liver metastases are present)
    c. Serum creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥40 mL/min
    d. Serum albumin ≥3.0 g/dL
    e. Hemoglobin ≥10 g/dL (transfusion and erythropoietic agents allowed)
    f. Absolute neutrophil count ≥1500 cells/mm^3
    g. Platelet count ≥100,000/mm^3
11. Female participants of childbearing potential (WOCBP) must have a negative urine or serum pregnancy test within 7 days before Day 1 (first dose of study medication).
12. For WOCBP and for men, agreement to use an effective contraceptive method from the time of screening throughout the study until 4 months (WOCBP) or 3 months (men) after administration of the last dose of any study medication. Highly effective contraceptive methods consist of prior sterilization, intrauterine device (IUD), intrauterine hormone releasing system (IUS), oral or injectable contraceptives, and/or barrier methods. Abstinence alone is not considered an adequate contraceptive measure for the purposes of this study.

13. Subjects must also satisfy the following inclusion criterion to be enrolled in the Dose Expansion portion of the study:
    a. Subjects (NSCLC and gastric adenocarcinoma) must be determined to have HA-high levels from their tumor biopsies. Tumor samples must meet the requirements noted in the Inclusion Criterion #4.
    b. NSCLC and gastric adenocarcinoma subjects must have tissue available for HA-selection and PD-L1 testing. Tumor samples must meet the requirements noted in the Inclusion Criterion #4.

7.2. Exclusion Criteria

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

1. Previous treatment with pembrolizumab, nivolumab, or other anti-PD-1 or anti-PD-L1 agents.
2. New York Heart Association Class III or IV (Appendix D) cardiac disease or myocardial infarction within the past 12 months before screening, or preexisting atrial fibrillation.
3. History of cerebrovascular accident or transient ischemic attack.
4. NSCLC subjects with known brain metastases (exception below)
    a. Subjects with treated brain metastases who meet all of the following criteria are eligible:
        i. Stable brain metastases for at least 1 month,
        ii. No evidence of progression or hemorrhage after treatment,
        iii. No ongoing requirement for corticosteroids.
5. Gastric adenocarcinoma subjects with brain metastases.
6. History of active bleeding within the last 3 months requiring transfusion.
7. Anti-angiogenic therapy within the last month.
8. Subjects with known interstitial fibrosis or interstitial lung disease.
9. History of pulmonary embolism or pulmonary embolism found on screening exam.
10. Pre-existing carotid artery disease.
11. History of DVT with contraindications to pharmacologic anticoagulation.
12. History of:
    a. Pneumonitis that requires oral or IV steroids;
    b. Or known cases of hepatobiliary diseases (e.g., primary biliary cholangitis, primary sclerosing cholangitis, history of immune-mediated cholangitis);
        i. Subjects with cholangitis attributed to infectious etiology (e.g., ascending cholangitis, bacterial cholangitis) are eligible if the infection has been fully resolved prior to the screening visit.
    c. Or known cases of drug-induced hepatobiliary toxicities.

13. NSCLC subjects with hypersensitivity to aspirin.
14. Gastric adenocarcinoma subjects with contraindications to enoxaparin.
15. Autoimmune diseases:
    a. Active autoimmune disease requiring systemic treatment within the past 3 months
    b. Documented history of clinically severe autoimmune disease (e.g., colitis, Crohn's disease)*
16. Active, uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.
17. Known infection with human immunodeficiency virus, active infection with hepatitis B, or hepatitis C.
18. Known allergy to hyaluronidase.
19. Hypersensitivity to the active substance or ingredients of PEGPH20 and pembrolizumab.
20. Known allergy to piroxicam or other NSAIDs.
21. Current use of megestrol acetate (within 10 days of Day 1).
22. Chronic use of steroids for pain or emesis management.
23. Women currently pregnant or breastfeeding.
24. History of another primary cancer within the last 3 years that required treatment, with the exception of non-melanoma skin cancer, early-stage prostate cancer, or curatively treated cervical carcinoma in situ.
25. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that lead to reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the subject at high risk for treatment complications.
26. Subject inability to comply with study and follow-up procedures, as judged by the Investigator.

*Any relevant diseases that are not listed as examples of exclusionary diseases are to be discussed with the Sponsor.

7.3. Subject Withdrawal Criteria

7.3.1. Discontinuation of Treatment

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

- Disease progression (defined in Section 6.1.4).
- AE.
- Any significant protocol violation (e.g., demonstrated lack of treatment compliance, subject starts taking any concomitant anti-cancer therapy).

- Withdrawal of consent by an enrolled subject, either for study treatment itself (and subsequent follow-up) or for participation in follow-up.
- 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.
- The subject becomes pregnant (treatment must be discontinued immediately).
- Treatment delay ≥21 days.
- Subjects experiencing any TE event that requires full-dose anticoagulation while on study (PEGPH20 will be discontinued; treatment with pembrolizumab may continue as deemed appropriate by the Investigator).
- Gastric adenocarcinoma subjects for whom enoxaparin is discontinued for any reason (PEGPH20 will be discontinued; treatment with pembrolizumab may continue as deemed appropriate by the Investigator).

Subjects who discontinue treatment with PEGPH20 and pembrolizumab should enter long-term follow-up unless they withdraw consent, die, or are lost to follow-up.

7.3.2. Discontinuation from Study

After discontinuing study treatment (PEGPH20 and pembrolizumab treatment), the subject will enter long-term follow-up for assessment of survival and subsequent anti-cancer therapies (Section 8.1.2.4). Long-term follow-up will continue until the subject discontinues from the study. The reason for the subject's discontinuation from the study should be documented in the subject's eCRF. Possible reasons for study discontinuation include the following:

- Death.
- Withdrawal of consent.
- Lost to follow-up.
- Sponsor termination of the study.
- Other.

7.4. Sponsor Study Stopping Rules

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

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

8. STUDY PROCEDURES AND ASSESSMENTS

Study procedures for each portion of the study are provided in the tables in Section 3. This section describes evaluations to be done before, during, and after treatment. Section 8.2 provides information on individual study assessments.

When duplicate evaluations are performed before study commencement, the data from the evaluation closest in time to study entry will be recorded. When duplicate evaluations are performed in a given time window, the worst case value will be recorded for safety evaluations, unless otherwise stipulated. Unless otherwise specified, clinical laboratory tests may be performed 1 day earlier than specified in the relevant 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. Where this is not possible because of extenuating circumstances (e.g., holidays), the reason should be noted and the doses should be separated by at least 45 hours.

8.1. Study Procedures by Visit

8.1.1. Screening

If the following procedures were done as per the standard of care prior to the subject signing the ICF, the results may be used for this study provided they were within the screening window (≤28 days before Day 1): physical examination, vital sign measurements, height, weight and CT/MRI scan.

Note: Plasma samples are required for PEGPH20 PK, hyaluronan, biomarker, and PEGPH20 immunogenicity analysis; serum samples are required for pembrolizumab PK analysis. All subjects will be monitored for study procedure-associated serious adverse events (SAEs) starting from the time of ICF signature as described in Section 10.2.

8.1.1.1. Within 28 Days Prior to Day 1 (Unless Otherwise Indicated)

- Sign and date prescreening ICF for HA testing in Dose Expansion (if applicable, [See Section 8.2.1.1]).
- Sign and date ICF.
- Register subjects into an Interactive Web Response System [IWRS] for screening/ prescreening (if conducted in Dose Expansion).
- Confirm availability of and retrieve tumor tissue (refer to Inclusion Criterion #4 for more details). Tumor tissue must be sent to central laboratory to assess HA status for eligibility into the Dose Expansion portion of the study.
- Obtain CT/MRI scan for disease assessment and eligibility review and send to Central Imaging Vendor (CIV) for storage.
- Obtain CT/MRI brain scan to assess potential CNS disease and/or metastases.
- Review inclusion/exclusion criteria.
- Collect medical and prior medication history.

- Optional (at selected sites only): Perform PET/CT scan and DCE-MRI. DCE-MRI scans must be obtained within 14 days prior to Day 1 (first dose of study medication).
- Perform the following assessments: 12-lead ECG, physical examination, vital signs, ECOG Performance Status, height, weight, and urine or serum pregnancy test within 7 days before Day 1 (first dose of study medication) (WOCBP; local laboratory).
- Obtain samples for the following tests and send to the central laboratory: plasma samples for HA level and exploratory biomarkers, thyroid hormones, hematology, blood chemistry (including glucose), urinalysis, coagulation.

8.1.2. Treatment Period

AEs and concomitant medications will be obtained throughout the study and at every visit.

8.1.2.1. Treatment Cycle 1

8.1.2.1.1. Cycle 1 Day 1

Before PEGPH20 and Pembrolizumab Infusion

- Confirm subjects' eligibility based on inclusion and exclusion criteria.
- Perform the following assessments: vital signs, ECOG Performance Status and weight.
- Obtain blood samples for the following tests and send to the central laboratory:
  - Hematology, blood chemistry (including glucose) and coagulation. NOTE: Measurements of total bilirubin, ALP, AST, and ALT (as part of blood chemistry) must be obtained prior to dosing (within 48 hours is acceptable). Local laboratories may be used for these measurements. Dosing can only take place if total bilirubin, ALP, AST and ALT values are within the ranges specified in the Inclusion Criteria.
  - Immunogenicity.
  - PEGPH20 PK, plasma HA, and exploratory biomarkers within 2 hours prior to PEGPH20 dosing (as specified in Table 3) (actual collection times to be recorded).
  - Pembrolizumab PK within 2 hours prior to dosing (as specified in Table 3) (actual collection times to be recorded).
- Administer piroxicam (20 mg) at least 1-2 hours prior to the start of the PEGPH20 infusion on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience) to minimize the severity of MSEs. Prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or OTC equivalent).

- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

PEGPH20 and Pembrolizumab Infusion

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min).
- Pembrolizumab IV infusion over 30 minutes, 4-6 hours after completion of PEGPH20 infusion.

After PEGPH20 and Pembrolizumab Infusion

- Obtain blood samples for the following tests and send to the central laboratory:
  - PEGPH20 PK 15 minutes (±5 minutes), 1 hour (±15 minutes), 2-4 hours and 6-8 hours after PEGPH20 infusion (as specified in Table 3) (actual collection times to be recorded).
  - Plasma HA and exploratory biomarkers 2-4 hours and 6-8 hours after PEGPH20 infusion (as specified in Table 3) (actual collection times to be recorded).
  - Pembrolizumab PK after 2 hours of dosing (as specified in Table 3) (actual collection times to be recorded).

8.1.2.1.2. Cycle 1 Day 2

- Optional at selected sites only: Perform DCE-MRI 24 hours after PEGPH20 infusion.
- Obtain blood samples for the following tests and send to the central laboratory:
  - PEGPH20 PK, Plasma HA, and exploratory biomarkers 24-26 hours after PEGPH20 infusion (as specified in Table 3) (actual collection times to be recorded).
  - PEGPH20 PK 28-32 hours after PEGPH20 infusion (as specified in Table 3) (actual collection times to be recorded).
  - Pembrolizumab PK 24-28 hours after pembrolizumab infusion (as specified in Table 3) (actual collection times to be recorded).
- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

8.1.2.1.3. Cycle 1 Day 8

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain a hematology blood sample and send to the central laboratory.
- Obtain a blood sample for blood chemistry and send to the central laboratory. NOTE: Measurements of total bilirubin, ALP, AST, and ALT (as part of blood chemistry) must be obtained prior to dosing (within 48 hours is acceptable). Local laboratories

may be used for these measurements. Dosing can only take place if total bilirubin, ALP, AST and ALT values are within the ranges specified in the Inclusion Criteria.

- Administer piroxicam (20 mg) within at least 1-2 hours prior to the start of the PEGPH20 infusion on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience) to minimize the severity of MSEs. The prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or OTC equivalent).
- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

PEGPH20 Infusion

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

8.1.2.1.4. Cycle 1 Day 15

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain a hematology blood sample and send to the central laboratory.
- Obtain a blood sample for blood chemistry and send to the central laboratory. NOTE: Measurements of total bilirubin, ALP, AST, and ALT (as part of blood chemistry) must be obtained prior to dosing (within 48 hours is acceptable). Local laboratories may be used for these measurements. Dosing can only take place if total bilirubin, ALP, AST and ALT values are within the ranges specified in the Inclusion Criteria.
- Administer piroxicam (20 mg) at least 1-2 hours prior to the start of the PEGPH20 infusion on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience) to minimize the severity of MSEs. The prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or OTC equivalent).
- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

PEGPH20 Infusion

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

8.1.2.1.5. Cycle 1 Day 18

- Optional selected sites only: Perform DCE-MRI and PET/CT scan.
- Perform optional post-dose tumor biopsy at the end of Cycle 1 (on or after Day 18 PEGPH20 dose) but prior to 1st PEGPH20 dose in Cycle 2.

- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

8.1.2.2. Treatment Cycle 2 and Beyond (Repeats Every 3 weeks)

8.1.2.2.1. Cycle 2 and Beyond, Day 1

Before PEGPH20 and Pembrolizumab Infusion

- Perform the following assessments: vital signs, ECOG Performance Status and weight.
- Obtain blood samples for the following tests and send to the central laboratory:
  - Hematology, blood chemistry (including glucose), coagulation. NOTE for Cycle 2 only: Measurements of total bilirubin, ALP, AST, and ALT (as part of blood chemistry) must be obtained prior to dosing (within 48 hours is acceptable). Local laboratories may be used for these measurements. Dosing can only take place if total bilirubin, ALP, AST and ALT values are within the ranges specified in the Inclusion Criteria. If a subject has any of these values outside the specified ranges on Day 1 of Cycle 2, the Investigator should discuss further dosing plans for the subject with the Sponsor.
  - Immunogenicity.
  - Thyroid hormones (to be collected every third cycle thereafter (i.e., Day 1 of Cycles 2, 5, 8, 11, 14, 17, 20, etc.).
  - Plasma HA and exploratory biomarkers within 2 hours prior to PEGPH20 dosing (as specified in Table 3) (actual collection times to be recorded).
  - Pembrolizumab PK within 2 hours prior to dosing (as specified in Table 3) (actual collection times to be recorded).
- Urine/serum pregnancy test (WOCBP; local laboratory).
- Administer piroxicam (20 mg) at least 1-2 hours prior to the start of the PEGPH20 infusion on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience) to minimize the severity of MSEs. The prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or OTC equivalent).
- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

PEGPH20 and Pembrolizumab Infusion

- PEGPH20 IV infusion over 10 to 12 minutes (approximately 1 mL/min).
- Pembrolizumab IV infusion over 30 minutes, 4-6 hours after completion of PEGPH20 infusion.

After PEGPH20 and Pembrolizumab Infusion

- Obtain blood samples for the following tests and send to the central laboratory:
  - PEGPH20 PK 15 minutes (±5 minutes), 6-8 hours after PEGPH20 infusion (as specified in Table 3) (actual collection times to be recorded).
  - Pembrolizumab PK 0-2 hours after PEM dose (as specified in Table 3) (actual collection times to be recorded).

8.1.2.2.2. Cycle 2 and Beyond, Day 2

- Obtain blood samples for the following tests and send to the central laboratory:
  - PEGPH20 PK samples 24-26 hours after PEGPH20 infusion (as specified in Table 3) (actual collection times to be recorded).
  - PEGPH20 PK samples 28-32 hours after PEGPH20 infusion (as specified in Table 3) (actual collection times to be recorded).
  - Pembrolizumab PK samples 24-28 hours after PEGPH20 infusion (as specified in Table 3) (actual collection times to be recorded).
- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

8.1.2.2.3. Cycle 2 and Beyond Day 8

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain blood sample for testing of glucose and send to the central laboratory.
- Obtain a hematology blood sample and send to the central laboratory.
- Administer piroxicam (20 mg) at least 1-2 hours prior to the start of the PEGPH20 infusion on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience) to minimize the severity of MSEs. The prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or OTC equivalent).
- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

8.1.2.2.4. Cycle 2 and Beyond Day 15

Before PEGPH20 Infusion

- Assess vital signs.
- Obtain a blood sample for testing of glucose and send to the central laboratory.
- Obtain a hematology blood sample and send to the central laboratory.
- Administer piroxicam (20 mg) at least 1-2 hours prior to the start of the PEGPH20 infusion on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience) to minimize the severity of MSEs. The prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving PEGPH20 (e.g. 20 mg omeprazole daily or OTC equivalent).
- Administer enteric-coated 81 mg of aspirin to all NSCLC subjects and 40 mg of enoxaparin (pre-filled syringes of enoxaparin are allowed) to all gastric adenocarcinoma subjects.

PEGPH20 Infusion

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

After PEGPH20 Infusion

- Optional at selected sites in Cycle 2 only: Perform PET/CT. The CIV will analyze PET/CT scans if they are conducted.

PEGPH20 Infusion

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

8.1.2.2.5. Selected Cycles from Cycle 2 Onwards, Day 15

- Obtain CT/MRI scans for tumor assessment (based on RECIST v1.1 and irRC) at the end of Cycles 2, 4, and then at the end of every fourth cycle thereafter (i.e., Week 3 of Cycles 2, 4, 8, 12, 16 and beyond). Scans may be obtained any time on or after Day 15 (of Cycles 2, 4, 8, 12, 16 and every fourth treatment cycle thereafter) to allow enough time for the scan to be reviewed locally prior to the subject's next scheduled dosing visit. The results should be interpreted before dosing in the next cycle begins. For subjects who are withdrawn from the study due to clinical disease progression, a CT/MRI scan should be requested as soon as possible after clinical progression is determined.

  Note: A confirmatory scan should be performed no sooner than 28 days if the initial scan showed a response (PR or CR) based on RECIST v1.1 and irRC. A confirmatory scan should also be performed to confirm disease progression based on irRC no sooner than 28 days after the initial scan that showed progression.

- For the duration of the study, post-baseline, CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a CR. For

NSCLC subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points.

8.1.2.3. End of Treatment Visit

The End of Treatment Visit procedures described below will be the same for all subjects, regardless of phase. Subjects should return to the study site for an End of Treatment Visit within approximately 7 days after determination of disease progression or within 7 days after treatment discontinuation of PEGPH20 and pembrolizumab for other reasons. AEs and concomitant medications will be obtained and the following procedures should be performed:

- Perform the following assessments: physical examination including vital signs, ECOG Performance Status and 12-lead ECG.
- Obtain CT/MRI scan and send to CIV for storage (CT/MRI should only be done if radiographic disease progression was not documented in the previous CT/MRI scan).
- Obtain samples for the following tests and send to the central laboratory: hematology, blood chemistry and coagulation.
- Obtain sample for immunogenicity testing and send to the central laboratory.

8.1.2.4. Long-Term Follow-Up

After the End of Treatment Visit, all subjects will enter long-term follow-up during which information on the subject's survival status and subsequent anti-cancer therapies (i.e., therapies received, responses) will be obtained by the site once every 12 weeks. Long-term follow-up will continue until the subject dies, is lost to follow-up, or withdraws consent.

8.1.3. Procedures for Study Treatment Discontinuation

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

8.2. Study Assessments

8.2.1. Informed Consent

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

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

8.2.1.1. Prescreening Informed Consent in Dose Expansion

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:** If the subject provides consent to participate in the study and undergoes the remaining screening procedures, the 28-day screening window will begin when the subject signs the study ICF (i.e., signature on a prescreening ICF does not initiate the screening window).

8.2.2. Inclusion/Exclusion Criteria

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

8.2.3. Medical History

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

8.2.4. Concomitant Medications

Information regarding collection of concomitant medications is provided in Section 10.12.

8.2.5. Adverse Events

AEs will be collected as defined in Section 10.

8.2.6. Physical Examination

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

8.2.7. Height and Weight

Height will be recorded in cm, and weight will be recorded in kg.

8.2.8. ECOG Performance Status

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

8.2.9. Vital Signs

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

8.2.10. 12-lead ECG

ECGs including clinical significance will be evaluated by the Investigator and recorded in the eCRF.

8.2.11. Hematology, Blood Chemistry, Glucose, Thyroid Hormones, Coagulation Parameters, and Urinalysis

Hematology, blood chemistry, blood glucose, thyroid hormones, coagulation parameters, and urinalysis will all be analyzed by the central laboratory. In addition, local laboratories may be used if immediate clinical decision making is required (e.g., for measurement of liver function, including total bilirubin, ALP, AST and ALT prior to dosing [within 48 hours is acceptable] during Cycle 1 through Day 1 of Cycle 2 [Table 2 and Section 8.1.2]). For study analysis and reporting purposes, only values derived from the central laboratories will be utilized. The Investigator must evaluate all results outside the reference range and determine the clinical significance (clinically significant or not clinically significant).

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count, neutrophils (ANC), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophils (absolute), granulocytes (absolute), mean corpuscular hemoglobin, mean corpuscular volume, and platelet count.
- Blood chemistry: glucose, blood urea nitrogen (BUN), albumin, total bilirubin, alkaline phosphatase, AST, ALT, electrolytes (including sodium, potassium, calcium, magnesium, chloride, and bicarbonate), and creatinine.
- Since the pembrolizumab Prescribing Information (Keytruda® US Prescribing Information 2017) advises monitoring of patients for hyperglycemia or other signs and symptoms of diabetes, blood glucose will be monitored throughout the study as either part of the chemistry panel or as a single assessment (see Schedule of Events Table 1 and Table 2).
- Since the pembrolizumab Prescribing Information (Keytruda® US Prescribing Information 2017) advises monitoring of patients for changes in thyroid function at the start of treatment and periodically during treatment, the thyroid hormones free triiodothyronine (T3); free total thyroxine (T4), and thyroid stimulating hormone (TSH) will be monitored throughout the study (see Schedule of Events Table 1 and Table 2).
- Coagulation: international normalized ratio (INR), prothrombin time (PT), and partial thromboplastin time (PTT).
- Urinalysis: protein, glucose, ketones, blood, specific gravity, nitrite, pH, and leukocytes.

8.2.12. 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 done by the local laboratory within 7 days before Day 1 (first dose of study medication). Pregnancy tests will be performed approximately every month at the beginning of each treatment cycle (Cycles 2 and beyond) during the study.

8.2.13. Contraception

Highly effective methods of contraception for participating WOCBP should be used during the study treatment and up to 4 months 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

Participating men can be fertile or vasectomized. Fertile men are advised to use effective methods of contraception during the study and until 3 months after administration of the last dose of any study medication.

8.2.14. Immunogenicity

A blood sample will be collected from all subjects who receive PEGPH20 and analyzed to determine if PEGPH20 is eliciting a humoral immune response. Initial anti-drug antibodies (ADA) testing will be done using a multi-tiered approach per the Guidance, and immunocompetition will be performed to confirm an initial positive response in the screening assay. Any samples confirmed as positive in the ADA assay will then be assayed for neutralizing antibodies.

Refer to the Prescribing information of pembrolizumab for information related to immunogenicity of pembrolizumab (Keytruda® US Prescribing Information 2017).

8.2.15. Imaging/Radiologic Evaluation

CT/MRI with contrast evaluations will be performed for all subjects in accordance with each site's Standard of Care Lung or Gastric Adenocarcinoma CT/MRI imaging protocols (include chest, abdomen, pelvis contrast-enhanced CT/MRI). CT/MRI scans of other areas of known or newly suspected disease must also be obtained. In the event that the subject is intolerant to any contrast agents needed for imaging, local/institutional guidelines should be followed for imaging evaluation.

All scans will be evaluated locally for disease assessment using RECIST v1.1 and irRC, and sent to the CIV for storage and possible analysis at the end of the study.

For study eligibility, the Investigator must determine the presence of 1 or more tumors based on CT/MRI scans performed within 28 days of Day 1. For subject eligibility in the Dose Escalation portion subjects need only have evaluable disease (evaluable disease may include measurable lesions, although not required, but also may include such lesions as bone metastasis or pleural effusions that can't be measured but can be evaluated). For subject eligibility in the Dose Expansion portion measurable disease must be determined using RECIST v1.1 (Eisenhauer 2009; Appendix C).

During the study, CT/MRI scans for objective tumor assessment (based on RECIST v1.1 and irRC) will be performed at the end of Cycle 2, at the end of Cycle 4, and at the end of every fourth treatment cycle thereafter (i.e., Week 3 of Cycles 2, 4, 8, 12, 16 and beyond). CT/MRI scans should be performed after the last dose in each cycle to allow time for reading of the scans by the Investigator prior to start of subsequent cycles. For subjects who are withdrawn from the study due to clinical disease progression, a CT/MRI scan should be requested as soon as possible. At the End of Treatment Visit, a CT/MRI scan is only required if radiographic disease progression was not documented in the previous CT/MRI scan.

Note: For disease assessment, if a CT/MRI scan is taken at screening then the same modality of scanning must be used for the subject throughout the course of the study.

A CT/MRI brain scan must also be performed at Screening (within 28 days prior to first dose of study drugs), to assess potential CNS disease and/or metastases.

For the duration of the study (i.e., post-baseline), CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a complete response (CR). For NSCLC subjects with a history of treated brain metastases, brain scans will be performed at tumor assessment time points.

Additional optional imaging using PET/CT and DCE-MRI will be performed at selected sites only to assess treatment effects of pembrolizumab based on tumor blood flow and metabolic activity. Details about the conduct of these assessments are provided in a separate manual.

8.2.16. Pharmacokinetic Assessments

Plasma samples will be collected to assess the potential effects of pembrolizumab on the PK of PEGPH20 (as specified in Table 3). Additionally, serum samples will be collected to potentially assess the PK of pembrolizumab as an exploratory endpoint. Post-dose PK time points should be relative to the stop time of the PEGPH20 infusion. If samples are collected from a central line, the line should be flushed with saline prior to collecting the PK samples. Samples should not be collected from the same line used to administer PEGPH20. Actual sampling times must be recorded. Initial testing will be done during the study; however, samples will be stored for possible re-analysis if deemed necessary and for potential future testing of other biomarkers that may be found to be relevant.

If a subject discontinues PEGPH20 therapy, PEGPH20 PK samples will not be collected from that subject. However, if that subject continues on pembrolizumab therapy at the discretion of the Investigator, pembrolizumab PK samples must be collected.

8.2.17. 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 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.

Refer to the Laboratory Manual for detailed instructions on the processing, storage, and shipping of samples.

8.2.17.1.1. Tumor Biopsies

Tumor tissue needs to meet specific tissue sample requirements as follows (see Laboratory Manual):

- A tumor tissue in FFPE block or 5-10 unstained, consecutive core biopsy slides from 1 tumor tissue block are preferred but not mandatory for subjects eligible for the Dose Escalation portion.
- A tumor tissue in FFPE block or 10-15 unstained, consecutive tumor tissue slides from 1 tumor tissue block are mandatory for subjects eligible for the Dose Expansion portion, that meet specific tissue sample requirements (see Laboratory Manual). Archived resection specimens from the primary tumor without radiologic evidence of metastasis at the time of resection are not suitable to establish histological confirmation and require new tumor tissue of a metastatic site.
- Fine needle aspiration and/or brushing biopsy are not acceptable.

The pathology report as well as any molecular pathology reports (e.g., for ALK or EGFR mutational status in NSCLC and HER2 status in gastric cancer) must be provided. Specific sampling and processing instructions will be outlined in a separate laboratory manual. The tumor biopsy, whether a block or unstained slides, must be sent to the appropriate laboratory as soon as possible after it is obtained; however, it should not be sent prior to the subject signing the ICF (or prescreening ICF if used in Dose Expansion). Tumor biopsy samples will be utilized for analysis of HA, PD-L1 expression levels (retrospectively), and other exploratory biomarkers.

An optional post-dose biopsy will be collected at the end of Cycle 1 for all subjects who provide separate informed consent. The sample will be analyzed for tumor HA, PD-L1 expression, and other exploratory biomarkers in comparison with the pre-dose sample to evaluate PEGPH20 and/or pembrolizumab effects.

8.2.17.1.2. Plasma Hyaluronan and Exploratory Biomarkers

Plasma HA is an indicator of PEGPH20 pharmacological activity. Baseline and post-dose HA levels in plasma samples will be analyzed to evaluate the PEGPH20 treatment effect, and assess

drug exposure. In addition, plasma samples may be analyzed for exploratory biomarkers of PEGPH20 and/or pembrolizumab activity.

8.2.17.1.3. Tumor-Associated Hyaluronan and Tissue-Based Biomarkers

Tumor tissue available at Screening and collected optionally during the study will be sent to a central laboratory and tested for HA levels using a co-developed investigational diagnostic assay (VENTANA RxDx). This assay uses an affinity-histochemistry-based staining method to evaluate HA levels in tumor biopsies.

Expression of exploratory biomarkers will also be assessed.

For screening purposes, the result for each subject screened (i.e., eligible/ineligible based on HA level) will be sent to the sites to determine eligibility of subjects to enter the study.

8.2.17.1.4. Tumor-Associated PD-L1 Expression in Gastric Adenocarcinoma

Tumor tissue available from gastric adenocarcinoma subjects at screening and collected optionally during the study will be tested for PD-L1 expression levels retrospectively.

8.2.17.1.5. Tumor-Associated PD-L1 expression in NSCLC

Tumor tissue available from NSCLC subjects at screening and collected optionally during the study will be tested retrospectively for PD-L1 expression levels.

8.3. Study Drug Administration

Each treatment cycle is 21 days (3 weeks).

In Dose Escalation, PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle (i.e. 3 doses/cycle) and pembrolizumab (2 mg/kg every 21 days) on Day 1 of each cycle (i.e. 1 dose/cycle), 4-6 hours after the completion of PEGPH20 administration.

In Dose Expansion, PEGPH20 will be administered on Day 1, Day 8 and Day 15 of each 21-day cycle (i.e. 3 doses/cycle) and pembrolizumab (200 mg every 21 days) on Day 1 of each cycle (i.e. 1 dose/cycle), 4-6 hours after the completion of PEGPH20 administration.

Treatment in both portions of the study will continue until disease progression or unacceptable toxicity, death, or withdrawal of consent from the study.

If a dose of PEGPH20 is missed on Day 1 of cycle 2 or beyond, the cycle will continue as scheduled. If it is known that pembrolizumab will be missed or held on Day 1, PEGPH20 should also be held and the cycle will not start until the first dose of pembrolizumab is administered. This will require planning such that the dose of PEGPH20 can be given before the pembrolizumab dose is set to resume.

8.3.1. PEGPH20

8.3.1.1. PEGPH20 Administration

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

After completion of pre-dose activities, PEGPH20 will be administered as an IV infusion over 10 minutes, approximately 1 mL/minute (a window of +2 minutes is allowed, i.e., infusion can be 10 to 12 minutes), under observation by qualified clinic staff. The volume and/or duration of PEGPH20 administration may change at the discretion of the Sponsor, based upon safety information. The study nurse or alternate designee by the Investigator will record the time the infusion was started and stopped. A saline flush should follow IV delivery of the complete PEGPH20 dose as per standard of care for flushing IV lines. Only a peripheral line should be used for the administration of PEGPH20 (heparin flushes should not be used on the same line as PEGPH20), but heparin flushes may be used for central lines as per standard of care. In the event that peripheral venous access cannot be obtained, the central line may be used. If this happens, ensure the line is flushed with saline (minimum of 10 mL) prior to administering PEGPH20 and after administering PEGPH20. Ensure the PEGPH20 administration is not done immediately before or after the central line has been flushed with a heparin flush (i.e., ensure the line is flushed with a heparin flush no earlier than 1 hour before or after the PEGPH20 administration).

8.3.1.2. Hypersensitivity to PEGPH20

In the event of a hypersensitivity reaction, the PEGPH20 infusion should be stopped and the symptoms should be treated as necessary. Halozyme should be contacted immediately (see study manual for contact information).

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

8.3.1.3. PEGPH20 Dose Modification Guidelines

PEGPH20 dose adjustments are allowed based on toxicities that are deemed related, possibly related, or probably related to PEGPH20. See Table 6 for guidelines.

Table 6: PEGPH20 Dose Adjustment and Toxicity Management Guidelines

Event	Management/Action
Musculoskeletal	
Any Grade 1 MSEs	• No change in PEGPH20 dose or frequency. Prescribed medication such as narcotics, muscle relaxants and other analgesics (with the exceptions of steroids), OTC drugs and physical therapy can be used at the Investigator's discretion.
Any Grade 2 MSEs	• Based on Investigator's discretion use prescribed medication such as narcotics, muscle relaxants and other analgesics (with the exceptions of steroids), OTC drugs and physical therapy. • If the MSEs resolve or decrease to Grade 1 with administration of prescribed medication such as narcotics, muscle relaxants and other analgesics (with the exceptions of steroids), OTC drugs and physical therapy, PEGPH20 can be continued. • If the MSEs persist at Grade 2 despite administration of prescribed medication such as narcotics, muscle relaxants and other analgesics (with the exceptions of steroids), OTC drugs and physical therapy, the Investigator must discuss any further PEGPH20 treatment with the Sponsor's Medical Monitor.
Any Grade 3 or 4 MSEs	• Hold PEGPH20 treatment. • Based on Investigator's discretion use prescribed medication such as narcotics, muscle relaxants and other analgesics (with the exceptions of steroids), OTC drugs and physical therapy. • If the MSEs decrease to ≤ Grade 2, the Investigator must discuss any PEGPH20 treatment reinitiation with the Sponsor's Medical Monitor. • If the MSEs persist at Grade 3 or 4 levels, PEGPH20 should not be resumed.

Table 6: PEGPH20 Dose Adjustment and Toxicity Management Guidelines (Continued)

Event	Management/Action
All non-MSE Events (Except TE Events) Potentially Related to PEGPH20	
Grade 1 or 2	• No change in PEGPH20 treatment.
Grade 3	• Hold PEGPH20 treatment. • If toxicity is resolved to baseline within 14 days, treatment may resume at the same dose level. • If toxicity is reduced to ≤ Grade 2 within 14 days, treatment may resume but at next lower dose but must be discussed and decided upon mutual agreement with the Sponsor's Medical Monitor. • If toxicity persists at Grade 3, any consideration to resume PEGPH20 treatment must be discussed with the Sponsor's Medical Monitor.
Grade 4	• Hold PEGPH20 treatment. • If toxicity is resolved or reduced to ≤ Grade 2, any PEGPH20 treatment reinitiation must be discussed with the Sponsor's Medical Monitor.
Thromboembolic Events (Regardless of Relatedness to PEGPH20)	
Any Grade TE event	• Discontinue PEGPH20 treatment for subjects who experience any TE requiring full dose anticoagulation while on study. Treatment with pembrolizumab may continue as deemed appropriate by the Investigator.

Abbreviations: MSE = musculoskeletal event; NSAIDs = non-steroidal anti-inflammatory drugs; PEGPH20 = PEGylated recombinant human hyaluronidase.

If PEGPH20 is held on Day 1 of treatment cycles 2+, pembrolizumab must still be given.

For details on administration of piroxicam and toradol for the management of MSEs, refer to Section 10.12.1; for information on administration of prophylactic enoxaparin and aspirin for management of TE events, refer to Section 10.12.2 and Section 10.12.3, respectively.

8.3.2. Pembrolizumab

8.3.2.1. Pembrolizumab Administration

Pembrolizumab will be administered by IV infusion at a dose of 2 mg/kg (in Dose Escalation) or 200 mg (in Dose Expansion) over 30 minutes once every 21 days on Day 1 of each cycle, 4-6 hours after the PEGPH20 dose.

The pembrolizumab dose will be individually calculated for all infusion visits in Dose Escalation according to the subject's screening weight. In calculating the dose, there will be no downward

adjustment to "ideal" body weight unless institution policy requires it. Doses should be re-adjusted if the subject's 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.

All Cycle Day 1 administrations of pembrolizumab should occur 4-6 hours after PEGPH20 administration.

8.3.2.2. Identified Risks of Pembrolizumab Treatment

Refer to the current Keytruda® US Prescribing Information for the identified risks associated with pembrolizumab treatment.

8.3.2.3. Pembrolizumab Dose Adjustment and Toxicity Management

Dose adjustments (reduction, interruption, and discontinuation) and toxicity management should be undertaken per the current Keytruda® US Prescribing Information.

8.4. Excluded Concomitant Medications and Study Restrictions

Concurrent chronic use of IV heparin is prohibited; however, for acute TEs, IV heparin may be used. PEGPH20 administration must be stopped during this period. Use of megestrol acetate is prohibited.

Any other anti-cancer agents or investigational agents are prohibited while the subject is on study. After treatment is discontinued and a subject enters long-term follow-up, the subject will not have any restrictions (i.e., when being followed every 12 weeks to collect survival and anti-cancer therapy data).

The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions (see Section 8.3.2.2).

8.5. Treatment Compliance

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

8.6. Randomization and Blinding

This is an open-label, non-randomized study.

A subject will be registered in the centralized IWRS and will be assigned a unique subject identification number. The subject's identification number will be used on all of that subject's eCRFs and SAE forms (if applicable). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

9. STUDY DRUG AND MATERIALS

9.1. Study Drug Description

9.1.1. PEGPH20

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

PEGPH20 is a multi-site PEGylated enzyme generated by conjugating N-hydroxysuccinimidyl ester of methoxypoly(ethylene glycol)-butanoic acid (MSBA30K or PEG) and PH20.

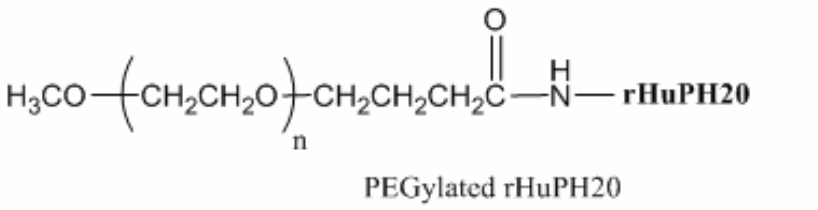
Chemical Name

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

Structural Formula

The structure of PEGPH20 is represented in Figure 2.

Figure 2: Structure of PEGPH20



PEGylated rHuPH20

The empirical formula for P is rHuPH20: $C_{2327}H_{3565}N_{589}O_{667}S_{20}$ and PEG: $C_{1371}H_{2737}NO_{686}$. PEGPH20 is a multi-site PEGylated enzyme. Its measured molecular weight is generally between 100,000 and 270,000 Da.

9.1.2. Pembrolizumab

Pembrolizumab is a human programmed death receptor-1-blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma; patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-based chemotherapy (patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab); and patients with recurrent or metastatic head and neck squamous cell carcinomas with disease progression on or after platinum-based chemotherapy.

Pembrolizumab will be considered investigational for the purpose of this study since the combination of pembrolizumab with PEGPH20 has not been indicated as yet for the treatment of the populations studied in this trial.

Refer to the Keytruda Prescribing Information for a thorough description and diagram of the structure of pembrolizumab (Keytruda® US Prescribing Information 2017).

9.2. Study Drug Packaging and Labeling

9.2.1. PEGPH20

PEGPH20 drug product is supplied as a refrigerated, sterile, single-use, injectable liquid. The PEGPH20 drug product is an aqueous solution containing 0.3 mg/mL PEGPH20 with 10 mM succinic acid, 130 mM NaCl, and 10 mM methionine at a pH of 6.2. Each vial contains 1.2 mL (0.36 mg) of PEGPH20 drug product. PEGPH20 drug product will be packaged in clear, Type 1 borosilicate glass vials with a 13 mm FLUROTEC®-coated chlorobutyl rubber stopper and a 13 mm aluminum overseal with white plastic flip-off cap.

PEGPH20 mixing instructions will be provided to sites in the pharmacy binder. PEGPH20 will be administered as an IV infusion over 10 minutes, approximately 1 mL/minute (a window of +2 minutes is allowed, i.e., infusion can be 10 to 12 minutes). In the Dose Escalation portion, the dose will depend on the escalation process. In the Dose Expansion portion, the dose selected in the escalation portion will be used.

Label information is provided in the Pharmacy Manual.

9.2.2. Pembrolizumab

Pembrolizumab will be administered as an IV infusion over 30 minutes every 21 days on Day 1 of each cycle at a dose of 2 mg/kg in Dose Escalation and 200 mg in Dose Expansion.

9.3. Study Drug Storage

9.3.1. PEGPH20

PEGPH20 drug product, supplied at a concentration of 0.3 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.

9.3.2. Pembrolizumab

The reconstituted and diluted solutions of pembrolizumab will be stored either:

- At room temperature for no more than 4 hours from the time of reconstitution. This will includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, the diluted solution will be allowed to come to room temperature prior to administration.

9.4. Study Drug Preparation

9.4.1. PEGPH20

Instructions for preparing PEGPH20 can be found in the pharmacy manual.

9.4.2. Pembrolizumab

Pembrolizumab will be prepared and administered according to local site standard of care and the appropriate package insert.

9.5. Study Drug Accountability

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

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

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

10. SAFETY ASSESSMENTS

Safety parameters monitored and recorded during this study include AEs; medical history; concomitant medications; immunogenicity, hematology, blood chemistry (including glucose), thyroid hormone levels, coagulation, and urinalysis results; physical examination findings; vital signs; ECG results; pregnancy test results; and ECOG Performance Status.

10.1. Management of Thromboembolic Events

TE events have been identified in the pancreatic cancer clinical studies with PEGPH20. While pancreatic cancer is considered to be one of the most thrombogenic malignancies, it is necessary to manage any potential risks in subjects with NSCLC and gastric adenocarcinoma. All NSCLC subjects will be given enteric-coated 81 mg of aspirin/day and all gastric adenocarcinoma subjects will be given enoxaparin 40 mg/day in this study, for prophylaxis of TE events, given

the high incidence seen in these tumor types. PEGPH20 will be discontinued for subjects who experience any TE requiring full-dose anticoagulation while on study. Treatment with pembrolizumab, however, may continue as deemed appropriate by the Investigator. If in gastric adenocarcinoma subjects, enoxaparin is discontinued for any reason, PEGPH20 will be discontinued. Treatment with pembrolizumab, however, may continue as deemed appropriate by the Investigator. Subjects who discontinue PEGPH20 and pembrolizumab treatment will have an End of Treatment Visit and enter long-term follow-up for survival.

Any anticoagulation therapy received by the subjects must be documented in the applicable eCRF pages.

10.2. Adverse Event Definitions

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

The recording of AEs (except for procedure-associated SAEs) will begin at the start of the administration of the first dose of a study drug and continue until 30 days after the last dose of study drug. Procedure-associated SAEs, will be recorded starting after the subject signs the informed consent for the study. AEs should include the development or increased severity of an undesirable medical condition or the worsening of a pre-existing medical condition during or following exposure to study drug, regardless of relationship to study drug. Only the highest severity will be recorded for a single AE in the eCRF.

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. Enter the study-specific SAE/AE of special interest information into the EDC and send 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/AE of special interest, entry of the new information into the EDC should be completed 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

10.4.1. Thromboembolic Events

TE events are considered AEs of special interest in the current trial. All TE events, regardless of type of event, severity, or seriousness, must be reported to the Sponsor **IMMEDIATELY AND NO LATER THAN 24 HOURS OF AWARENESS**. Details regarding timelines for the reporting of such events are available on the AE of Special Interest form (guidance regarding completion of associated eCRF pages will be provided to the study sites). Complete the study-specific AE of Special Interest form and send to the designated safety contact (contact information is provided in the study reference binder).

The current version of the NCI CTCAE (i.e. Version 4.03 [14 June 2010]) should be utilized when grading TE events. Table 7 denotes the most commonly reported TE events and the associated grading scale per CTCAE Version 4.03 (14 June 2010). If the CTCAE is updated during the study, the current version of the CTCAE (i.e. Version 4.03 [14 June 2010]) should be used.

Table 7: 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 7: 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: NCI CTCAE 4.03 June 14, 2010.

10.4.2. Disease-Related Events That Are Endpoints

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

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

10.5. Adverse Events

Events that occur before the first administration of study drug are not considered AEs, by definition (Section 10.2); record these events on the Medical History eCRF. However, as noted in Section 10.2, any study procedure-associated events occurring after the subject's signing of the informed consent for the study (including prior to the administration of study drug) 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.

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

Wherever possible, record syndromes rather than individual signs or symptoms to avoid duplication and to facilitate meaningful interpretation of data. For example, a subject presenting with rhinitis, fever, and headache should be reported as having "flu-like symptoms," without independently recording each accompanying sign. When no clearly recognizable clinical syndrome can be described, record individual clinical signs and symptoms. In addition, "disease progression" or "death" should not be reported as an AE or SAE term; instead the underlying cause of the disease progression or death should be reported.

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

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

Halozyme will conduct reviews of all available AEs to determine dose escalation steps, to determine the optimal pembrolizumab schedule at the end of Dose Escalation, and at a minimum of once every 3 months during Dose Expansion.

10.5.1. Classification of Adverse Events by Severity

The Investigator must categorize the severity of each AE using the NCI CTCAE v4.03 (Table 6).

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 PEGPH20 or pembrolizumab. The Investigator should make this decision after careful consideration of the following questions:

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

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

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

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

10.6. Abnormal Laboratory Results

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

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

subject. Changes in trial dosing or study discontinuation resulting from an abnormal laboratory value not associated with an AE should also be captured as an AE.

If test results lead to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or requires medical/surgical intervention and/or is considered to be an AE by the Investigator or Sponsor as an abnormal objective test finding, it should be reported as an AE.

10.7. Pregnancy

Pregnancy itself is not regarded as an AE unless there is suspicion that the study drug may have interfered with the effectiveness of the contraceptive medication. Refer to the pembrolizumab Prescribing Information for the summary of risks in this specific population. Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should therefore use highly effective contraception during treatment with pembrolizumab and refrain from breast feeding for 4 months after the last dose of pembrolizumab. Pregnancy within 120 days of study drug discontinuation in a subject must be reported to the designated safety contact (contact information is provided in the study reference binder) **IMMEDIATELY AND NO LATER THAN 24 HOURS OF AWARENESS**. Complete the study-specific Pregnancy Report Form with all available information and submit the form with pregnancy test results and any other pertinent information. Also, within 24 hours, complete the eCRF with all available AE, demographic, medical history, concomitant medication, and study drug administration information. As additional information on a previously reported pregnancy becomes available, a follow-up Pregnancy Report Form should be prepared with the new information and submitted to the safety contact.

Subjects who become pregnant during the study will not receive any additional study drug and will be withdrawn from the study. The Investigator must strongly encourage these subjects to return to the study site for the final protocol-specified visit and assessments. In addition, the Investigator will monitor the pregnancies of subjects exposed to study drug or the partner of a male subject who may become pregnant while that subject is on study until final resolution (delivery, miscarriage, or early termination). Follow-up should occur monthly and should be documented in the study file. A follow-up Pregnancy Report Form must be completed for each follow-up contact with the subject or the partner of a male subject who became pregnant while that 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

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

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

Overdose of pembrolizumab should be managed per the Prescribing Information.

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

10.9. Data Monitoring Committee

An independent DMC will review all available safety data from the first 3 NSCLC subjects and first 3 gastric adenocarcinoma subjects who have completed Cycle 1 in Dose Expansion to determine if the safety and tolerability profile of the PEGPEM combination is acceptable (refer to the DMC charter for additional details). The DMC will also continue to periodically review safety data to protect subject welfare and identify potential safety signals.

10.10. Unblinding

No part of the study is 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 received during the study, other than a designated study drug (PEGPH20 or pembrolizumab), is regarded as concomitant medication. Record concomitant medications taken after the subject signs the ICF during the Screening period (≤28 days prior to Study Day 1) through 30 days after the End of Treatment Visit on the Concomitant Medications eCRF.

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

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

Piroxicam and toradol used to decrease the severity of musculoskeletal symptoms should be documented and recorded in the eCRF. Prescribed medication such as narcotics, muscle relaxants and other analgesics (with the exceptions of steroids), OTC drugs and physical therapy can also be used at the Investigator's discretion and should be documented and recorded in the eCRF. Dexamethasone may be used at the Investigator's discretion and following a discussion with the Sponsor, and should be documented and recorded in the eCRF. For additional details, refer to Table 6.

Enoxaparin and any other anticoagulants should also be documented and recorded in the eCRF.

10.12.1. Piroxicam and Toradol

Refer to the current piroxicam and toradol Prescribing Information for prescribing information and toxicity profile.

Piroxicam and toradol have been investigated in an animal model of MS events and may be helpful in decreasing the severity of MSEs in subjects. Piroxicam (20 mg) will be administered at least 1-2 hours prior to PEGPH20 administration on the day of dosing (timing will be at the Investigator's discretion based on the piroxicam manufacturer's Prescribing Information and subject's convenience) to minimize the severity of MSEs. The prophylactic use of a proton pump inhibitor is mandated for all subjects while receiving the study drug (e.g. 20 mg omeprazole daily or OTC equivalent).

Toradol should not be administered concurrently with piroxicam as it is contraindicated in the Toradol Prescribing Information to administer toradol simultaneously with other NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects. If piroxicam is used chronically, consideration should be given to begin an H2 blocker to decrease the risk of gastric irritation.

If side effects are observed following administration of NSAIDs, the dosing of piroxicam may be adjusted at the Investigator's discretion upon discussion with the Sponsor.

10.12.2. Enoxaparin

Refer to the current enoxaparin Prescribing Information for prescribing information and toxicity profile.

All gastric adenocarcinoma subjects with or without a history of DVT will be given enoxaparin 40 mg/day (pre-filled syringes of enoxaparin are allowed), for prophylaxis of TE events, given the high incidence seen in this tumor type. PEGPH20 will be discontinued for subjects who experience any TE requiring full-dose anticoagulation while on study. Treatment with pembrolizumab, however, may continue as deemed appropriate by the Investigator.

If in gastric adenocarcinoma subjects, enoxaparin is discontinued for any reason, PEGPH20 will also be discontinued. Treatment with pembrolizumab, however, may continue as deemed appropriate by the Investigator.

10.12.3. Aspirin

All NSCLC subjects will be given enteric-coated 81 mg of aspirin/day for prophylaxis of TE events, given the high incidence seen in this tumor type.

10.12.4. Dexamethasone

As this study uses an immunotherapeutic agent and dexamethasone may suppress an immune response, it should only be used when prescribed by the Investigator and following a discussion with the Sponsor. Dexamethasone may be used to attenuate musculoskeletal symptoms that may occur in subjects treated with PEGPH20 and/or pembrolizumab if prescribed by the Investigator (and following a discussion with the Sponsor). In this situation dexamethasone may be given orally, intramuscularly, or intravenously.

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

11. STATISTICS

11.1. Statistical Methods

In general, continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum). Categorical variables will be presented using frequencies and percentages. Dose escalation data summaries will be presented by PEGPH20 dose level. All statistical analyses and data listings will be performed using SAS version 9.3 or higher (Cary, NC).

11.1.1. Randomization and Blinding

This is a multicenter, open-label, non-randomized study.

11.1.2. Sample Size

In the dose escalating portion, there may be up to 5 dose levels for a total of approximately 30 subjects.

In the Dose Expansion portion, approximately 51 subjects with HA-high tumors will be enrolled (30 with HA-high tumors in NSCLC cohort and 21 with HA-high tumors in the gastric adenocarcinoma cohort).

KEYNOTE-001 study data presented at the American Society of Clinical Oncology 2016 (Hui 2016) showed that when treated with pembrolizumab alone, treatment naïve subjects who had evaluable PD-L1 Tumor Proportion Score [TPS] levels had an ORR of 29% and previously treated subjects who had evaluable PD-L1 TPS levels had an ORR of 21%. Under the assumption that no more than 40% of the subjects enrolled in this study will be treatment naïve, ORR in the combined NSCLC population is expected to be approximately 24% when treated with pembrolizumab alone. A 20% improvement in ORR is considered clinically meaningful when PEGPH20 is added to pembrolizumab. Under these conditions, 30 NSCLC subjects would provide approximately 80% power at the hypothesized ORR of 44% when the null hypothesis H0: ORR $\leq$24% is tested against H1: ORR >24% using an exact one-sided binomial test at a 10% significance level.

KEYNOTE-012 study data showed that the ORR in PD-L1 positive gastric cancer subjects is about 22% (Muro 2016). Since subjects will not be selected based on PD-L1 expression levels prospectively in this study, in order to accommodate all subjects (irrespective of PD-L1 expression levels), a conservative ORR of 15% is assumed with pembrolizumab treatment alone and it is further assumed that the addition of PEGPH20 to pembrolizumab will lead to a clinically meaningful improvement of 20% in ORR to 35%.Under these assumptions, 21 subjects will provide approximately 80% power at the hypothesized ORR of 35% when the null hypothesis H0: ORR ≤15% tested against H1: ORR >15% using an exact one sided binomial test at a 10% significance level.

11.1.3. Analysis Populations

11.1.3.1. Safety Population

All subjects who receive any study medication. The Safety Population will be used for subject disposition, demographics and safety analyses.

11.1.3.2. DLT Evaluable Population

All subjects who receive at least 1 of the 3 full planned doses of PEGPH20 and 1 complete dose of pembrolizumab in Cycle 1 and have been followed for the first 21 days of treatment or have experienced a DLT during the initial 21 days (Cycle 1) of the study. The DLT Evaluable Population will be used for DLT analysis.

11.1.3.3. PK Analysis Population

All subjects who receive any PEGPH20 and have measurable PEGPH20 concentrations in at least 1 sample collected for PK analysis. PK Analysis Population will be used for PK analysis.

11.1.3.4. Efficacy Evaluable Population

All HA-high subjects who receive at least 1 dose of the RP2D of PEGPH20 and at least 1 dose of pembrolizumab. The efficacy evaluable population will be used for all efficacy analyses.

11.1.3.5. Tumor Response Evaluable Population

Subjects in the Efficacy Evaluable Population who have at least one post-baseline tumor assessment. Tumor Response Evaluable Population will also be used for overall tumor response analysis.

11.1.4. Subject Disposition

Subject disposition data (including analysis populations) will be summarized.

Subject disposition will be tabulated with number of subjects enrolled, receiving study treatment, on study treatment, discontinuation from treatment, and reasons for discontinuing treatment.

Enrollment by center, major protocol deviations will also be summarized.

11.1.5. Analysis of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using safety population by dose level for subjects in the Dose Escalation portion and separately for all subjects in the Dose Expansion portion. The following demographic and baseline characteristics will be summarized: age, race, height, weight, medical history, disease characteristics, and treatment history.

11.1.6. Efficacy Analyses

All efficacy analyses will be conducted using the Efficacy Evaluable Population. ORR and DOR will also be analyzed using Tumor Response Evaluable population.

11.1.6.1. Analyses of the Primary ORR Efficacy Endpoint

The primary efficacy endpoint of the study is PEGPEM treatment effect on ORR (based on RECIST v1.1). The statistical hypothesis tests for the primary endpoint are as follows:

- NSCLC cohort: H_0: ORR ≤23%; H_1: ORR >23%
- Gastric adenocarcinoma cohort: H_0: ORR ≤15%; H_1: ORR >15%

The hypothesis tests will be conducted using the one-sided exact binomial test at the significance level of 0.1.

ORR will be calculated as the number of subjects with a confirmed CR or PR divided by the number of subjects in the analysis population multiplied by 100. The exact 80% confidence interval of ORR will also be constructed.

11.1.6.2. Analyses of Secondary Efficacy Endpoints

Median DOR, PFS and OS will be estimated using the Kaplan-Meier method.

- DOR is defined as the time from the date on which objective response (CR or PR) is first determined until the first date on which radiographic disease progression is determined, and will only be calculated for subjects with a confirmed objective response. Subjects achieving a confirmed objective response who do not have radiographic disease progression will be censored at the date of the last available post-baseline evaluable tumor assessment. DOR will be analyzed using Kaplan-Meier methods.
- PFS, defined as the time from first dose date until the first occurrence of either radiographic or clinical disease progression as determined by the Investigator or death from any cause before discontinuation from treatment. PFS for surviving subjects without disease progression will be censored at the date of the last available post-baseline evaluable tumor assessment. Surviving subjects without any post-baseline disease assessment will be censored on Day 1.
- OS is defined as the time from first dose date until death from any cause. OS data from surviving subjects will be censored at time of the last contact.
- DCR is defined as the proportion of subjects who achieve CR, PR, or stable disease, and will be analyzed using the same method as ORR.

Descriptive summaries will be provided for estimation of ORR, DOR, DCR and PFS based on RECIST v1.1 and irRC.

11.1.7. Analysis of Treatment Exposure

The study medication exposure will be summarized using the Safety Population by dose level. Study medication exposure will include exposure duration, dosing cycles, dosing information for study medication, such as number of doses, relative dose intensity, and dose changes.

11.1.7.1. Pharmacokinetic Analyses

For PEGPH20 noncompartmental and compartmental PK modeling will be performed. The AUC, the C_{max}, and $T_{1/2}$ will be summarized from noncompartmental analysis along with descriptive statistics. Other PK analyses may be performed and population PK parameters including $T_{1/2}$, V_D, and CL will be evaluated and reported if the data are sufficient.

11.1.7.2. Plasma Hyaluronan

Descriptive statistics will be used to summarize measured plasma concentrations of HA.

11.1.7.3. Exploratory Analyses

Descriptive summaries will be provided for all exploratory analysis data, which include estimation of ORR, DOR, DCR, and PFS based on RECIST v1.1 and irRC, by PD-L1 expression levels, changes in tumor blood flow as measured by DCE-MRI and changes in tumor metabolism as measured by PET/CT, and changes in potential biomarkers in plasma and tumor biopsy and their correlation to study endpoints. For pembrolizumab, noncompartmental and compartmental PK modeling will be performed. The AUC, C_{max}, and $T_{1/2}$ will be summarized from the noncompartmental analysis along with descriptive statistics.

11.1.8. Safety Analyses

All safety parameters will be summarized using the Safety Population by dose level will be descriptive in nature. No inferential statistical tests will be conducted for safety parameters.

All AEs will be presented in incidence tables coded by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term and System Organ Class.

Additionally, separate AE incidence tables, coded by MedDRA term, will be presented by: 1) toxicity grade (severity) graded by the CTCAE and 2) relationship to study medication (PEGPH20 and pembrolizumab).

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

In addition, subjects who experienced TE will be summarized by SMQ term and MedDRA preferred term by grade.

Laboratory parameters and vital signs and the corresponding change from baseline over time will be summarized using descriptive statistics.

11.1.9. Interim Analysis

No interim analysis will be performed for this study.

12. SPONSOR AND INVESTIGATOR RESPONSIBILITIES

12.1. Protocol Compliance

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

12.1.1. Protocol Waivers

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

12.1.2. Protocol Deviations

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

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

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

12.2. Study Monitoring

Site visits will be conducted by an authorized Halozyme representative, who will inspect study data, subject 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 Electronic Case Report Forms

eCRFs 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.

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

12.4. Financial Disclosure

The Investigator is required to provide a financial disclosure statement or certification to Halozyme before study initiation. In accordance with 21 Code of Federal Regulations (CFR) 54, Investigators and all sub-Investigators are required to disclose all financial interests to the study Sponsor (Halozyme), to permit complete and accurate certification statements in an application for marketing authorization. This disclosure includes compensation affected by the outcome of a clinical study, significant equity interest in Halozyme's parent entity, Halozyme Therapeutics, Inc., and proprietary interest in the tested product. Investigators must promptly update this information if any relevant changes occur during the study and for 1 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 US Investigational New Drug Application according to the provisions of the US CFR, FDA regulations and guidelines, GCP guidelines, and the Declaration of Helsinki, revised version of Seoul, October, 2008. All applicable US regulations governing human subject protection must be followed. All ethical and regulatory requirements are necessary to comply with the principles of GCP. This includes inspection by the Sponsor, its representatives, health authority representatives, or IRB/EC representatives at any time. The Investigator must agree to the inspection of study-related records by the health authority, the Sponsor, and/or the Sponsor's representatives.

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

14.1. Institutional Review Board and Approval

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

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

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

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

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

14.2. Written Informed Consent

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

Each subject found eligible for the study must have voluntarily provided written informed consent, using the IRB/EC-approved ICF, before study screening (i.e., before any protocol-specified procedures that are not part of normal subject care).

15. DATA HANDLING AND RECORD KEEPING

15.1. Record Inspection

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

15.2. Study Documentation and Record Retention

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

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

The period for which these documents must be retained is governed by US law and, when applicable, non-US regulations. The Investigator must retain all records for at least 2 years after the FDA has approved the New Drug Application, or until 2 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 antibodies
AE	adverse event
AG	nab-paclitaxel plus gemcitabine
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	Asia Pacific
AST	aspartate aminotransferase
AUC	area-under-the-concentration time curve
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIV	Central Imaging Vendor
CL	clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCE-MRI	dynamic-contrast enhanced magnetic resonance imaging
DCR	disease control rate
DLT	dose limiting toxicity
Doc	docetaxel alone
DOR	duration of response
DVT	deep vein thrombosis

Abbreviation	Term
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EE	efficacy evaluable
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
FDA	Food and Drug Administration
FNA	Fine Needle Aspirates
GCP	Good Clinical Practice
GEM	Gemcitabine
HA	Hyaluronan
HER2+	human epidermal growth factor receptor 2 positive
High-HA	high expression of HA
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgE	immunoglobulin E
IgG	immunoglobulin G
INR	international normalized ratio
IRB	Institutional Review Board
irRC	Immune-response related criteria
ITT	Intent-to-treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary of Regulatory Activities
MRI	Magnetic Resonance Imaging
MSE	Musculoskeletal Event
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural Killer Cells

Abbreviation	Term
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	over-the-counter
PAG	PEGPH20 combined with nab-paclitaxel plus gemcitabine
PDoc	PEGPH20 plus docetaxel
PD-1	programmed cell death-1
PDA	pancreatic ductal adenocarcinoma
PD-L1	PD-1 ligand 1
PEG	Polyethylene glycol
PEGPH20	PEGylated recombinant human hyaluronidase
PEGPEM	PEGylated recombinant human hyaluronidase (PEGPH20) combined with pembrolizumab (Keytruda®)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PRO	patient reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	PH20 recombinant human hyaluronidase enzyme
ROW	Rest Of The World
RP2D	recommended Phase 2 dose
rHuPH20	recombinant human hyaluronidase PH20
SAE	serious adverse event
SD	stable disease
$t_{1/2}$	terminal half-life
TB	total bilirubin
TE	thromboembolic event
t_{max}	time to maximum concentration

Abbreviation	Term
TME	tumor microenvironment
TPS	Tumor Proportion Score
ULN	upper limit of normal
US	United States
Vd	volume of distribution
WBC	white blood cell
WOCBP	women of childbearing potential

APPENDIX B. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCES STATUS

Activity Status	Description
0	Asymptomatic, fully active, and able to carry on all predisease performance without restrictions.
1	Symptomatic, fully ambulatory but restricted in physical strenuous activity and able to carry out performance of a light or sedentary nature, e.g., light housework, office work.
2	Symptomatic, ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours, but not bedridden.
3	Symptomatic, capable of only limited self-care, confined to a bed/chair more than 50% of waking hours, but not bedridden.
4	Completely disabled. Cannot carry on self-care. Totally bedridden.
5	Dead

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

Target Lesion Response 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 thus far, nadir (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 Response 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.

Overall Response Evaluation:

Target Lesion Response	Non-Target Lesion Response	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated or NA	No	PR
SD	Non-PD or not all evaluated or NA	No	SD
Not all evaluated	Non-PD or NA	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NA=Not Applicable (i.e., no non-target lesions identified at baseline); NE=Not Evaluable.
Source: Eisenhauer 2009

APPENDIX D. 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 E. IMMUNE-RESPONSE RELATED CRITERIA

Immune-response related criteria (irRC) based on bidimensional measurements of measurable lesions were first introduced by Wolchok et al in 2009. This protocol will adopt a modified version of the criteria based on unidimensional measurements of measurable lesions, as described by Nishino et al in 2013 and 2014, as follows:

At the baseline tumor assessment, the sum of the longest diameters (SLD) of all identified index lesions (2 per organ, up to 5 in total) will be calculated. At each subsequent tumor assessment, the SLD of the index lesions and of new measurable lesions (2 per organ, up to 5 in total) are added together to provide the total tumor burden = $SLD_{index\ lesions} + SLD_{new,\ measurable\ lesions}$. Total tumor burden will be used to assess the immune related response as described in the table below.

Immune-Response Related Criteria	
Index Lesions (Baseline Measurable Lesions)	Up to 2 per organ, up to 5 in total (see RECIST 1.1 for guidelines on measurable lesions) • ≥10 mm in the longest diameter for all except for lymph nodes • ≥15 mm in short axis for lymph nodes
New Lesions (Measurable)	Up to 2 per organ, up to 5 in total • ≥10 mm in the longest diameter for all except for lymph nodes • ≥15 mm in short axis for lymph nodes
Tumor Burden	$SLD_{index\ lesions} + SLD_{new,\ measurable\ lesions}$ If a lymph node qualifies and chosen as a new measurable lesion for tumor burden calculations, its short axis length is included in the sum ($SLD_{new,\ measurable\ lesions}$)
Immune Related Response Assessment	PD: ≥20% increase in tumor burden from nadir PR: ≥30% decrease in tumor burden from baseline SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD CR: Disappearance of **all** lesions including non-index lesions and new non-measurable lesions, lymph nodes must be <10 mm in short axis)
Confirmation	Confirmation is required for CR, PR and PD by a consecutive observation not less than 4 weeks apart

Source: Wolchok 2009; Nishino 2013; Nishino 2014.